



## Clinical trial results:

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

#### Summary

|                          |                                                    |
|--------------------------|----------------------------------------------------|
| EudraCT number           | 2011-005334-20                                     |
| Trial protocol           | AT FI FR ES SI GB NL DE BE HU PT GR SE IT EE LT PL |
| Global end of trial date | 20 September 2019                                  |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 16 September 2020 |
| First version publication date | 16 September 2020 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MO28047 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01572038 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                           |
|------------------------------|-----------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche, Ltd.                                                                                |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070                                                        |
| Public contact               | F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 20 September 2019 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 20 September 2019 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 20 September 2019 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. All participants were required to read and sign an informed consent form.

Background therapy:

Trastuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 8 mg/kg, followed by 6 mg/kg on Day 1 or Day 2 of each subsequent 3-weekly cycle; in line with approved local Product Information and/or recognized clinical practice guidelines. Commercial Herceptin (trastuzumab) was obtained directly by the site for intravenous use during this study. A taxane (docetaxel or paclitaxel or nab-paclitaxel) was administered in line with the respective Product Information and/or recognized clinical practice guidelines. The taxane could have been administered before or after the monoclonal antibody (pertuzumab and trastuzumab) infusions. Commercial docetaxel and/or paclitaxel and nab-paclitaxel was obtained locally by the investigational sites.

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 01 June 2012 |
| Long term follow-up planned                               | Yes          |
| Long term follow-up rationale                             | Efficacy     |
| Long term follow-up duration                              | 5 Years      |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Algeria: 29   |
| Country: Number of subjects enrolled | Argentina: 5  |
| Country: Number of subjects enrolled | Australia: 24 |
| Country: Number of subjects enrolled | Austria: 19   |
| Country: Number of subjects enrolled | Belgium: 23   |
| Country: Number of subjects enrolled | Brazil: 44    |
| Country: Number of subjects enrolled | Canada: 34    |
| Country: Number of subjects enrolled | China: 52     |
| Country: Number of subjects enrolled | Ecuador: 4    |
| Country: Number of subjects enrolled | Egypt: 26     |
| Country: Number of subjects enrolled | Estonia: 3    |

|                                      |                                      |
|--------------------------------------|--------------------------------------|
| Country: Number of subjects enrolled | Finland: 15                          |
| Country: Number of subjects enrolled | France: 185                          |
| Country: Number of subjects enrolled | Germany: 82                          |
| Country: Number of subjects enrolled | Greece: 40                           |
| Country: Number of subjects enrolled | Hong Kong: 5                         |
| Country: Number of subjects enrolled | Hungary: 35                          |
| Country: Number of subjects enrolled | Israel: 49                           |
| Country: Number of subjects enrolled | Italy: 115                           |
| Country: Number of subjects enrolled | Lebanon: 8                           |
| Country: Number of subjects enrolled | Lithuania: 8                         |
| Country: Number of subjects enrolled | Mexico: 46                           |
| Country: Number of subjects enrolled | Morocco: 16                          |
| Country: Number of subjects enrolled | Netherlands: 20                      |
| Country: Number of subjects enrolled | Pakistan: 17                         |
| Country: Number of subjects enrolled | Peru: 11                             |
| Country: Number of subjects enrolled | Poland: 47                           |
| Country: Number of subjects enrolled | Portugal: 24                         |
| Country: Number of subjects enrolled | Saudi Arabia: 11                     |
| Country: Number of subjects enrolled | Serbia: 15                           |
| Country: Number of subjects enrolled | Slovenia: 8                          |
| Country: Number of subjects enrolled | Spain: 168                           |
| Country: Number of subjects enrolled | Sweden: 25                           |
| Country: Number of subjects enrolled | Turkey: 30                           |
| Country: Number of subjects enrolled | Ukraine: 35                          |
| Country: Number of subjects enrolled | United Arab Emirates: 5              |
| Country: Number of subjects enrolled | United Kingdom: 142                  |
| Country: Number of subjects enrolled | Uruguay: 6                           |
| Country: Number of subjects enrolled | Venezuela, Bolivarian Republic of: 5 |
| Worldwide total number of subjects   | 1436                                 |
| EEA total number of subjects         | 959                                  |

Notes:

### Subjects enrolled per age group

|                                           |      |
|-------------------------------------------|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 1124 |
| From 65 to 84 years                       | 310  |
| 85 years and over                         | 2    |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1697 patients were screened: 261 failed screening and 1436 were enrolled in the study.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                  |                                   |
|------------------|-----------------------------------|
| <b>Arm title</b> | Pertuzumab + Trastuzumab + Taxane |
|------------------|-----------------------------------|

Arm description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Pertuzumab                            |
| Investigational medicinal product code | RO4358451                             |
| Other name                             | Perjeta                               |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Pertuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 or Day 2 of each subsequent 3 weekly cycle.

| Number of subjects in period 1           | Pertuzumab + Trastuzumab + Taxane |
|------------------------------------------|-----------------------------------|
| Started                                  | 1436                              |
| Received at Least One Dose of Study Drug | 1436                              |
| Completed                                | 445                               |
| Not completed                            | 991                               |
| Enrolled into Another Trial              | 3                                 |
| Participated in Another Trial            | 3                                 |
| Termination by Sponsor                   | 2                                 |
| Consent withdrawn by subject             | 204                               |
| Physician decision                       | 20                                |
| Patient Decision                         | 14                                |
| Death                                    | 648                               |
| Progressive Disease                      | 8                                 |

|                                    |    |
|------------------------------------|----|
| Site Closed Before Completing Form | 6  |
| Sponsor Decision                   | 1  |
| Lost to follow-up                  | 81 |
| Patient Deterioration              | 1  |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                            |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                      | Pertuzumab + Trastuzumab + Taxane |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                               |                                   |
| Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |

| Reporting group values                                | Pertuzumab +<br>Trastuzumab +<br>Taxane | Total |  |
|-------------------------------------------------------|-----------------------------------------|-------|--|
| Number of subjects                                    | 1436                                    | 1436  |  |
| Age categorical                                       |                                         |       |  |
| Units: Subjects                                       |                                         |       |  |
| In utero                                              | 0                                       | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                       | 0     |  |
| Newborns (0-27 days)                                  | 0                                       | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0                                       | 0     |  |
| Children (2-11 years)                                 | 0                                       | 0     |  |
| Adolescents (12-17 years)                             | 0                                       | 0     |  |
| Adults (18-64 years)                                  | 1124                                    | 1124  |  |
| From 65-84 years                                      | 310                                     | 310   |  |
| 85 years and over                                     | 2                                       | 2     |  |
| Age Continuous                                        |                                         |       |  |
| Units: Years                                          |                                         |       |  |
| arithmetic mean                                       | 54.4                                    |       |  |
| standard deviation                                    | ± 12.10                                 | -     |  |
| Sex: Female, Male                                     |                                         |       |  |
| Units: Participants                                   |                                         |       |  |
| Female                                                | 1429                                    | 1429  |  |
| Male                                                  | 7                                       | 7     |  |
| Age Categorical (≤65 or >65 Years Old)                |                                         |       |  |
| Units: Subjects                                       |                                         |       |  |
| ≤65 Years Old                                         | 1167                                    | 1167  |  |
| >65 Years Old                                         | 269                                     | 269   |  |
| Race/Ethnicity, Customized                            |                                         |       |  |
| Units: Subjects                                       |                                         |       |  |
| Caucasian                                             | 1032                                    | 1032  |  |
| Black                                                 | 9                                       | 9     |  |
| Asian                                                 | 88                                      | 88    |  |
| Native American                                       | 28                                      | 28    |  |
| Other                                                 | 57                                      | 57    |  |
| Not Applicable as per Local<br>Regulations            | 222                                     | 222   |  |
| Ethnicity                                             |                                         |       |  |
| Units: Subjects                                       |                                         |       |  |
| Hispanic/Latino                                       | 269                                     | 269   |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |      |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|--|
| Chinese                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 57   | 57   |  |
| Japanese                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2    | 2    |  |
| Mixed Ethnicity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 18   | 18   |  |
| Indian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 21   | 21   |  |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 495  | 495  |  |
| Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 574  | 574  |  |
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |      |  |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |      |      |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |      |  |
| Europe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 1009 | 1009 |  |
| Asia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 177  | 177  |  |
| North America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 34   | 34   |  |
| South America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 121  | 121  |  |
| Africa                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 71   | 71   |  |
| Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 24   | 24   |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                             |      |      |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                                                                                                               |      |      |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |      |  |
| Grade 0 or 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1371 | 1371 |  |
| Grade 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 63   | 63   |  |
| Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2    | 2    |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |      |      |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                                                                                                                                |      |      |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |      |  |
| Visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 992  | 992  |  |
| Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 444  | 444  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |      |      |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                                                                                                                                          |      |      |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |      |  |
| Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 918  | 918  |  |
| Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 512  | 512  |  |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 6    | 6    |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |      |      |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |      |      |  |
| Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 786  | 786  |  |
| No Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 650  | 650  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                              |      |      |  |

|                                                                                            |      |      |  |
|--------------------------------------------------------------------------------------------|------|------|--|
| Units: Subjects                                                                            |      |      |  |
| Previous Trastuzumab Therapy                                                               | 400  | 400  |  |
| No Previous Trastuzumab Therapy                                                            | 1036 | 1036 |  |
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel |      |      |  |
| Units: Subjects                                                                            |      |      |  |
| Docetaxel                                                                                  | 775  | 775  |  |
| Paclitaxel                                                                                 | 588  | 588  |  |
| Nab-Paclitaxel                                                                             | 65   | 65   |  |
| None                                                                                       | 8    | 8    |  |
| Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline                         |      |      |  |
| Units: Subjects                                                                            |      |      |  |
| Measurable Disease                                                                         | 1198 | 1198 |  |
| Non-Measurable Disease                                                                     | 238  | 238  |  |

### Subject analysis sets

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Europe             |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Asia               |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | North America      |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | South America      |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Africa             |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Other (Australia)  |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Age ≤65 Years      |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Age >65 Years      |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Docetaxel          |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received docetaxel as their taxane chemotherapy, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Paclitaxel         |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received paclitaxel as their taxane chemotherapy, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Nab-Paclitaxel     |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received nab-paclitaxel as their taxane chemotherapy, per the investigator's choice.

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | ECOG Performance Status 0 or 1 |
| Subject analysis set type  | Sub-group analysis             |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | ECOG Performance Status 2 |
| Subject analysis set type  | Sub-group analysis        |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Visceral Disease   |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of

consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Non-Visceral Disease |
| Subject analysis set type  | Sub-group analysis   |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Prior (Neo)Adjuvant Chemotherapy |
| Subject analysis set type  | Sub-group analysis               |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | No Prior (Neo)Adjuvant Chemotherapy |
| Subject analysis set type  | Sub-group analysis                  |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Hormone Receptor Positive |
| Subject analysis set type  | Sub-group analysis        |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Hormone Receptor Negative |
| Subject analysis set type  | Sub-group analysis        |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | Hormone Receptor Status Unknown |
| Subject analysis set type  | Sub-group analysis              |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Previous Trastuzumab Therapy |
| Subject analysis set type  | Sub-group analysis           |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | No Previous Trastuzumab Therapy |
| Subject analysis set type  | Sub-group analysis              |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

| <b>Reporting group values</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Europe  | Asia    | North America |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|---------|---------------|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 1009    | 177     | 34            |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |         |               |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over                                                                                                                                                                                                                                                            |         |         |               |
| Age Continuous<br>Units: Years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |         |               |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 55.4    | 50.8    | 56.3          |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | ± 12.14 | ± 11.75 | ± 11.32       |
| Sex: Female, Male<br>Units: Participants                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |         |               |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |         |               |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |         |               |
| Age Categorical (≤65 or >65 Years Old)<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |         |               |
| ≤65 Years Old                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |         |               |
| >65 Years Old                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |         |               |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |         |               |
| Caucasian<br>Black<br>Asian<br>Native American<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                                                   |         |         |               |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |         |               |
| Hispanic/Latino<br>Chinese<br>Japanese<br>Mixed Ethnicity<br>Indian<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                              |         |         |               |
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |         |               |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |         |         |               |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |         |               |

|                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Europe<br>Asia<br>North America<br>South America<br>Africa<br>Other (Australia)                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Grade 0 or 1<br>Grade 2<br>Missing                                                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                           |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                  |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Visceral Disease<br>Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                            |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Positive<br>Negative<br>Unknown                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received                                                                                                                                                                                                                                                                                                                                                    |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Prior (Neo)Adjuvant Chemotherapy<br>No Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Previous Trastuzumab Therapy<br>No Previous Trastuzumab Therapy                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel                                                                                                                                                                                                                                                                                                             |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Docetaxel<br>Paclitaxel<br>Nab-Paclitaxel<br>None                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |

|                        |  |  |  |
|------------------------|--|--|--|
| Measurable Disease     |  |  |  |
| Non-Measurable Disease |  |  |  |

| Reporting group values                                                                                                                                                                                                                                    | South America | Africa  | Other (Australia) |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|---------|-------------------|
| Number of subjects                                                                                                                                                                                                                                        | 121           | 71      | 24                |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |               |         |                   |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |               |         |                   |
| Age Continuous<br>Units: Years                                                                                                                                                                                                                            |               |         |                   |
| arithmetic mean                                                                                                                                                                                                                                           | 54.5          | 48.0    | 53.8              |
| standard deviation                                                                                                                                                                                                                                        | ± 11.53       | ± 10.55 | ± 11.49           |
| Sex: Female, Male<br>Units: Participants                                                                                                                                                                                                                  |               |         |                   |
| Female                                                                                                                                                                                                                                                    |               |         |                   |
| Male                                                                                                                                                                                                                                                      |               |         |                   |
| Age Categorical (≤65 or >65 Years Old)<br>Units: Subjects                                                                                                                                                                                                 |               |         |                   |
| ≤65 Years Old                                                                                                                                                                                                                                             |               |         |                   |
| >65 Years Old                                                                                                                                                                                                                                             |               |         |                   |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                             |               |         |                   |
| Caucasian<br>Black<br>Asian<br>Native American<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                        |               |         |                   |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                              |               |         |                   |
| Hispanic/Latino<br>Chinese<br>Japanese<br>Mixed Ethnicity<br>Indian<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                   |               |         |                   |
| Geographic Region of Enrollment                                                                                                                                                                                                                           |               |         |                   |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia,                                                       |               |         |                   |

Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia.

|                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Europe                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| Asia                                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |
| North America                                                                                                                                                                                                                                                                                                                                                                                          |  |  |  |
| South America                                                                                                                                                                                                                                                                                                                                                                                          |  |  |  |
| Africa                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Grade 0 or 1                                                                                                                                                                                                                                                                                                                                                                                           |  |  |  |
| Grade 2                                                                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Missing                                                                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                           |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                  |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Visceral Disease                                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                            |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Positive                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Negative                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received                                                                                                                                                                                                                                                                                                                                                    |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| No Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                    |  |  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Previous Trastuzumab Therapy                                                                                                                                                                                                                                                                                                                                                                           |  |  |  |
| No Previous Trastuzumab Therapy                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel                                                                                                                                                                                                                                                                                                             |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Docetaxel                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Paclitaxel                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Nab-Paclitaxel                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |

|                                                                                          |  |  |  |
|------------------------------------------------------------------------------------------|--|--|--|
| None                                                                                     |  |  |  |
| Measurable or Non-Measurable Disease<br>(per RECIST v1.1) at Baseline<br>Units: Subjects |  |  |  |
| Measurable Disease<br>Non-Measurable Disease                                             |  |  |  |

| Reporting group values                                                                                                                                                                                                                                       | Age ≤65 Years  | Age >65 Years  | Docetaxel       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|-----------------|
| Number of subjects                                                                                                                                                                                                                                           | 1167           | 269            | 775             |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                           |                |                |                 |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                |                |                 |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                      | 50.3<br>± 9.30 | 72.0<br>± 4.68 | 52.9<br>± 11.77 |
| Sex: Female, Male<br>Units: Participants                                                                                                                                                                                                                     |                |                |                 |
| Female<br>Male                                                                                                                                                                                                                                               |                |                |                 |
| Age Categorical (≤65 or >65 Years Old)<br>Units: Subjects                                                                                                                                                                                                    |                |                |                 |
| ≤65 Years Old<br>>65 Years Old                                                                                                                                                                                                                               |                |                |                 |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                                |                |                |                 |
| Caucasian<br>Black<br>Asian<br>Native American<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                           |                |                |                 |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                 |                |                |                 |
| Hispanic/Latino<br>Chinese<br>Japanese<br>Mixed Ethnicity<br>Indian<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                      |                |                |                 |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Europe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Asia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| North America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| South America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Africa                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                                                                                                               |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Grade 0 or 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Grade 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                                                                                                                                          |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| No Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Previous Trastuzumab Therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| No Previous Trastuzumab Therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel                                                                                                                                                                                                                                                                                                                                                                                                                           |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |

|                                                                                          |  |  |  |
|------------------------------------------------------------------------------------------|--|--|--|
| Docetaxel<br>Paclitaxel<br>Nab-Paclitaxel<br>None                                        |  |  |  |
| Measurable or Non-Measurable Disease<br>(per RECIST v1.1) at Baseline<br>Units: Subjects |  |  |  |
| Measurable Disease<br>Non-Measurable Disease                                             |  |  |  |

| <b>Reporting group values</b>                                                                                                                                                                                                                                   | Paclitaxel      | Nab-Paclitaxel  | ECOG Performance<br>Status 0 or 1 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|-----------------------------------|
| Number of subjects                                                                                                                                                                                                                                              | 588             | 65              | 1371                              |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                              |                 |                 |                                   |
| In utero<br>Preterm newborn infants<br>(gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23<br>months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                 |                 |                                   |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                         | 56.3<br>± 12.21 | 54.1<br>± 12.53 | 54.2<br>± 12.00                   |
| Sex: Female, Male<br>Units: Participants                                                                                                                                                                                                                        |                 |                 |                                   |
| Female<br>Male                                                                                                                                                                                                                                                  |                 |                 |                                   |
| Age Categorical (≤65 or >65 Years Old)<br>Units: Subjects                                                                                                                                                                                                       |                 |                 |                                   |
| ≤65 Years Old<br>>65 Years Old                                                                                                                                                                                                                                  |                 |                 |                                   |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                                   |                 |                 |                                   |
| Caucasian<br>Black<br>Asian<br>Native American<br>Other<br>Not Applicable as per Local<br>Regulations                                                                                                                                                           |                 |                 |                                   |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                    |                 |                 |                                   |
| Hispanic/Latino<br>Chinese<br>Japanese<br>Mixed Ethnicity                                                                                                                                                                                                       |                 |                 |                                   |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Indian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Europe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Asia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| North America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| South America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Africa                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                                                                                                               |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Grade 0 or 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Grade 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                                                                                                                                          |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| No Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Previous Trastuzumab Therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| No Previous Trastuzumab Therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |

|                                                                                                               |  |  |  |
|---------------------------------------------------------------------------------------------------------------|--|--|--|
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel<br>Units: Subjects |  |  |  |
| Docetaxel<br>Paclitaxel<br>Nab-Paclitaxel<br>None                                                             |  |  |  |
| Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline<br>Units: Subjects                         |  |  |  |
| Measurable Disease<br>Non-Measurable Disease                                                                  |  |  |  |

| Reporting group values                                                                                                                                                                                                                                    | ECOG Performance Status 2 | Visceral Disease | Non-Visceral Disease |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------|----------------------|
| Number of subjects                                                                                                                                                                                                                                        | 63                        | 992              | 444                  |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                           |                  |                      |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                           |                  |                      |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                   | 58.1<br>± 13.81           | 54.6<br>± 12.05  | 53.8<br>± 12.21      |
| Sex: Female, Male<br>Units: Participants                                                                                                                                                                                                                  |                           |                  |                      |
| Female<br>Male                                                                                                                                                                                                                                            |                           |                  |                      |
| Age Categorical (≤65 or >65 Years Old)<br>Units: Subjects                                                                                                                                                                                                 |                           |                  |                      |
| ≤65 Years Old<br>>65 Years Old                                                                                                                                                                                                                            |                           |                  |                      |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                             |                           |                  |                      |
| Caucasian<br>Black<br>Asian<br>Native American<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                        |                           |                  |                      |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                              |                           |                  |                      |
| Hispanic/Latino                                                                                                                                                                                                                                           |                           |                  |                      |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Chinese                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Japanese                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Mixed Ethnicity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Indian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Europe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Asia                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| North America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| South America                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Africa                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |
| Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                                                                                                               |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Grade 0 or 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Grade 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                                                                                                                                          |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Positive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |  |  |
| No Prior (Neo)Adjuvant Chemotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |

|                                                                                            |  |  |  |
|--------------------------------------------------------------------------------------------|--|--|--|
| Units: Subjects                                                                            |  |  |  |
| Previous Trastuzumab Therapy                                                               |  |  |  |
| No Previous Trastuzumab Therapy                                                            |  |  |  |
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel |  |  |  |
| Units: Subjects                                                                            |  |  |  |
| Docetaxel                                                                                  |  |  |  |
| Paclitaxel                                                                                 |  |  |  |
| Nab-Paclitaxel                                                                             |  |  |  |
| None                                                                                       |  |  |  |
| Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline                         |  |  |  |
| Units: Subjects                                                                            |  |  |  |
| Measurable Disease                                                                         |  |  |  |
| Non-Measurable Disease                                                                     |  |  |  |

| <b>Reporting group values</b>                         | Prior (Neo)Adjuvant<br>Chemotherapy | No Prior<br>(Neo)Adjuvant<br>Chemotherapy | Hormone Receptor<br>Positive |
|-------------------------------------------------------|-------------------------------------|-------------------------------------------|------------------------------|
| Number of subjects                                    | 786                                 | 650                                       | 918                          |
| Age categorical                                       |                                     |                                           |                              |
| Units: Subjects                                       |                                     |                                           |                              |
| In utero                                              |                                     |                                           |                              |
| Preterm newborn infants<br>(gestational age < 37 wks) |                                     |                                           |                              |
| Newborns (0-27 days)                                  |                                     |                                           |                              |
| Infants and toddlers (28 days-23<br>months)           |                                     |                                           |                              |
| Children (2-11 years)                                 |                                     |                                           |                              |
| Adolescents (12-17 years)                             |                                     |                                           |                              |
| Adults (18-64 years)                                  |                                     |                                           |                              |
| From 65-84 years                                      |                                     |                                           |                              |
| 85 years and over                                     |                                     |                                           |                              |
| Age Continuous                                        |                                     |                                           |                              |
| Units: Years                                          |                                     |                                           |                              |
| arithmetic mean                                       | 54.6                                | 54.0                                      | 54.1                         |
| standard deviation                                    | ± 11.79                             | ± 12.46                                   | ± 12.07                      |
| Sex: Female, Male                                     |                                     |                                           |                              |
| Units: Participants                                   |                                     |                                           |                              |
| Female                                                |                                     |                                           |                              |
| Male                                                  |                                     |                                           |                              |
| Age Categorical (≤65 or >65 Years Old)                |                                     |                                           |                              |
| Units: Subjects                                       |                                     |                                           |                              |
| ≤65 Years Old                                         |                                     |                                           |                              |
| >65 Years Old                                         |                                     |                                           |                              |
| Race/Ethnicity, Customized                            |                                     |                                           |                              |
| Units: Subjects                                       |                                     |                                           |                              |
| Caucasian                                             |                                     |                                           |                              |
| Black                                                 |                                     |                                           |                              |
| Asian                                                 |                                     |                                           |                              |
| Native American                                       |                                     |                                           |                              |
| Other                                                 |                                     |                                           |                              |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Hispanic/Latino<br>Chinese<br>Japanese<br>Mixed Ethnicity<br>Indian<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Europe<br>Asia<br>North America<br>South America<br>Africa<br>Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                                                                                                               |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Grade 0 or 1<br>Grade 2<br>Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Visceral Disease<br>Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                                                                                                                                          |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Positive<br>Negative<br>Unknown                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |  |

|                                                                                                               |  |  |  |
|---------------------------------------------------------------------------------------------------------------|--|--|--|
| Prior (Neo)Adjuvant Chemotherapy<br>No Prior (Neo)Adjuvant Chemotherapy                                       |  |  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer<br>Units: Subjects                                    |  |  |  |
| Previous Trastuzumab Therapy<br>No Previous Trastuzumab Therapy                                               |  |  |  |
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel<br>Units: Subjects |  |  |  |
| Docetaxel<br>Paclitaxel<br>Nab-Paclitaxel<br>None                                                             |  |  |  |
| Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline<br>Units: Subjects                         |  |  |  |
| Measurable Disease<br>Non-Measurable Disease                                                                  |  |  |  |

| <b>Reporting group values</b>                                                                                                                                                                                                                             | Hormone Receptor Negative | Hormone Receptor Status Unknown | Previous Trastuzumab Therapy |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------------|------------------------------|
| Number of subjects                                                                                                                                                                                                                                        | 512                       | 6                               | 400                          |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                           |                                 |                              |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                           |                                 |                              |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                   | 54.9<br>± 12.17           | 46.7<br>± 7.31                  | 52.8<br>± 11.80              |
| Sex: Female, Male<br>Units: Participants                                                                                                                                                                                                                  |                           |                                 |                              |
| Female<br>Male                                                                                                                                                                                                                                            |                           |                                 |                              |
| Age Categorical (≤65 or >65 Years Old)<br>Units: Subjects                                                                                                                                                                                                 |                           |                                 |                              |
| ≤65 Years Old<br>>65 Years Old                                                                                                                                                                                                                            |                           |                                 |                              |
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                             |                           |                                 |                              |
| Caucasian                                                                                                                                                                                                                                                 |                           |                                 |                              |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Black<br>Asian<br>Native American<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                                                                |  |  |  |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Hispanic/Latino<br>Chinese<br>Japanese<br>Mixed Ethnicity<br>Indian<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Europe<br>Asia<br>North America<br>South America<br>Africa<br>Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                                                                                                               |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Grade 0 or 1<br>Grade 2<br>Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Visceral Disease<br>Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                                                                                                                                          |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Positive<br>Negative                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |  |  |

|                                                                                                               |  |  |  |
|---------------------------------------------------------------------------------------------------------------|--|--|--|
| Unknown                                                                                                       |  |  |  |
| Prior Neoadjuvant or Adjuvant Chemotherapy Received<br>Units: Subjects                                        |  |  |  |
| Prior (Neo)Adjuvant Chemotherapy<br>No Prior (Neo)Adjuvant Chemotherapy                                       |  |  |  |
| Previous Trastuzumab Therapy Received for Breast Cancer<br>Units: Subjects                                    |  |  |  |
| Previous Trastuzumab Therapy<br>No Previous Trastuzumab Therapy                                               |  |  |  |
| Initial Type of Taxane Received During the Study: Docetaxel, Paclitaxel, or Nab-Paclitaxel<br>Units: Subjects |  |  |  |
| Docetaxel<br>Paclitaxel<br>Nab-Paclitaxel<br>None                                                             |  |  |  |
| Measurable or Non-Measurable Disease (per RECIST v1.1) at Baseline<br>Units: Subjects                         |  |  |  |
| Measurable Disease<br>Non-Measurable Disease                                                                  |  |  |  |

|                                                                                                                                                                                                                                                           |                                 |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|--|--|
| <b>Reporting group values</b>                                                                                                                                                                                                                             | No Previous Trastuzumab Therapy |  |  |
| Number of subjects                                                                                                                                                                                                                                        | 1036                            |  |  |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                                 |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                 |  |  |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                   | 55.0<br>± 12.16                 |  |  |
| Sex: Female, Male<br>Units: Participants                                                                                                                                                                                                                  |                                 |  |  |
| Female<br>Male                                                                                                                                                                                                                                            |                                 |  |  |
| Age Categorical (≤65 or >65 Years Old)<br>Units: Subjects                                                                                                                                                                                                 |                                 |  |  |
| ≤65 Years Old<br>>65 Years Old                                                                                                                                                                                                                            |                                 |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|--|
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |  |
| Caucasian<br>Black<br>Asian<br>Native American<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |
| Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| Hispanic/Latino<br>Chinese<br>Japanese<br>Mixed Ethnicity<br>Indian<br>Other<br>Not Applicable as per Local Regulations                                                                                                                                                                                                                                                                                                                                                                                              |  |  |  |
| Geographic Region of Enrollment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Geographic region of enrollment was categorized as follows: Europe = Austria, Belgium, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Serbia, Slovenia, Spain, Sweden, United Kingdom, Ukraine; Asia = China, Hong Kong, Israel, Lebanon, Pakistan, Saudi Arabia, Turkey, United Arab Emirates; North America = Canada; South America = Argentina, Brazil, Ecuador, Mexico, Peru, Uruguay, Venezuela; Africa = Algeria, Egypt, Morocco; and Other = Australia. |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Europe<br>Asia<br>North America<br>South America<br>Africa<br>Other (Australia)                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Grade 0: Fully active, able to carry on all pre-disease performance without restriction; Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.                                                                                                               |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Grade 0 or 1<br>Grade 2<br>Missing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |  |  |
| Visceral Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |  |
| The disease was considered as "visceral" if at least one lesion in a location other than breast, bone, bone marrow, lymph nodes, skin and soft tissue was observed during baseline tumor assessment. The disease was considered as "non-visceral" if all lesions observed at baseline were localized in breast, bone, bone marrow, lymph nodes, skin and soft tissue.                                                                                                                                                |  |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |  |
| Visceral Disease<br>Non-visceral Disease                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |  |  |
| Hormone Receptor Status of Disease at Baseline                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |  |  |
| Hormone receptor status of the primary tumor and metastatic disease (combined) was defined as follows: Positive: if either estrogen receptor (ER) or progesterone receptor (PgR) status was positive; Negative: if both ER and PgR status was negative; Unknown: if both the ER and PgR status was unknown.                                                                                                                                                                                                          |  |  |  |

|                                                                                                  |  |  |  |
|--------------------------------------------------------------------------------------------------|--|--|--|
| Units: Subjects                                                                                  |  |  |  |
| Positive                                                                                         |  |  |  |
| Negative                                                                                         |  |  |  |
| Unknown                                                                                          |  |  |  |
| Prior Neoadjuvant or Adjuvant<br>Chemotherapy Received                                           |  |  |  |
| Units: Subjects                                                                                  |  |  |  |
| Prior (Neo)Adjuvant Chemotherapy                                                                 |  |  |  |
| No Prior (Neo)Adjuvant<br>Chemotherapy                                                           |  |  |  |
| Previous Trastuzumab Therapy Received<br>for Breast Cancer                                       |  |  |  |
| Units: Subjects                                                                                  |  |  |  |
| Previous Trastuzumab Therapy                                                                     |  |  |  |
| No Previous Trastuzumab Therapy                                                                  |  |  |  |
| Initial Type of Taxane Received During<br>the Study: Docetaxel, Paclitaxel, or<br>Nab-Paclitaxel |  |  |  |
| Units: Subjects                                                                                  |  |  |  |
| Docetaxel                                                                                        |  |  |  |
| Paclitaxel                                                                                       |  |  |  |
| Nab-Paclitaxel                                                                                   |  |  |  |
| None                                                                                             |  |  |  |
| Measurable or Non-Measurable Disease<br>(per RECIST v1.1) at Baseline                            |  |  |  |
| Units: Subjects                                                                                  |  |  |  |
| Measurable Disease                                                                               |  |  |  |
| Non-Measurable Disease                                                                           |  |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                 |                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                           | Pertuzumab + Trastuzumab + Taxane |
| Reporting group description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.      |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                      | Europe                            |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                       | Sub-group analysis                |
| Subject analysis set description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                      | Asia                              |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                       | Sub-group analysis                |
| Subject analysis set description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                      | North America                     |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                       | Sub-group analysis                |
| Subject analysis set description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                      | South America                     |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                       | Sub-group analysis                |
| Subject analysis set description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                      | Africa                            |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                       | Sub-group analysis                |
| Subject analysis set description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                      | Other (Australia)                 |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                       | Sub-group analysis                |
| Subject analysis set description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                      | Age ≤65 Years                     |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                       | Sub-group analysis                |
| Subject analysis set description:<br>Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice. |                                   |

paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Age >65 Years      |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Docetaxel          |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received docetaxel as their taxane chemotherapy, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Paclitaxel         |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received paclitaxel as their taxane chemotherapy, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Nab-Paclitaxel     |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Participants in this subgroup received nab-paclitaxel as their taxane chemotherapy, per the investigator's choice.

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | ECOG Performance Status 0 or 1 |
| Subject analysis set type  | Sub-group analysis             |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | ECOG Performance Status 2 |
| Subject analysis set type  | Sub-group analysis        |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Visceral Disease   |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Non-Visceral Disease |
| Subject analysis set type  | Sub-group analysis   |

Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                  |
|----------------------------|----------------------------------|
| Subject analysis set title | Prior (Neo)Adjuvant Chemotherapy |
| Subject analysis set type  | Sub-group analysis               |

#### Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                     |
|----------------------------|-------------------------------------|
| Subject analysis set title | No Prior (Neo)Adjuvant Chemotherapy |
| Subject analysis set type  | Sub-group analysis                  |

#### Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Hormone Receptor Positive |
| Subject analysis set type  | Sub-group analysis        |

#### Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Hormone Receptor Negative |
| Subject analysis set type  | Sub-group analysis        |

#### Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | Hormone Receptor Status Unknown |
| Subject analysis set type  | Sub-group analysis              |

#### Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                              |
|----------------------------|------------------------------|
| Subject analysis set title | Previous Trastuzumab Therapy |
| Subject analysis set type  | Sub-group analysis           |

#### Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

|                            |                                 |
|----------------------------|---------------------------------|
| Subject analysis set title | No Previous Trastuzumab Therapy |
| Subject analysis set type  | Sub-group analysis              |

#### Subject analysis set description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

### **Primary: Overview of the Number of Participants with at Least One Treatment-Emergent Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0)**

|                 |                                                                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Overview of the Number of Participants with at Least One Treatment-Emergent Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0) <sup>[1]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed

as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade  $\geq 3$ , pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent. TEAEs of special interest included LVEF decreased, liver enzymes increased, and suspected transmission of infectious agent by the study drug.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                   | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                 | Reporting group                         |  |  |  |
| Number of subjects analysed                        | 1436                                    |  |  |  |
| Units: Participants                                |                                         |  |  |  |
| Any TEAE - Any Grade                               | 1419                                    |  |  |  |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )          | 879                                     |  |  |  |
| Any Serious TEAE                                   | 535                                     |  |  |  |
| Any TEAE Leading to Death                          | 31                                      |  |  |  |
| Any TEAE Related to Pertuzumab - Any Grade         | 1037                                    |  |  |  |
| Any TEAE Related to Trastuzumab - Any Grade        | 946                                     |  |  |  |
| Any TEAE Related to Taxane - Any Grade             | 1342                                    |  |  |  |
| Any TEAE Related to Pertuzumab - Grade $\geq 3$    | 286                                     |  |  |  |
| Any TEAE Related to Trastuzumab - Grade $\geq 3$   | 245                                     |  |  |  |
| Any TEAE Related to Taxane - Grade $\geq 3$        | 514                                     |  |  |  |
| Any TEAE Leading to Interruption of Pertuzumab     | 334                                     |  |  |  |
| Any TEAE Leading to Interruption of Trastuzumab    | 386                                     |  |  |  |
| Any TEAE Leading to Interruption of Taxane         | 354                                     |  |  |  |
| Any TEAE Leading to Discontinuation of Pertuzumab  | 140                                     |  |  |  |
| Any TEAE Leading to Discontinuation of Trastuzumab | 133                                     |  |  |  |
| Any TEAE Leading to Discontinuation of Taxane      | 286                                     |  |  |  |
| Any TEAE to Monitor - Any Grade                    | 1320                                    |  |  |  |
| Any TEAE to Monitor - Grade $\geq 3$               | 535                                     |  |  |  |
| Any TEAE of Special Interest                       | 91                                      |  |  |  |
| Any TEAE Within 28 Days of Treatmt Discontinuation | 975                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants Who Died Over the Course of the Study by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term)

|                 |                                                                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Who Died Over the Course of the Study by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term) <sup>[2]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

All adverse events leading to death, regardless of whether they were classified as treatment emergent, are listed by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities, version 22.1 (MedDRA version 22.1); PTs that are part of a given SOC are listed in the rows directly below each SOC within the results table. Admin. = administration; Mediast. = mediastinal

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                    | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|-----------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                  | Reporting group                         |  |  |  |
| Number of subjects analysed                         | 1436                                    |  |  |  |
| Units: Participants                                 |                                         |  |  |  |
| Total Number of Deaths                              | 658                                     |  |  |  |
| Number of Deaths by Cause:<br>Progressive Disease   | 581                                     |  |  |  |
| Number of Deaths by Cause: Other                    | 42                                      |  |  |  |
| Number of Deaths by Cause: Adverse<br>Event (Total) | 35                                      |  |  |  |
| Infections and Infestations (SOC)                   | 11                                      |  |  |  |
| Peritonitis (PT)                                    | 1                                       |  |  |  |
| Pneumonia (PT)                                      | 5                                       |  |  |  |
| Respiratory Tract Infection (PT)                    | 1                                       |  |  |  |
| Sepsis (PT)                                         | 3                                       |  |  |  |
| Septic Shock (PT)                                   | 1                                       |  |  |  |
| Cardiac Disorders (SOC)                             | 7                                       |  |  |  |
| Cardiac Arrest (PT)                                 | 2                                       |  |  |  |
| Cardiac Failure (PT)                                | 1                                       |  |  |  |
| Cardiac Failure Congestive (PT)                     | 1                                       |  |  |  |
| Cardio-respiratory Arrest (PT)                      | 1                                       |  |  |  |
| Myocardial Infarction (PT)                          | 1                                       |  |  |  |

|                                                  |   |  |  |  |
|--------------------------------------------------|---|--|--|--|
| Right Ventricular Failure (PT)                   | 1 |  |  |  |
| General Disorders & Admin. Site Conditions (SOC) | 6 |  |  |  |
| Death (PT)                                       | 6 |  |  |  |
| Blood and Lymphatic System Disorders (SOC)       | 3 |  |  |  |
| Febrile Neutropenia (PT)                         | 1 |  |  |  |
| Neutropenia (PT)                                 | 1 |  |  |  |
| Thrombocytopenia (PT)                            | 1 |  |  |  |
| Respiratory, Thoracic & Mediast. Disorders (SOC) | 3 |  |  |  |
| Acute Respiratory Distress Syndrome (PT)         | 1 |  |  |  |
| Aspiration (PT)                                  | 1 |  |  |  |
| Pneumonitis (PT)                                 | 1 |  |  |  |
| Gastrointestinal Disorders (SOC)                 | 2 |  |  |  |
| Pancreatitis (PT)                                | 1 |  |  |  |
| Pancreatitis Chronic (PT)                        | 1 |  |  |  |
| Nervous System Disorders (SOC)                   | 2 |  |  |  |
| Hepatic Encephalopathy (PT)                      | 1 |  |  |  |
| Ischemic Stroke (PT)                             | 1 |  |  |  |
| Metabolism and Nutrition Disorders (SOC)         | 1 |  |  |  |
| Hypoglycaemia (PT)                               | 1 |  |  |  |
| Hepatobiliary Disorders (SOC)                    | 1 |  |  |  |
| Hepatic Failure (PT)                             | 1 |  |  |  |
| Psychiatric Disorders (SOC)                      | 1 |  |  |  |
| Delirium (PT)                                    | 1 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants Who Died Within 6 Months of Starting Study Treatment by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term)

|                 |                                                                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants Who Died Within 6 Months of Starting Study Treatment by Reported Cause of Death (Adverse Events Leading to Death by System Organ Class and Preferred Term) <sup>[3]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

All adverse events leading to death, regardless of whether they were classified as treatment emergent, are listed by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities, version 22.1 (MedDRA version 22.1); PTs that are part of a given SOC are listed in the rows directly below each SOC within the results table. Admin. = administration; Mediast. = mediastinal

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

|                                                     |                                         |  |  |  |
|-----------------------------------------------------|-----------------------------------------|--|--|--|
| <b>End point values</b>                             | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
| Subject group type                                  | Reporting group                         |  |  |  |
| Number of subjects analysed                         | 1436                                    |  |  |  |
| Units: Participants                                 |                                         |  |  |  |
| Total Number of Deaths                              | 38                                      |  |  |  |
| Number of Deaths by Cause:<br>Progressive Disease   | 18                                      |  |  |  |
| Number of Deaths by Cause: Other                    | 1                                       |  |  |  |
| Number of Deaths by Cause: Adverse<br>Event (Total) | 19                                      |  |  |  |
| Infections and Infestations (SOC)                   | 6                                       |  |  |  |
| Peritonitis (PT)                                    | 1                                       |  |  |  |
| Pneumonia (PT)                                      | 2                                       |  |  |  |
| Respiratory Tract Infection (PT)                    | 1                                       |  |  |  |
| Sepsis (PT)                                         | 2                                       |  |  |  |
| General Disorders & Admin. Site<br>Conditions (SOC) | 4                                       |  |  |  |
| Death (PT)                                          | 4                                       |  |  |  |
| Blood and Lymphatic System Disorders<br>(SOC)       | 3                                       |  |  |  |
| Febrile Neutropenia (PT)                            | 1                                       |  |  |  |
| Neutropenia (PT)                                    | 1                                       |  |  |  |
| Thrombocytopenia (PT)                               | 1                                       |  |  |  |
| Cardiac Disorders (SOC)                             | 2                                       |  |  |  |
| Cardiac Arrest (PT)                                 | 1                                       |  |  |  |
| Cardio-Respiratory Arrest (PT)                      | 1                                       |  |  |  |
| Respiratory, Thoracic & Mediast.<br>Disorders (SOC) | 2                                       |  |  |  |
| Acute Respiratory Distress Syndrome<br>(PT)         | 1                                       |  |  |  |
| Pneumonitis (PT)                                    | 1                                       |  |  |  |
| Gastrointestinal Disorders (SOC)                    | 1                                       |  |  |  |
| Pancreatitis (PT)                                   | 1                                       |  |  |  |
| Nervous System Disorders (SOC)                      | 1                                       |  |  |  |
| Hepatic Encephalopathy (PT)                         | 1                                       |  |  |  |
| Metabolism and Nutrition Disorders<br>(SOC)         | 1                                       |  |  |  |
| Hypoglycaemia (PT)                                  | 1                                       |  |  |  |
| Hepatobiliary Disorders (SOC)                       | 1                                       |  |  |  |
| Hepatic Failure (PT)                                | 1                                       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events, Occurring in ≥1% of Participants by System Organ Class and Preferred Term

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Grade ≥3 Treatment-Emergent Adverse Events, Occurring in ≥1% of Participants by System Organ Class and Preferred Term <sup>[4]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

# End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs by system organ class (SOC) and preferred term (PT); PTs that are part of a given SOC are listed in the rows directly below each SOC within the results table. If a participant experienced the same AE at more than one severity grade, only the most severe grade was presented.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

# End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

# Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                   | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                 | Reporting group                         |  |  |  |
| Number of subjects analysed                        | 1436                                    |  |  |  |
| Units: Participants                                |                                         |  |  |  |
| Any TEAE - Grade (Gr.) 3                           | 676                                     |  |  |  |
| Any TEAE - Gr. 4                                   | 172                                     |  |  |  |
| Any TEAE - Gr. 5                                   | 31                                      |  |  |  |
| Gastrointestinal Disorders (SOC) - Gr. 3           | 163                                     |  |  |  |
| Gastrointestinal Disorders (SOC) - Gr. 4           | 4                                       |  |  |  |
| Gastrointestinal Disorders (SOC) - Gr. 5           | 2                                       |  |  |  |
| Diarrhoea (PT) - Gr. 3                             | 119                                     |  |  |  |
| Diarrhoea (PT) - Gr. 4                             | 1                                       |  |  |  |
| Diarrhoea (PT) - Gr. 5                             | 0                                       |  |  |  |
| Vomiting (PT) - Gr. 3                              | 19                                      |  |  |  |
| Vomiting (PT) - Gr. 4                              | 0                                       |  |  |  |
| Vomiting (PT) - Gr. 5                              | 0                                       |  |  |  |
| Skin & Subcutaneous Tissue Disorders (SOC) - Gr. 3 | 56                                      |  |  |  |
| Skin & Subcutaneous Tissue Disorders (SOC) - Gr. 4 | 0                                       |  |  |  |
| Skin & Subcutaneous Tissue Disorders (SOC) - Gr. 5 | 0                                       |  |  |  |
| Gen. Disorders & Admin.Site Conditions (SOC)-Gr. 3 | 100                                     |  |  |  |
| Gen. Disorders & Admin.Site Conditions (SOC)-Gr. 4 | 0                                       |  |  |  |
| Gen. Disorders & Admin.Site Conditions (SOC)-Gr. 5 | 3                                       |  |  |  |
| Fatigue (PT) - Gr. 3                               | 36                                      |  |  |  |
| Fatigue (PT) - Gr. 4                               | 0                                       |  |  |  |
| Fatigue (PT) - Gr. 5                               | 0                                       |  |  |  |
| Asthenia (PT) - Gr. 3                              | 29                                      |  |  |  |
| Asthenia (PT) - Gr. 4                              | 0                                       |  |  |  |
| Asthenia (PT) - Gr. 5                              | 0                                       |  |  |  |
| Mucosal Inflammation (PT) - Gr. 3                  | 14                                      |  |  |  |

|                                                    |     |  |  |  |
|----------------------------------------------------|-----|--|--|--|
| Mucosal Inflammation (PT) - Gr. 4                  | 0   |  |  |  |
| Mucosal Inflammation (PT) - Gr. 5                  | 0   |  |  |  |
| Nervous System Disorders (SOC) - Gr. 3             | 139 |  |  |  |
| Nervous System Disorders (SOC) - Gr. 4             | 0   |  |  |  |
| Nervous System Disorders (SOC) - Gr. 5             | 2   |  |  |  |
| Neuropathy Peripheral (PT) - Gr. 3                 | 26  |  |  |  |
| Neuropathy Peripheral (PT) - Gr. 4                 | 0   |  |  |  |
| Neuropathy Peripheral (PT) - Gr. 5                 | 0   |  |  |  |
| Syncope (PT) - Gr. 3                               | 24  |  |  |  |
| Syncope (PT) - Gr. 4                               | 0   |  |  |  |
| Syncope (PT) - Gr. 5                               | 0   |  |  |  |
| Headache (PT) - Gr. 3                              | 17  |  |  |  |
| Headache (PT) - Gr. 4                              | 0   |  |  |  |
| Headache (PT) - Gr. 5                              | 0   |  |  |  |
| Paraesthesia (PT) - Gr. 3                          | 14  |  |  |  |
| Paraesthesia (PT) - Gr. 4                          | 0   |  |  |  |
| Paraesthesia (PT) - Gr. 5                          | 0   |  |  |  |
| Peripheral Sensory Neuropathy (PT) - Gr. 3         | 14  |  |  |  |
| Peripheral Sensory Neuropathy (PT) - Gr. 4         | 0   |  |  |  |
| Peripheral Sensory Neuropathy (PT) - Gr. 5         | 0   |  |  |  |
| Infections and Infestations (SOC) - Gr. 3          | 148 |  |  |  |
| Infections and Infestations (SOC) - Gr. 4          | 19  |  |  |  |
| Infections and Infestations (SOC) - Gr. 5          | 10  |  |  |  |
| Pneumonia (PT) - Gr. 3                             | 22  |  |  |  |
| Pneumonia (PT) - Gr. 4                             | 1   |  |  |  |
| Pneumonia (PT) - Gr. 5                             | 4   |  |  |  |
| Vascular Device Infection (PT) - Gr. 3             | 14  |  |  |  |
| Vascular Device Infection (PT) - Gr. 4             | 0   |  |  |  |
| Vascular Device Infection (PT) - Gr. 5             | 0   |  |  |  |
| Device Related Infection (PT) - Gr. 3              | 14  |  |  |  |
| Device Related Infection (PT) - Gr. 4              | 0   |  |  |  |
| Device Related Infection (PT) - Gr. 5              | 0   |  |  |  |
| Musculo. & Connective Tissue Disorders (SOC)-Gr. 3 | 75  |  |  |  |
| Musculo. & Connective Tissue Disorders (SOC)-Gr. 4 | 0   |  |  |  |
| Musculo. & Connective Tissue Disorders (SOC)-Gr. 5 | 0   |  |  |  |
| Resp., Thoracic & Mediast. Disorders (SOC) - Gr. 3 | 62  |  |  |  |
| Resp., Thoracic & Mediast. Disorders (SOC) - Gr. 4 | 5   |  |  |  |
| Resp., Thoracic & Mediast. Disorders (SOC) - Gr. 5 | 3   |  |  |  |
| Pulmonary Embolism (PT) - Gr. 3                    | 21  |  |  |  |
| Pulmonary Embolism (PT) - Gr. 4                    | 2   |  |  |  |
| Pulmonary Embolism (PT) - Gr. 5                    | 0   |  |  |  |
| Dyspnoea (PT) - Gr. 3                              | 19  |  |  |  |
| Dyspnoea (PT) - Gr. 4                              | 1   |  |  |  |
| Dyspnoea (PT) - Gr. 5                              | 0   |  |  |  |

|                                                  |     |  |  |  |
|--------------------------------------------------|-----|--|--|--|
| Blood & Lymphatic System Disorders (SOC) - Gr. 3 | 158 |  |  |  |
| Blood & Lymphatic System Disorders (SOC) - Gr. 4 | 104 |  |  |  |
| Blood & Lymphatic System Disorders (SOC) - Gr. 5 | 3   |  |  |  |
| Neutropenia (PT) - Gr. 3                         | 77  |  |  |  |
| Neutropenia (PT) - Gr. 4                         | 67  |  |  |  |
| Neutropenia (PT) - Gr. 5                         | 1   |  |  |  |
| Febrile Neutropenia (PT) - Gr. 3                 | 51  |  |  |  |
| Febrile Neutropenia (PT) - Gr. 4                 | 38  |  |  |  |
| Febrile Neutropenia (PT) - Gr. 5                 | 1   |  |  |  |
| Anaemia (PT) - Gr. 3                             | 29  |  |  |  |
| Anaemia (PT) - Gr. 4                             | 0   |  |  |  |
| Anaemia (PT) - Gr. 5                             | 0   |  |  |  |
| Leukopenia (PT) - Gr. 3                          | 15  |  |  |  |
| Leukopenia (PT) - Gr. 4                          | 3   |  |  |  |
| Leukopenia (PT) - Gr. 5                          | 0   |  |  |  |
| Investigations (SOC) - Gr. 3                     | 116 |  |  |  |
| Investigations (SOC) - Gr. 4                     | 20  |  |  |  |
| Investigations (SOC) - Gr. 5                     | 0   |  |  |  |
| Neutrophil Count Decreased (PT) - Gr. 3          | 25  |  |  |  |
| Neutrophil Count Decreased (PT) - Gr. 4          | 13  |  |  |  |
| Neutrophil Count Decreased (PT) - Gr. 5          | 0   |  |  |  |
| Ejection Fraction Decreased (PT) - Gr. 3         | 22  |  |  |  |
| Ejection Fraction Decreased (PT) - Gr. 4         | 2   |  |  |  |
| Ejection Fraction Decreased (PT) - Gr. 5         | 0   |  |  |  |
| Gamma-Glutamyltransferase Increased (PT) - Gr. 3 | 19  |  |  |  |
| Gamma-Glutamyltransferase Increased (PT) - Gr. 4 | 1   |  |  |  |
| Gamma-Glutamyltransferase Increased (PT) - Gr. 5 | 0   |  |  |  |
| White Blood Cell Count Decreased (PT) - Gr. 3    | 16  |  |  |  |
| White Blood Cell Count Decreased (PT) - Gr. 4    | 2   |  |  |  |
| White Blood Cell Count Decreased (PT) - Gr. 5    | 0   |  |  |  |
| Alanine Aminotransferase Increased (PT) - Gr. 3  | 16  |  |  |  |
| Alanine Aminotransferase Increased (PT) - Gr. 4  | 0   |  |  |  |
| Alanine Aminotransferase Increased (PT) - Gr. 5  | 0   |  |  |  |
| Metabolism and Nutrition Disorders (SOC) - Gr. 3 | 63  |  |  |  |
| Metabolism and Nutrition Disorders (SOC) - Gr. 4 | 8   |  |  |  |
| Metabolism and Nutrition Disorders (SOC) - Gr. 5 | 1   |  |  |  |
| Hypokalaemia (PT) - Gr. 3                        | 19  |  |  |  |
| Hypokalaemia (PT) - Gr. 4                        | 1   |  |  |  |
| Hypokalaemia (PT) - Gr. 5                        | 0   |  |  |  |
| Vascular Disorders (SOC) - Gr. 3                 | 62  |  |  |  |
| Vascular Disorders (SOC) - Gr. 4                 | 2   |  |  |  |
| Vascular Disorders (SOC) - Gr. 5                 | 0   |  |  |  |

|                                                    |    |  |  |  |
|----------------------------------------------------|----|--|--|--|
| Hypertension (PT) - Gr. 3                          | 45 |  |  |  |
| Hypertension (PT) - Gr. 4                          | 1  |  |  |  |
| Hypertension (PT) - Gr. 5                          | 0  |  |  |  |
| Psychiatric Disorders (SOC) - Gr. 3                | 15 |  |  |  |
| Psychiatric Disorders (SOC) - Gr. 4                | 3  |  |  |  |
| Psychiatric Disorders (SOC) - Gr. 5                | 1  |  |  |  |
| Injury, Poisoning & Proced. Complicat. (SOC)-Gr. 3 | 43 |  |  |  |
| Injury, Poisoning & Proced. Complicat. (SOC)-Gr. 4 | 6  |  |  |  |
| Injury, Poisoning & Proced. Complicat. (SOC)-Gr. 5 | 0  |  |  |  |
| Cardiac Disorders (SOC) - Gr. 3                    | 35 |  |  |  |
| Cardiac Disorders (SOC) - Gr. 4                    | 5  |  |  |  |
| Cardiac Disorders (SOC) - Gr. 5                    | 7  |  |  |  |
| Immune System Disorders (SOC) - Gr. 3              | 17 |  |  |  |
| Immune System Disorders (SOC) - Gr. 4              | 1  |  |  |  |
| Immune System Disorders (SOC) - Gr. 5              | 0  |  |  |  |
| Renal and Urinary Disorders (SOC) - Gr. 3          | 15 |  |  |  |
| Renal and Urinary Disorders (SOC) - Gr. 4          | 3  |  |  |  |
| Renal and Urinary Disorders (SOC) - Gr. 5          | 0  |  |  |  |
| Neoplasms Benign, Malignant & Unspec. (SOC) -Gr. 3 | 13 |  |  |  |
| Neoplasms Benign, Malignant & Unspec. (SOC) -Gr. 4 | 5  |  |  |  |
| Neoplasms Benign, Malignant & Unspec. (SOC) -Gr. 5 | 0  |  |  |  |
| Hepatobiliary Disorders (SOC) - Gr. 3              | 13 |  |  |  |
| Hepatobiliary Disorders (SOC) - Gr. 4              | 0  |  |  |  |
| Hepatobiliary Disorders (SOC) - Gr. 5              | 1  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Treatment-Emergent Adverse Events of Any Grade That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥10% of Participants by System Organ Class

|                 |                                                                                                                                                                                                                              |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse Events of Any Grade That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in ≥10% of Participants by System Organ Class <sup>[5]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs and the system organ classes are presented in descending order according to the total

frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                   | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                 | Reporting group                         |  |  |  |
| Number of subjects analysed                        | 1436                                    |  |  |  |
| Units: Participants                                |                                         |  |  |  |
| Any TEAE Related to Pertuzumab (Rel to Ptz)        | 1037                                    |  |  |  |
| Rel to Ptz: Gastrointestinal Disorders             | 629                                     |  |  |  |
| Rel to Ptz: Skin and Subcutaneous Tissue Disorders | 491                                     |  |  |  |
| Rel to Ptz: Gen. Disorders & Admin.Site Conditions | 462                                     |  |  |  |
| Rel to Ptz: Investigations                         | 252                                     |  |  |  |
| Rel to Ptz: Nervous System Disorders               | 207                                     |  |  |  |
| Rel to Ptz: Resp., Thoracic & Mediast. Disorders   | 188                                     |  |  |  |
| Rel to Ptz: Musculo. & Connective Tissue Disorders | 184                                     |  |  |  |
| Rel to Ptz: Blood & Lymphatic System Disorders     | 182                                     |  |  |  |
| Rel to Ptz: Infections and Infestations            | 151                                     |  |  |  |
| Any TEAE Related to Trastuzumab (Rel to Trz)       | 946                                     |  |  |  |
| Rel to Trz: Gastrointestinal Disorders             | 435                                     |  |  |  |
| Rel to Trz: Gen. Disorders & Admin.Site Conditions | 434                                     |  |  |  |
| Rel to Trz: Skin and Subcutaneous Tissue Disorders | 384                                     |  |  |  |
| Rel to Trz: Investigations                         | 262                                     |  |  |  |
| Rel to Trz: Nervous System Disorders               | 184                                     |  |  |  |
| Rel to Trz: Musculo. & Connective Tissue Disorders | 179                                     |  |  |  |
| Rel to Trz: Blood & Lymphatic System Disorders     | 163                                     |  |  |  |
| Rel to Trz: Resp., Thoracic & Mediast. Disorders   | 153                                     |  |  |  |
| Any TEAE Related to Taxane (Rel to Tax)            | 1342                                    |  |  |  |
| Rel to Tax: Gastrointestinal Disorders             | 984                                     |  |  |  |
| Rel to Tax: Skin and Subcutaneous Tissue Disorders | 938                                     |  |  |  |
| Rel to Tax: Gen. Disorders & Admin.Site Conditions | 834                                     |  |  |  |
| Rel to Tax: Nervous System Disorders               | 764                                     |  |  |  |

|                                                    |     |  |  |  |
|----------------------------------------------------|-----|--|--|--|
| Rel to Tax: Blood & Lymphatic System Disorders     | 457 |  |  |  |
| Rel to Tax: Musculo. & Connective Tissue Disorders | 386 |  |  |  |
| Rel to Tax: Infections and Infestations            | 293 |  |  |  |
| Rel to Tax: Resp., Thoracic & Mediast. Disorders   | 290 |  |  |  |
| Rel to Tax: Metabolism and Nutrition Disorders     | 227 |  |  |  |
| Rel to Tax: Investigations                         | 201 |  |  |  |
| Rel to Tax: Eye Disorders                          | 174 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Grade $\geq 3$ Treatment-Emergent Adverse Events That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in $\geq 0.5\%$ of Participants by Preferred Term

|                 |                                                                                                                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Grade $\geq 3$ Treatment-Emergent Adverse Events That Were Related to Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in $\geq 0.5\%$ of Participants by Preferred Term <sup>[6]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs and the preferred terms are presented in descending order according to the total frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                        | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|---------------------------------------------------------|-----------------------------------|--|--|--|
| Subject group type                                      | Reporting group                   |  |  |  |
| Number of subjects analysed                             | 1436                              |  |  |  |
| Units: Participants                                     |                                   |  |  |  |
| Any Grade $\geq 3$ TEAE Related to Pertuz. (Rel to Ptz) | 286                               |  |  |  |
| Rel to Ptz: Diarrhoea                                   | 59                                |  |  |  |
| Rel to Ptz: Neutropenia                                 | 28                                |  |  |  |
| Rel to Ptz: Febrile Neutropenia                         | 28                                |  |  |  |
| Rel to Ptz: Ejection Fraction Decreased                 | 19                                |  |  |  |

|                                                          |     |  |  |  |
|----------------------------------------------------------|-----|--|--|--|
| Rel to Ptz: Neutrophil Count Decreased                   | 15  |  |  |  |
| Rel to Ptz: Fatigue                                      | 15  |  |  |  |
| Rel to Ptz: Left Ventricular Dysfunction                 | 10  |  |  |  |
| Rel to Ptz: Asthenia                                     | 10  |  |  |  |
| Rel to Ptz: White Blood Cell Count Decreased             | 10  |  |  |  |
| Rel to Ptz: Cardiac Failure                              | 9   |  |  |  |
| Any Grade $\geq 3$ TEAE Related to Trastuz. (Rel to Trz) | 245 |  |  |  |
| Rel to Trz: Diarrhoea                                    | 32  |  |  |  |
| Rel to Trz: Neutropenia                                  | 30  |  |  |  |
| Rel to Trz: Ejection Fraction Decreased                  | 23  |  |  |  |
| Rel to Trz: Febrile Neutropenia                          | 21  |  |  |  |
| Rel to Trz: Neutrophil Count Decreased                   | 15  |  |  |  |
| Rel to Trz: Fatigue                                      | 14  |  |  |  |
| Rel to Trz: Left Ventricular Dysfunction                 | 11  |  |  |  |
| Rel to Trz: White Blood Cell Count Decreased             | 10  |  |  |  |
| Rel to Trz: Cardiac Failure                              | 8   |  |  |  |
| Rel to Trz: Asthenia                                     | 8   |  |  |  |
| Any Grade $\geq 3$ TEAE Related to Taxane (Rel to Tax)   | 514 |  |  |  |
| Rel to Tax: Neutropenia                                  | 140 |  |  |  |
| Rel to Tax: Febrile Neutropenia                          | 86  |  |  |  |
| Rel to Tax: Diarrhoea                                    | 80  |  |  |  |
| Rel to Tax: Neutrophil Count Decreased                   | 34  |  |  |  |
| Rel to Tax: Fatigue                                      | 26  |  |  |  |
| Rel to Tax: Peripheral Neuropathy                        | 24  |  |  |  |
| Rel to Tax: Asthenia                                     | 20  |  |  |  |
| Rel to Tax: Leukopenia                                   | 16  |  |  |  |
| Rel to Tax: White Blood Cell Count Decreased             | 16  |  |  |  |
| Rel to Tax: Mucosal Inflammation                         | 14  |  |  |  |
| Rel to Tax: Paraesthesia                                 | 13  |  |  |  |
| Rel to Tax: Peripheral Sensory Neuropathy                | 13  |  |  |  |
| Rel to Tax: Onycholysis                                  | 10  |  |  |  |
| Rel to Tax: Neutropenic Sepsis                           | 10  |  |  |  |
| Rel to Tax: Anaemia                                      | 10  |  |  |  |
| Rel to Tax: Vomiting                                     | 7   |  |  |  |
| Rel to Tax: Neurotoxicity                                | 7   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in $\geq 0.2\%$ of Participants by Preferred Term

|                 |                                                                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in $\geq 0.2\%$ of |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was used to code AEs and the preferred terms are presented in descending order according to the total frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category. Discont. = discontinuation; Ptz = pertuzumab; Tax = taxane; Trz = trastuzumab

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

## End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

## Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                   | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                 | Reporting group                         |  |  |  |
| Number of subjects analysed                        | 1436                                    |  |  |  |
| Units: Participants                                |                                         |  |  |  |
| Any TEAE, Pertuzumab Discontinuation (Ptz Discont) | 140                                     |  |  |  |
| Ptz Discont: Ejection Fraction Decreased           | 37                                      |  |  |  |
| Ptz Discont: Cardiac Failure                       | 10                                      |  |  |  |
| Ptz Discont: Left Ventricular Dysfunction          | 7                                       |  |  |  |
| Ptz Discont: Diarrhoea                             | 7                                       |  |  |  |
| Ptz Discont: Dyspnoea                              | 4                                       |  |  |  |
| Ptz Discont: Infusion Related Reaction             | 4                                       |  |  |  |
| Ptz Discont: Sepsis                                | 3                                       |  |  |  |
| Ptz Discont: Neuropathy Peripheral                 | 3                                       |  |  |  |
| Ptz Discont: Hypersensitivity                      | 3                                       |  |  |  |
| Ptz Discont: General Physical Health Deterioration | 3                                       |  |  |  |
| Any TEAE, Trastuzumab Discontinuation(Trz Discont) | 133                                     |  |  |  |
| Trz Discont: Ejection Fraction Decreased           | 37                                      |  |  |  |
| Trz Discont: Cardiac Failure                       | 10                                      |  |  |  |
| Trz Discont: Left Ventricular Dysfunction          | 7                                       |  |  |  |
| Trz Discont: Diarrhoea                             | 6                                       |  |  |  |
| Trz Discont: Sepsis                                | 3                                       |  |  |  |
| Trz Discont: Dyspnoea                              | 3                                       |  |  |  |
| Trz Discont: Neuropathy Peripheral                 | 3                                       |  |  |  |
| Trz Discont: Hypersensitivity                      | 3                                       |  |  |  |
| Trz Discont: General Physical Health Deterioration | 3                                       |  |  |  |
| Any TEAE, Taxane Discontinuation (Tax Discont)     | 286                                     |  |  |  |
| Tax Discont: Neuropathy Peripheral                 | 52                                      |  |  |  |

|                                                    |    |  |  |  |
|----------------------------------------------------|----|--|--|--|
| Tax Discont: Peripheral Sensory Neuropathy         | 25 |  |  |  |
| Tax Discont: Paraesthesia                          | 24 |  |  |  |
| Tax Discont: Diarrhoea                             | 19 |  |  |  |
| Tax Discont: Fatigue                               | 16 |  |  |  |
| Tax Discont: Asthenia                              | 13 |  |  |  |
| Tax Discont: Onycholysis                           | 8  |  |  |  |
| Tax Discont: Nail Toxicity                         | 7  |  |  |  |
| Tax Discont: Neurotoxicity                         | 7  |  |  |  |
| Tax Discont: Polyneuropathy                        | 7  |  |  |  |
| Tax Discont: Oedema Peripheral                     | 7  |  |  |  |
| Tax Discont: Febrile Neutropenia                   | 7  |  |  |  |
| Tax Discont: Neutropenia                           | 7  |  |  |  |
| Tax Discont: Dyspnoea                              | 6  |  |  |  |
| Tax Discont: Decreased Appetite                    | 6  |  |  |  |
| Tax Discont: Ejection Fraction Decreased           | 5  |  |  |  |
| Tax Discont: General Physical Health Deterioration | 4  |  |  |  |
| Tax Discont: Mucosal Inflammation                  | 4  |  |  |  |
| Tax Discont: Rash                                  | 4  |  |  |  |
| Tax Discont: Anaemia                               | 4  |  |  |  |
| Tax Discont: Arthralgia                            | 4  |  |  |  |
| Tax Discont: Drug Hypersensitivity                 | 4  |  |  |  |
| Tax Discont: Dysgeusia                             | 3  |  |  |  |
| Tax Discont: Nail Disorder                         | 3  |  |  |  |
| Tax Discont: Nail Dystrophy                        | 3  |  |  |  |
| Tax Discont: Skin Toxicity                         | 3  |  |  |  |
| Tax Discont: Pneumonia                             | 3  |  |  |  |
| Tax Discont: Sepsis                                | 3  |  |  |  |
| Tax Discont: Pleural Effusion                      | 3  |  |  |  |
| Tax Discont: Pneumonitis                           | 3  |  |  |  |
| Tax Discont: Cardiac Failure                       | 3  |  |  |  |
| Tax Discont: Myalgia                               | 3  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Treatment-Emergent Adverse Events Leading to Dose Interruption of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in $\geq 0.5\%$ of Participants by Preferred Term

|                 |                                                                                                                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse Events Leading to Dose Interruption of Study Treatment (Pertuzumab, Trastuzumab, or Taxane), Occurring in $\geq 0.5\%$ of Participants by Preferred Term <sup>[8]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. MedDRA version 22.1 was

used to code AEs and the preferred terms are presented in descending order according to the total frequency of occurrence. If a participant experienced more than one event in a category, they were counted only once in that category. Interrupt. = interruption; Ptz = pertuzumab; Tax = taxane; Trz = trastuzumab

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                   | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                 | Reporting group                         |  |  |  |
| Number of subjects analysed                        | 1436                                    |  |  |  |
| Units: Participants                                |                                         |  |  |  |
| Any TEAE, Pertuzumab Interruption (Ptz Interrupt)  | 334                                     |  |  |  |
| Ptz Interrupt: Ejection Fraction Decreased         | 51                                      |  |  |  |
| Ptz Interrupt: Diarrhoea                           | 21                                      |  |  |  |
| Ptz Interrupt: Neutropenia                         | 17                                      |  |  |  |
| Ptz Interrupt: Pneumonia                           | 14                                      |  |  |  |
| Ptz Interrupt: Upper Respiratory Tract Infection   | 13                                      |  |  |  |
| Ptz Interrupt: Pyrexia                             | 11                                      |  |  |  |
| Ptz Interrupt: Dyspnoea                            | 11                                      |  |  |  |
| Ptz Interrupt: Drug Hypersensitivity               | 9                                       |  |  |  |
| Ptz Interrupt: Influenza                           | 8                                       |  |  |  |
| Ptz Interrupt: Asthenia                            | 8                                       |  |  |  |
| Ptz Interrupt: Neutrophil Count Decreased          | 8                                       |  |  |  |
| Ptz Interrupt: Nasopharyngitis                     | 7                                       |  |  |  |
| Ptz Interrupt: Anaemia                             | 7                                       |  |  |  |
| Any TEAE, Trastuzumab Interruption (Trz Interrupt) | 386                                     |  |  |  |
| Trz Interrupt: Ejection Fraction Decreased         | 52                                      |  |  |  |
| Trz Interrupt: Drug Hypersensitivity               | 31                                      |  |  |  |
| Trz Interrupt: Diarrhoea                           | 20                                      |  |  |  |
| Trz Interrupt: Pyrexia                             | 18                                      |  |  |  |
| Trz Interrupt: Neutropenia                         | 17                                      |  |  |  |
| Trz Interrupt: Dyspnoea                            | 17                                      |  |  |  |
| Trz Interrupt: Pneumonia                           | 14                                      |  |  |  |
| Trz Interrupt: Chills                              | 13                                      |  |  |  |
| Trz Interrupt: Infusion Related Reaction           | 13                                      |  |  |  |
| Trz Interrupt: Upper Respiratory Tract Infection   | 12                                      |  |  |  |
| Trz Interrupt: Neutrophil Count Decreased          | 8                                       |  |  |  |
| Trz Interrupt: Influenza                           | 7                                       |  |  |  |
| Trz Interrupt: Asthenia                            | 7                                       |  |  |  |

|                                                  |     |  |  |  |
|--------------------------------------------------|-----|--|--|--|
| Trz Interrupt: Vomiting                          | 7   |  |  |  |
| Trz Interrupt: Anaemia                           | 7   |  |  |  |
| Trz Interrupt: Nasopharyngitis                   | 7   |  |  |  |
| Any TEAE, Taxane Interruption (Tax Interrupt)    | 354 |  |  |  |
| Tax Interrupt: Neutropenia                       | 46  |  |  |  |
| Tax Interrupt: Diarrhoea                         | 30  |  |  |  |
| Tax Interrupt: Leukopenia                        | 17  |  |  |  |
| Tax Interrupt: Dyspnoea                          | 15  |  |  |  |
| Tax Interrupt: Pyrexia                           | 14  |  |  |  |
| Tax Interrupt: Neutrophil Count Decreased        | 14  |  |  |  |
| Tax Interrupt: Ejection Fraction Decreased       | 13  |  |  |  |
| Tax Interrupt: Neuropathy Peripheral             | 13  |  |  |  |
| Tax Interrupt: Nasopharyngitis                   | 10  |  |  |  |
| Tax Interrupt: Drug Hypersensitivity             | 10  |  |  |  |
| Tax Interrupt: Fatigue                           | 10  |  |  |  |
| Tax Interrupt: Upper Respiratory Tract Infection | 9   |  |  |  |
| Tax Interrupt: Infusion Related Reaction         | 9   |  |  |  |
| Tax Interrupt: Asthenia                          | 9   |  |  |  |
| Tax Interrupt: Erythema                          | 8   |  |  |  |
| Tax Interrupt: Pneumonia                         | 7   |  |  |  |
| Tax Interrupt: Flushing                          | 7   |  |  |  |
| Tax Interrupt: Hypersensitivity                  | 7   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Treatment-Emergent Adverse Events to Monitor of Any Grade, Occurring in $\geq 5\%$ of Participants by Category

|                 |                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse Events to Monitor of Any Grade, Occurring in $\geq 5\%$ of Participants by Category <sup>[9]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first dose of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, it was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. If a participant had more than one event in a category, they were counted only once in that category. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade  $\geq 3$ , pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent. MedDRA version 22.1 was used to code AEs; AEs may fall within multiple categories.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                              | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|-----------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                            | Reporting group                         |  |  |  |
| Number of subjects analysed                   | 1436                                    |  |  |  |
| Units: Participants                           |                                         |  |  |  |
| Any TEAE to Monitor                           | 1320                                    |  |  |  |
| Infusion-/Administration-Related<br>Reactions | 1096                                    |  |  |  |
| Rash/Skin Reactions                           | 668                                     |  |  |  |
| Mucositis                                     | 618                                     |  |  |  |
| Cardiac Dysfunction                           | 478                                     |  |  |  |
| Neutropenia/Febrile Neutropenia               | 439                                     |  |  |  |
| Anaphylaxis and Hypersensitivity              | 124                                     |  |  |  |
| Diarrhoea Grade $\geq 3$                      | 120                                     |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Grade $\geq 3$ Treatment-Emergent Adverse Events to Monitor, Occurring in $\geq 0.5\%$ of Participants by Category and Preferred Term

|                 |                                                                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Grade $\geq 3$ Treatment-Emergent Adverse Events to Monitor, Occurring in $\geq 0.5\%$ of Participants by Category and Preferred Term <sup>[10]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first dose of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, it was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. If a participant had more than one event in a category, they were counted only once in that category. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade  $\geq 3$ , pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent. MedDRA version 22.1 was used to code AEs; preferred terms (PT) that are part of a given category are listed in the rows directly below each category within the results table.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

|                                                    |                                         |  |  |  |
|----------------------------------------------------|-----------------------------------------|--|--|--|
| <b>End point values</b>                            | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
| Subject group type                                 | Reporting group                         |  |  |  |
| Number of subjects analysed                        | 1436                                    |  |  |  |
| Units: Participants                                |                                         |  |  |  |
| Any Grade $\geq 3$ TEAE to Monitor                 | 535                                     |  |  |  |
| Neutropenia/Febrile Neutropenia<br>(Category)      | 279                                     |  |  |  |
| Neutropenia (PT)                                   | 145                                     |  |  |  |
| Febrile Neutropenia (PT)                           | 90                                      |  |  |  |
| Neutrophil Count Decreased (PT)                    | 38                                      |  |  |  |
| Leukopenia (PT)                                    | 18                                      |  |  |  |
| White Blood Cell Count Decreased (PT)              | 18                                      |  |  |  |
| Neutropenic Sepsis (PT)                            | 10                                      |  |  |  |
| Infusion-/Admin.-Related Reactions<br>(Category)   | 123                                     |  |  |  |
| Hypertension (PT)                                  | 27                                      |  |  |  |
| IRR/ARR: Drug Hypersensitivity (PT)                | 12                                      |  |  |  |
| Asthenia (PT)                                      | 11                                      |  |  |  |
| Fatigue (PT)                                       | 11                                      |  |  |  |
| Dyspnoea (PT)                                      | 10                                      |  |  |  |
| Infusion Related Reaction (PT)                     | 8                                       |  |  |  |
| Paraesthesia (PT)                                  | 7                                       |  |  |  |
| Diarrhoea Grade $\geq 3$ (Category)                | 120                                     |  |  |  |
| Diarrhoea (PT)                                     | 120                                     |  |  |  |
| Cardiac Dysfunction (Category)                     | 51                                      |  |  |  |
| Ejection Fraction Decreased (PT)                   | 24                                      |  |  |  |
| Left Ventricular Dysfunction (PT)                  | 11                                      |  |  |  |
| Cardiac Failure (PT)                               | 9                                       |  |  |  |
| Mucositis (Category)                               | 33                                      |  |  |  |
| Mucosal Inflammation (PT)                          | 14                                      |  |  |  |
| Stomatitis (PT)                                    | 9                                       |  |  |  |
| Rash/Skin Reactions (Category)                     | 28                                      |  |  |  |
| Rash (PT)                                          | 10                                      |  |  |  |
| Anaphylaxis and Hypersensitivity<br>(Category)     | 18                                      |  |  |  |
| Anaphyl./Hypersens.: Drug<br>Hypersensitivity (PT) | 13                                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Treatment-Emergent Adverse Events of Special Interest by Category and Preferred Term

|                 |                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Treatment-Emergent Adverse Events of Special Interest by Category and Preferred Term <sup>[11]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed

as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs of special interest included LVEF decreased, liver enzymes (ALT or AST) increased, and suspected transmission of infectious agent by the study drug. MedDRA version 22.1 was used to code AEs; preferred terms (PT) that are part of a given category are listed in the rows directly below each category within the results table. If a participant experienced more than one event in a category, they were counted only once in that category.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

|                                   |                                         |  |  |  |
|-----------------------------------|-----------------------------------------|--|--|--|
| <b>End point values</b>           | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
| Subject group type                | Reporting group                         |  |  |  |
| Number of subjects analysed       | 1436                                    |  |  |  |
| Units: Participants               |                                         |  |  |  |
| Any TEAE of Special Interest      | 91                                      |  |  |  |
| Decline in LVEF (Category)        | 90                                      |  |  |  |
| Ejection Fraction Decreased (PT)  | 75                                      |  |  |  |
| Left Ventricular Dysfunction (PT) | 8                                       |  |  |  |
| Cardiac Failure (PT)              | 7                                       |  |  |  |
| Cardiac Failure Congestive (PT)   | 1                                       |  |  |  |
| Elevated ALT or AST (Category)    | 1                                       |  |  |  |
| Hepatic Failure (PT)              | 1                                       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Subgroup Analysis by Region of Enrollment: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab

|                 |                                                                                                                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Region of Enrollment: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab <sup>[12]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2

(0.0-86.4) months.

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                              | Europe               | Asia                 | North America        | South America        |
|-----------------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                            | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed                   | 1009                 | 177                  | 34                   | 121                  |
| Units: Percentage of participants             |                      |                      |                      |                      |
| number (not applicable)                       |                      |                      |                      |                      |
| Any Serious TEAE                              | 38.16                | 41.81                | 26.47                | 30.58                |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 62.64                | 61.58                | 64.71                | 52.07                |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 18.53                | 24.86                | 14.71                | 22.31                |

| End point values                              | Africa               | Other (Australia)    |  |  |
|-----------------------------------------------|----------------------|----------------------|--|--|
| Subject group type                            | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                   | 71                   | 24                   |  |  |
| Units: Percentage of participants             |                      |                      |  |  |
| number (not applicable)                       |                      |                      |  |  |
| Any Serious TEAE                              | 22.54                | 58.33                |  |  |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 52.11                | 66.67                |  |  |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 26.76                | 16.67                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Subgroup Analysis by Age ( $\leq 65$ vs. $> 65$ Years): Overview of Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade $\geq 3$ TEAEs, Any-Grade and Grade $\geq 3$ TEAEs Related to Pertuzumab, and TEAEs to Monitor

|                 |                                                                                                                                                                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Age ( $\leq 65$ vs. $> 65$ Years): Overview of Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade $\geq 3$ TEAEs, Any-Grade and Grade $\geq 3$ TEAEs Related to Pertuzumab, and TEAEs to Monitor <sup>[13]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade  $\geq 3$ , pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                           | Age ≤65 Years        | Age >65 Years        |  |  |
|--------------------------------------------|----------------------|----------------------|--|--|
| Subject group type                         | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                | 1167                 | 269                  |  |  |
| Units: Percentage of participants          |                      |                      |  |  |
| number (not applicable)                    |                      |                      |  |  |
| Any Serious TEAE                           | 35.56                | 44.61                |  |  |
| Any TEAE Leading to Death                  | 1.46                 | 5.20                 |  |  |
| Any TEAE - Grade 3 or Higher (≥3)          | 58.95                | 71.00                |  |  |
| Any TEAE Related to Pertuzumab - Any Grade | 72.41                | 71.38                |  |  |
| Any Grade ≥3 TEAE Related to Pertuzumab    | 19.19                | 23.05                |  |  |
| Any TEAE to Monitor - Any Grade            | 92.63                | 88.85                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Subgroup Analysis by Taxane Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade ≥3 TEAEs, Any-Grade and Grade ≥3 TEAEs Related to Pertuzumab, and TEAEs to Monitor

|                 |                                                                                                                                                                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Taxane Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), TEAEs Leading to Death, Grade ≥3 TEAEs, Any-Grade and Grade ≥3 TEAEs Related to Pertuzumab, and TEAEs to Monitor <sup>[14]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. TEAEs to monitor included anaphylaxis and hypersensitivity, cardiac dysfunction, diarrhoea Grade ≥3, pregnancy-related AEs, interstitial lung disease, infusion-/administration-related reactions, mucositis, (febrile) neutropenia, rash/skin reactions, and suspected transmission of infectious agent.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were

summarized by descriptive statistics.

| End point values                              | Docetaxel            | Paclitaxel           | Nab-Paclitaxel       |  |
|-----------------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                            | Subject analysis set | Subject analysis set | Subject analysis set |  |
| Number of subjects analysed                   | 775                  | 588                  | 65                   |  |
| Units: Percentage of participants             |                      |                      |                      |  |
| number (not applicable)                       |                      |                      |                      |  |
| Any Serious TEAE                              | 38.71                | 35.71                | 33.85                |  |
| Any TEAE Leading to Death                     | 1.81                 | 2.72                 | 1.54                 |  |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 63.35                | 59.35                | 55.38                |  |
| Any TEAE Related to Pertuzumab - Any Grade    | 70.58                | 73.81                | 80.00                |  |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 22.06                | 17.86                | 13.85                |  |
| Any TEAE to Monitor - Any Grade               | 91.48                | 92.01                | 98.46                |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Subgroup Analysis by ECOG Performance Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab

|                 |                                                                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by ECOG Performance Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab <sup>[15]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                  | ECOG Performance Status 0 or 1 | ECOG Performance Status 2 |  |  |
|-----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type                | Subject analysis set           | Subject analysis set      |  |  |
| Number of subjects analysed       | 1371                           | 63                        |  |  |
| Units: Percentage of participants |                                |                           |  |  |
| number (not applicable)           |                                |                           |  |  |

|                                               |       |       |  |  |
|-----------------------------------------------|-------|-------|--|--|
| Any Serious TEAE                              | 36.62 | 52.38 |  |  |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 61.05 | 65.08 |  |  |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 19.91 | 20.63 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Subgroup Analysis by Visceral Disease at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab

|                 |                                                                                                                                                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Visceral Disease at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab <sup>[16]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                              | Visceral Disease     | Non-Visceral Disease |  |  |
|-----------------------------------------------|----------------------|----------------------|--|--|
| Subject group type                            | Subject analysis set | Subject analysis set |  |  |
| Number of subjects analysed                   | 992                  | 444                  |  |  |
| Units: Percentage of participants             |                      |                      |  |  |
| number (not applicable)                       |                      |                      |  |  |
| Any Serious TEAE                              | 35.58                | 40.99                |  |  |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 61.49                | 60.59                |  |  |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 19.86                | 20.05                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab

|                 |                                                                                                                                                                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab <sup>[17]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                              | Prior (Neo)Adjuvant Chemotherapy | No Prior (Neo)Adjuvant Chemotherapy |  |  |
|-----------------------------------------------|----------------------------------|-------------------------------------|--|--|
| Subject group type                            | Subject analysis set             | Subject analysis set                |  |  |
| Number of subjects analysed                   | 786                              | 650                                 |  |  |
| Units: Percentage of participants             |                                  |                                     |  |  |
| number (not applicable)                       |                                  |                                     |  |  |
| Any Serious TEAE                              | 36.01                            | 38.77                               |  |  |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 62.72                            | 59.38                               |  |  |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 21.5                             | 18.00                               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Subgroup Analysis by Hormone Receptor Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab

|                 |                                                                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Hormone Receptor Status at Baseline: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab <sup>[18]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                              | Hormone Receptor Positive | Hormone Receptor Negative | Hormone Receptor Status Unknown |  |
|-----------------------------------------------|---------------------------|---------------------------|---------------------------------|--|
| Subject group type                            | Subject analysis set      | Subject analysis set      | Subject analysis set            |  |
| Number of subjects analysed                   | 918                       | 512                       | 6                               |  |
| Units: Percentage of participants             |                           |                           |                                 |  |
| number (not applicable)                       |                           |                           |                                 |  |
| Any Serious TEAE                              | 38.45                     | 34.96                     | 50.00                           |  |
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 62.42                     | 59.18                     | 50.00                           |  |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 19.72                     | 20.12                     | 33.33                           |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Subgroup Analysis by Previous Trastuzumab Therapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab

|                 |                                                                                                                                                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Previous Trastuzumab Therapy: Overview of the Percentage of Participants with Serious Treatment-Emergent Adverse Events (TEAEs), Grade $\geq 3$ TEAEs, and Grade $\geq 3$ TEAEs Related to Pertuzumab <sup>[19]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Treatment-emergent adverse events (TEAEs) were adverse events (AEs) that started or worsened in severity on or after the first administration of study drug, up to and including 28 days after the last dose. The investigator graded all AEs for severity per NCI-CTCAE v4.0; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after, or 7 months after (only for serious AEs related to study drug), the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                  | Previous Trastuzumab Therapy | No Previous Trastuzumab Therapy |  |  |
|-----------------------------------|------------------------------|---------------------------------|--|--|
| Subject group type                | Subject analysis set         | Subject analysis set            |  |  |
| Number of subjects analysed       | 400                          | 1036                            |  |  |
| Units: Percentage of participants |                              |                                 |  |  |
| number (not applicable)           |                              |                                 |  |  |
| Any Serious TEAE                  | 33.75                        | 38.61                           |  |  |

|                                               |       |       |  |  |
|-----------------------------------------------|-------|-------|--|--|
| Any TEAE - Grade 3 or Higher ( $\geq 3$ )     | 59.50 | 61.87 |  |  |
| Any Grade $\geq 3$ TEAE Related to Pertuzumab | 19.25 | 20.17 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with a Congestive Heart Failure Event

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Number of Participants with a Congestive Heart Failure |
|-----------------|--------------------------------------------------------|

End point description:

Congestive heart failure was defined as the Standardised MedDRA Query (SMQ) 'Cardiac failure (wide)' from the Medical Dictionary for Regulatory Activities, version 22.1 (MedDRA version 22.1).

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values            | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|-----------------------------|-----------------------------------|--|--|--|
| Subject group type          | Reporting group                   |  |  |  |
| Number of subjects analysed | 1436                              |  |  |  |
| Units: Participants         | 478                               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Time to Onset of the First Episode of Congestive Heart Failure

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Time to Onset of the First Episode of Congestive Heart |
|-----------------|--------------------------------------------------------|

End point description:

Congestive heart failure was defined as SMQ 'Cardiac failure (wide)' from the MedDRA version 22.1. Time to onset of the first episode of congestive heart failure was analyzed using a Kaplan-Meier approach. Participants who did not experience any congestive heart failure at the time of data-cut were censored at the date of the last attended visit whilst on-treatment (including visits up to and including 28 days after last dose of study treatment). Only treatment emergent congestive heart failure events are included.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                 | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------|-----------------------------------------|--|--|--|
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 1436 <sup>[22]</sup>                    |  |  |  |
| Units: Months                    |                                         |  |  |  |
| median (confidence interval 95%) | 999999 (73.82<br>to 999999)             |  |  |  |

Notes:

[22] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

## Statistical analyses

No statistical analyses for this end point

## Primary: Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Values Over the Course of the Study

|                 |                                                                                                                       |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Values Over the Course of the Study <sup>[23]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------|

End point description:

All participants must have had a baseline LVEF  $\geq 50\%$  to enroll in the study; patients with significant cardiac disease or baseline LVEF below 50% were not eligible for this study. The change from baseline LVEF values were reported at every 3 cycles over the course of the study and at the final treatment, worst treatment, and maximum decrease values. The final treatment value was defined as the last LVEF value observed before all study treatment discontinuation. The worst treatment value was defined as the lowest LVEF value observed before all study treatment discontinuation. The maximum decrease value was defined as the largest decrease of LVEF value from baseline, or minimum increase if a participant's post-baseline LVEF measures were all larger than the baseline value.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, predose on Day 1 of every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                  | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|---------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                | Reporting group                         |  |  |  |
| Number of subjects analysed                       | 1436 <sup>[24]</sup>                    |  |  |  |
| Units: Percentage points of LVEF                  |                                         |  |  |  |
| arithmetic mean (standard deviation)              |                                         |  |  |  |
| Baseline (BL): Absolute Value at Visit (n = 1435) | 64.6 ( $\pm$ 6.46)                      |  |  |  |
| Change from BL at Cycle 3 (n = 1311)              | -1.1 ( $\pm$ 6.49)                      |  |  |  |
| Change from BL at Cycle 6 (n = 1248)              | -1.5 ( $\pm$ 6.60)                      |  |  |  |
| Change from BL at Cycle 9 (n = 1150)              | -2.1 ( $\pm$ 6.56)                      |  |  |  |
| Change from BL at Cycle 12 (n = 1028)             | -1.9 ( $\pm$ 6.66)                      |  |  |  |

|                                                   |                 |  |  |  |
|---------------------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 15 (n = 898)              | -2.2 (± 6.50)   |  |  |  |
| Change from BL at Cycle 18 (n = 816)              | -1.8 (± 6.77)   |  |  |  |
| Change from BL at Cycle 21 (n = 731)              | -1.9 (± 6.79)   |  |  |  |
| Change from BL at Cycle 24 (n = 681)              | -1.9 (± 6.93)   |  |  |  |
| Change from BL at Cycle 27 (n = 633)              | -2.1 (± 6.81)   |  |  |  |
| Change from BL at Cycle 30 (n = 589)              | -1.8 (± 6.80)   |  |  |  |
| Change from BL at Cycle 33 (n = 558)              | -1.9 (± 6.97)   |  |  |  |
| Change from BL at Cycle 36 (n = 509)              | -2.1 (± 6.53)   |  |  |  |
| Change from BL at Cycle 39 (n = 480)              | -2.1 (± 6.77)   |  |  |  |
| Change from BL at Cycle 42 (n = 451)              | -1.9 (± 6.52)   |  |  |  |
| Change from BL at Cycle 45 (n = 428)              | -2.2 (± 6.94)   |  |  |  |
| Change from BL at Cycle 48 (n = 390)              | -2.1 (± 6.67)   |  |  |  |
| Change from BL at Cycle 51 (n = 357)              | -1.6 (± 6.75)   |  |  |  |
| Change from BL at Cycle 54 (n = 325)              | -1.7 (± 6.38)   |  |  |  |
| Change from BL at Cycle 57 (n = 332)              | -1.7 (± 6.87)   |  |  |  |
| Change from BL at Cycle 60 (n = 313)              | -1.5 (± 6.46)   |  |  |  |
| Change from BL at Cycle 63 (n = 302)              | -1.6 (± 7.13)   |  |  |  |
| Change from BL at Cycle 66 (n = 284)              | -2.0 (± 6.63)   |  |  |  |
| Change from BL at Cycle 69 (n = 270)              | -1.9 (± 6.45)   |  |  |  |
| Change from BL at Cycle 72 (n = 259)              | -2.1 (± 6.80)   |  |  |  |
| Change from BL at Cycle 75 (n = 254)              | -1.5 (± 6.84)   |  |  |  |
| Change from BL at Cycle 78 (n = 245)              | -1.8 (± 7.41)   |  |  |  |
| Change from BL at Cycle 81 (n = 226)              | -1.8 (± 6.98)   |  |  |  |
| Change from BL at Cycle 84 (n = 215)              | -1.6 (± 6.89)   |  |  |  |
| Change from BL at Cycle 87 (n = 196)              | -1.9 (± 6.31)   |  |  |  |
| Change from BL at Cycle 90 (n = 177)              | -1.1 (± 6.68)   |  |  |  |
| Change from BL at Cycle 93 (n = 156)              | -1.6 (± 6.78)   |  |  |  |
| Change from BL at Cycle 96 (n = 128)              | -1.8 (± 6.33)   |  |  |  |
| Change from BL at Cycle 99 (n = 106)              | -2.0 (± 7.20)   |  |  |  |
| Change from BL at Cycle 102 (n = 82)              | -2.5 (± 7.95)   |  |  |  |
| Change from BL at Cycle 105 (n = 65)              | -2.5 (± 6.86)   |  |  |  |
| Change from BL at Cycle 108 (n = 49)              | -1.8 (± 8.04)   |  |  |  |
| Change from BL at Cycle 111 (n = 42)              | -3.3 (± 7.47)   |  |  |  |
| Change from BL at Cycle 114 (n = 23)              | -1.1 (± 8.12)   |  |  |  |
| Change from BL at Cycle 117 (n = 17)              | -5.8 (± 7.48)   |  |  |  |
| Change from BL at Cycle 120 (n = 7)               | -8.6 (± 6.70)   |  |  |  |
| Change from BL at Cycle 123 (n = 3)               | -9.3 (± 3.51)   |  |  |  |
| Change from BL at Cycle 126 (n = 1)               | -9.0 (± 999999) |  |  |  |
| Change from BL at End of Treatment (n = 546)      | -3.8 (± 8.34)   |  |  |  |
| Change from BL at Day 28 of Follow-Up (n = 584)   | -3.2 (± 8.19)   |  |  |  |
| Change from BL: Final Treatment Value (n = 1360)  | -2.0 (± 6.77)   |  |  |  |
| Change from BL: Worst Treatment Value (n = 1360)  | -7.1 (± 6.88)   |  |  |  |
| Change from BL: Maximum Decrease Value (n = 1398) | -7.7 (± 7.45)   |  |  |  |

Notes:

[24] - '999999' means the standard deviation could not be calculated with data from a single participant.

## Statistical analyses

**Primary: Number of Participants by Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Categories Over the Course of the Study**

|                 |                                                                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants by Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Categories Over the Course of the Study <sup>[25]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

All participants must have had a baseline LVEF greater than or equal to ( $\geq$ )50% to enroll in the study; patients with significant cardiac disease or baseline LVEF below 50% were not eligible for this study. The number of participants are reported according to four change from baseline in LVEF value categories over the course of the study: 1) an increase or decrease from baseline LVEF less than ( $<$ )10% points or no change in LVEF; 2) an absolute LVEF value  $<$ 45% points and a decrease from baseline LVEF  $\geq$ 10% points to  $<$ 15% points; 3) an absolute LVEF value  $<$ 45% points and a decrease from baseline LVEF  $\geq$ 15% points; or 4) an absolute LVEF value  $\geq$ 45% points and a decrease from baseline LVEF  $\geq$ 10% points. BL = baseline; Cyc = cycle; D28FU = Day 28 of follow-up; Dec = decrease; EOT = end of treatment; Inc = increase

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

## End point timeframe:

Baseline, predose on Day 1 of every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

## Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                                | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|-----------------------------------------------------------------|-----------------------------------|--|--|--|
| Subject group type                                              | Reporting group                   |  |  |  |
| Number of subjects analysed                                     | 1436                              |  |  |  |
| Units: Participants                                             |                                   |  |  |  |
| Cyc3: Inc/Dec from BL $<$ 10% or No Change (n=1311)             | 1190                              |  |  |  |
| Cyc3: LVEF $<$ 45% and Dec from BL $\geq$ 10%– $<$ 15% (n=1311) | 2                                 |  |  |  |
| Cyc3: LVEF $<$ 45% and Dec from BL $\geq$ 15% (n=1311)          | 5                                 |  |  |  |
| Cyc3: LVEF $\geq$ 45% and Dec from BL $\geq$ 10% (n=1311)       | 114                               |  |  |  |
| Cyc6: Inc/Dec from BL $<$ 10% or No Change (n=1248)             | 1110                              |  |  |  |
| Cyc6: LVEF $<$ 45% and Dec from BL $\geq$ 10%– $<$ 15% (n=1248) | 0                                 |  |  |  |
| Cyc6: LVEF $<$ 45% and Dec from BL $\geq$ 15% (n=1248)          | 2                                 |  |  |  |
| Cyc6: LVEF $\geq$ 45% and Dec from BL $\geq$ 10% (n=1248)       | 136                               |  |  |  |
| Cyc9: Inc/Dec from BL $<$ 10% or No Change (n=1150)             | 1005                              |  |  |  |
| Cyc9: LVEF $<$ 45% and Dec from BL $\geq$ 10%– $<$ 15% (n=1150) | 2                                 |  |  |  |
| Cyc9: LVEF $<$ 45% and Dec from BL $\geq$ 15% (n=1150)          | 4                                 |  |  |  |
| Cyc9: LVEF $\geq$ 45% and Dec from BL $\geq$ 10% (n=1150)       | 139                               |  |  |  |
| Cyc12: Inc/Dec from BL $<$ 10% or No Change (n=1028)            | 906                               |  |  |  |

|                                                       |     |  |  |  |
|-------------------------------------------------------|-----|--|--|--|
| Cyc12: LVEF<45% and Dec from BL<br>≥10%–<15% (n=1028) | 0   |  |  |  |
| Cyc12: LVEF<45% and Dec from BL<br>≥15% (n=1028)      | 6   |  |  |  |
| Cyc12: LVEF ≥45% and Dec from BL<br>≥10% (n=1028)     | 116 |  |  |  |
| Cyc15: Inc/Dec from BL<10% or No<br>Change (n=898)    | 780 |  |  |  |
| Cyc15: LVEF<45% and Dec from BL<br>≥10%–<15% (n=898)  | 3   |  |  |  |
| Cyc15: LVEF<45% and Dec from BL<br>≥15% (n=898)       | 6   |  |  |  |
| Cyc15: LVEF ≥45% and Dec from BL<br>≥10% (n=898)      | 109 |  |  |  |
| Cyc18: Inc/Dec from BL<10% or No<br>Change (n=816)    | 719 |  |  |  |
| Cyc18: LVEF<45% and Dec from BL<br>≥10%–<15% (n=816)  | 0   |  |  |  |
| Cyc18: LVEF<45% and Dec from BL<br>≥15% (n=816)       | 5   |  |  |  |
| Cyc18: LVEF ≥45% and Dec from BL<br>≥10% (n=816)      | 92  |  |  |  |
| Cyc21: Inc/Dec from BL<10% or No<br>Change (n=731)    | 639 |  |  |  |
| Cyc21: LVEF<45% and Dec from BL<br>≥10%–<15% (n=731)  | 0   |  |  |  |
| Cyc21: LVEF<45% and Dec from BL<br>≥15% (n=731)       | 4   |  |  |  |
| Cyc21: LVEF ≥45% and Dec from BL<br>≥10% (n=731)      | 88  |  |  |  |
| Cyc24: Inc/Dec from BL<10% or No<br>Change (n=681)    | 588 |  |  |  |
| Cyc24: LVEF<45% and Dec from BL<br>≥10%–<15% (n=681)  | 0   |  |  |  |
| Cyc24: LVEF<45% and Dec from BL<br>≥15% (n=681)       | 2   |  |  |  |
| Cyc24: LVEF ≥45% and Dec from BL<br>≥10% (n=681)      | 91  |  |  |  |
| Cyc27: Inc/Dec from BL<10% or No<br>Change (n=633)    | 553 |  |  |  |
| Cyc27: LVEF<45% and Dec from BL<br>≥10%–<15% (n=633)  | 0   |  |  |  |
| Cyc27: LVEF<45% and Dec from BL<br>≥15% (n=633)       | 2   |  |  |  |
| Cyc27: LVEF ≥45% and Dec from BL<br>≥10% (n=633)      | 78  |  |  |  |
| Cyc30: Inc/Dec from BL<10% or No<br>Change (n=589)    | 518 |  |  |  |
| Cyc30: LVEF<45% and Dec from BL<br>≥10%–<15% (n=589)  | 0   |  |  |  |
| Cyc30: LVEF<45% and Dec from BL<br>≥15% (n=589)       | 1   |  |  |  |
| Cyc30: LVEF ≥45% and Dec from BL<br>≥10% (n=589)      | 70  |  |  |  |
| Cyc33: Inc/Dec from BL<10% or No<br>Change (n=558)    | 485 |  |  |  |
| Cyc33: LVEF<45% and Dec from BL<br>≥10%–<15% (n=558)  | 0   |  |  |  |
| Cyc33: LVEF<45% and Dec from BL<br>≥15% (n=558)       | 1   |  |  |  |
| Cyc33: LVEF ≥45% and Dec from BL<br>≥10% (n=558)      | 72  |  |  |  |

|                                                   |     |  |  |  |
|---------------------------------------------------|-----|--|--|--|
| Cyc36: Inc/Dec from BL<10% or No Change (n=509)   | 446 |  |  |  |
| Cyc36: LVEF<45% and Dec from BL ≥10%–<15% (n=509) | 0   |  |  |  |
| Cyc36: LVEF<45% and Dec from BL ≥15% (n=509)      | 1   |  |  |  |
| Cyc36: LVEF ≥45% and Dec from BL ≥10% (n=509)     | 62  |  |  |  |
| Cyc39: Inc/Dec from BL<10% or No Change (n=480)   | 414 |  |  |  |
| Cyc39: LVEF<45% and Dec from BL ≥10%–<15% (n=480) | 1   |  |  |  |
| Cyc39: LVEF<45% and Dec from BL ≥15% (n=480)      | 0   |  |  |  |
| Cyc39: LVEF ≥45% and Dec from BL ≥10% (n=480)     | 65  |  |  |  |
| Cyc42: Inc/Dec from BL<10% or No Change (n=451)   | 405 |  |  |  |
| Cyc42: LVEF<45% and Dec from BL ≥10%–<15% (n=451) | 0   |  |  |  |
| Cyc42: LVEF<45% and Dec from BL ≥15% (n=451)      | 0   |  |  |  |
| Cyc42: LVEF ≥45% and Dec from BL ≥10% (n=451)     | 46  |  |  |  |
| Cyc45: Inc/Dec from BL<10% or No Change (n=428)   | 358 |  |  |  |
| Cyc45: LVEF<45% and Dec from BL ≥10%–<15% (n=428) | 0   |  |  |  |
| Cyc45: LVEF<45% and Dec from BL ≥15% (n=428)      | 1   |  |  |  |
| Cyc45: LVEF ≥45% and Dec from BL ≥10% (n=428)     | 69  |  |  |  |
| Cyc48: Inc/Dec from BL<10% or No Change (n=390)   | 340 |  |  |  |
| Cyc48: LVEF<45% and Dec from BL ≥10%–<15% (n=390) | 0   |  |  |  |
| Cyc48: LVEF<45% and Dec from BL ≥15% (n=390)      | 1   |  |  |  |
| Cyc48: LVEF ≥45% and Dec from BL ≥10% (n=390)     | 49  |  |  |  |
| Cyc51: Inc/Dec from BL<10% or No Change (n=357)   | 314 |  |  |  |
| Cyc51: LVEF<45% and Dec from BL ≥10%–<15% (n=357) | 0   |  |  |  |
| Cyc51: LVEF<45% and Dec from BL ≥15% (n=357)      | 0   |  |  |  |
| Cyc51: LVEF ≥45% and Dec from BL ≥10% (n=357)     | 43  |  |  |  |
| Cyc54: Inc/Dec from BL<10% or No Change (n=325)   | 292 |  |  |  |
| Cyc54: LVEF<45% and Dec from BL ≥10%–<15% (n=325) | 0   |  |  |  |
| Cyc54: LVEF<45% and Dec from BL ≥15% (n=325)      | 3   |  |  |  |
| Cyc54: LVEF ≥45% and Dec from BL ≥10% (n=325)     | 30  |  |  |  |
| Cyc57: Inc/Dec from BL<10% or No Change (n=332)   | 291 |  |  |  |
| Cyc57: LVEF<45% and Dec from BL ≥10%–<15% (n=332) | 0   |  |  |  |
| Cyc57: LVEF<45% and Dec from BL ≥15% (n=332)      | 0   |  |  |  |

|                                                                     |     |  |  |  |
|---------------------------------------------------------------------|-----|--|--|--|
| Cyc57: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=332)         | 41  |  |  |  |
| Cyc60: Inc/Dec from BL $< 10\%$ or No Change (n=313)                | 284 |  |  |  |
| Cyc60: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=313) | 0   |  |  |  |
| Cyc60: LVEF $< 45\%$ and Dec from BL $\geq 15\%$ (n=313)            | 0   |  |  |  |
| Cyc60: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=313)         | 29  |  |  |  |
| Cyc63: Inc/Dec from BL $< 10\%$ or No Change (n=302)                | 263 |  |  |  |
| Cyc63: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=302) | 0   |  |  |  |
| Cyc63: LVEF $< 45\%$ and Dec from BL $\geq 15\%$ (n=302)            | 0   |  |  |  |
| Cyc63: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=302)         | 39  |  |  |  |
| Cyc66: Inc/Dec from BL $< 10\%$ or No Change (n=284)                | 249 |  |  |  |
| Cyc66: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=284) | 0   |  |  |  |
| Cyc66: LVEF $< 45\%$ and Dec from BL $\geq 15\%$ (n=284)            | 0   |  |  |  |
| Cyc66: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=284)         | 35  |  |  |  |
| Cyc69: Inc/Dec from BL $< 10\%$ or No Change (n=270)                | 237 |  |  |  |
| Cyc69: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=270) | 0   |  |  |  |
| Cyc69: LVEF $< 45\%$ and Dec from BL $\geq 15\%$ (n=270)            | 0   |  |  |  |
| Cyc69: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=270)         | 33  |  |  |  |
| Cyc72: Inc/Dec from BL $< 10\%$ or No Change (n=259)                | 224 |  |  |  |
| Cyc72: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=259) | 0   |  |  |  |
| Cyc72: LVEF $< 45\%$ and Dec from BL $\geq 15\%$ (n=259)            | 0   |  |  |  |
| Cyc72: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=259)         | 35  |  |  |  |
| Cyc75: Inc/Dec from BL $< 10\%$ or No Change (n=254)                | 224 |  |  |  |
| Cyc75: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=254) | 0   |  |  |  |
| Cyc75: LVEF $< 45\%$ and Dec from BL $\geq 15\%$ (n=254)            | 1   |  |  |  |
| Cyc75: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=254)         | 29  |  |  |  |
| Cyc78: Inc/Dec from BL $< 10\%$ or No Change (n=245)                | 214 |  |  |  |
| Cyc78: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=245) | 0   |  |  |  |
| Cyc78: LVEF $< 45\%$ and Dec from BL $\geq 15\%$ (n=245)            | 2   |  |  |  |
| Cyc78: LVEF $\geq 45\%$ and Dec from BL $\geq 10\%$ (n=245)         | 29  |  |  |  |
| Cyc81: Inc/Dec from BL $< 10\%$ or No Change (n=226)                | 196 |  |  |  |
| Cyc81: LVEF $< 45\%$ and Dec from BL $\geq 10\%$ - $< 15\%$ (n=226) | 0   |  |  |  |

|                                                      |     |  |  |  |
|------------------------------------------------------|-----|--|--|--|
| Cyc81: LVEF<45% and Dec from BL<br>≥15% (n=226)      | 0   |  |  |  |
| Cyc81: LVEF ≥45% and Dec from BL<br>≥10% (n=226)     | 30  |  |  |  |
| Cyc84: Inc/Dec from BL<10% or No<br>Change (n=215)   | 192 |  |  |  |
| Cyc84: LVEF<45% and Dec from BL<br>≥10%–<15% (n=215) | 0   |  |  |  |
| Cyc84: LVEF<45% and Dec from BL<br>≥15% (n=215)      | 0   |  |  |  |
| Cyc84: LVEF ≥45% and Dec from BL<br>≥10% (n=215)     | 23  |  |  |  |
| Cyc87: Inc/Dec from BL<10% or No<br>Change (n=196)   | 174 |  |  |  |
| Cyc87: LVEF<45% and Dec from BL<br>≥10%–<15% (n=196) | 0   |  |  |  |
| Cyc87: LVEF<45% and Dec from BL<br>≥15% (n=196)      | 0   |  |  |  |
| Cyc87: LVEF ≥45% and Dec from BL<br>≥10% (n=196)     | 22  |  |  |  |
| Cyc90: Inc/Dec from BL<10% or No<br>Change (n=177)   | 161 |  |  |  |
| Cyc90: LVEF<45% and Dec from BL<br>≥10%–<15% (n=177) | 0   |  |  |  |
| Cyc90: LVEF<45% and Dec from BL<br>≥15% (n=177)      | 0   |  |  |  |
| Cyc90: LVEF ≥45% and Dec from BL<br>≥10% (n=177)     | 16  |  |  |  |
| Cyc93: Inc/Dec from BL<10% or No<br>Change (n=156)   | 140 |  |  |  |
| Cyc93: LVEF<45% and Dec from BL<br>≥10%–<15% (n=156) | 0   |  |  |  |
| Cyc93: LVEF<45% and Dec from BL<br>≥15% (n=156)      | 0   |  |  |  |
| Cyc93: LVEF ≥45% and Dec from BL<br>≥10% (n=156)     | 16  |  |  |  |
| Cyc96: Inc/Dec from BL<10% or No<br>Change (n=128)   | 115 |  |  |  |
| Cyc96: LVEF<45% and Dec from BL<br>≥10%–<15% (n=128) | 0   |  |  |  |
| Cyc96: LVEF<45% and Dec from BL<br>≥15% (n=128)      | 0   |  |  |  |
| Cyc96: LVEF ≥45% and Dec from BL<br>≥10% (n=128)     | 13  |  |  |  |
| Cyc99: Inc/Dec from BL<10% or No<br>Change (n=106)   | 92  |  |  |  |
| Cyc99: LVEF<45% and Dec from BL<br>≥10%–<15% (n=106) | 0   |  |  |  |
| Cyc99: LVEF<45% and Dec from BL<br>≥15% (n=106)      | 0   |  |  |  |
| Cyc99: LVEF ≥45% and Dec from BL<br>≥10% (n=106)     | 14  |  |  |  |
| Cyc102: Inc/Dec from BL<10% or No<br>Change (n=82)   | 68  |  |  |  |
| Cyc102: LVEF<45% and Dec from BL<br>≥10%–<15% (n=82) | 0   |  |  |  |
| Cyc102: LVEF<45% and Dec from BL<br>≥15% (n=82)      | 0   |  |  |  |
| Cyc102: LVEF ≥45% and Dec from BL<br>≥10% (n=82)     | 14  |  |  |  |
| Cyc105: Inc/Dec from BL<10% or No<br>Change (n=65)   | 56  |  |  |  |

|                                                      |    |  |  |  |
|------------------------------------------------------|----|--|--|--|
| Cyc105: LVEF<45% and Dec from BL<br>≥10%–<15% (n=65) | 0  |  |  |  |
| Cyc105: LVEF<45% and Dec from BL<br>≥15% (n=65)      | 0  |  |  |  |
| Cyc105: LVEF ≥45% and Dec from BL<br>≥10% (n=65)     | 9  |  |  |  |
| Cyc108: Inc/Dec from BL<10% or No<br>Change (n=49)   | 41 |  |  |  |
| Cyc108: LVEF<45% and Dec from BL<br>≥10%–<15% (n=49) | 0  |  |  |  |
| Cyc108: LVEF<45% and Dec from BL<br>≥15% (n=49)      | 0  |  |  |  |
| Cyc108: LVEF ≥45% and Dec from BL<br>≥10% (n=49)     | 8  |  |  |  |
| Cyc111: Inc/Dec from BL<10% or No<br>Change (n=42)   | 34 |  |  |  |
| Cyc111: LVEF<45% and Dec from BL<br>≥10%–<15% (n=42) | 0  |  |  |  |
| Cyc111: LVEF<45% and Dec from BL<br>≥15% (n=42)      | 0  |  |  |  |
| Cyc111: LVEF ≥45% and Dec from BL<br>≥10% (n=42)     | 8  |  |  |  |
| Cyc114: Inc/Dec from BL<10% or No<br>Change (n=23)   | 19 |  |  |  |
| Cyc114: LVEF<45% and Dec from BL<br>≥10%–<15% (n=23) | 0  |  |  |  |
| Cyc114: LVEF<45% and Dec from BL<br>≥15% (n=23)      | 0  |  |  |  |
| Cyc114: LVEF ≥45% and Dec from BL<br>≥10% (n=23)     | 4  |  |  |  |
| Cyc117: Inc/Dec from BL<10% or No<br>Change (n=17)   | 11 |  |  |  |
| Cyc117: LVEF<45% and Dec from BL<br>≥10%–<15% (n=17) | 0  |  |  |  |
| Cyc117: LVEF<45% and Dec from BL<br>≥15% (n=17)      | 0  |  |  |  |
| Cyc117: LVEF ≥45% and Dec from BL<br>≥10% (n=17)     | 6  |  |  |  |
| Cyc120: Inc/Dec from BL<10% or No<br>Change (n=7)    | 4  |  |  |  |
| Cyc120: LVEF<45% and Dec from BL<br>≥10%–<15% (n=7)  | 0  |  |  |  |
| Cyc120: LVEF<45% and Dec from BL<br>≥15% (n=7)       | 0  |  |  |  |
| Cyc120: LVEF ≥45% and Dec from BL<br>≥10% (n=7)      | 3  |  |  |  |
| Cyc123: Inc/Dec from BL<10% or No<br>Change (n=3)    | 2  |  |  |  |
| Cyc123: LVEF<45% and Dec from BL<br>≥10%–<15% (n=3)  | 0  |  |  |  |
| Cyc123: LVEF<45% and Dec from BL<br>≥15% (n=3)       | 0  |  |  |  |
| Cyc123: LVEF ≥45% and Dec from BL<br>≥10% (n=3)      | 1  |  |  |  |
| Cyc126: Inc/Dec from BL<10% or No<br>Change (n=1)    | 1  |  |  |  |
| Cyc126: LVEF<45% and Dec from BL<br>≥10%–<15% (n=1)  | 0  |  |  |  |
| Cyc126: LVEF<45% and Dec from BL<br>≥15% (n=1)       | 0  |  |  |  |
| Cyc126: LVEF ≥45% and Dec from BL<br>≥10% (n=1)      | 0  |  |  |  |

|                                                   |     |  |  |  |
|---------------------------------------------------|-----|--|--|--|
| EOT: Inc/Dec from BL<10% or No Change (n=546)     | 431 |  |  |  |
| EOT: LVEF<45% and Dec from BL ≥10%–<15% (n=546)   | 2   |  |  |  |
| EOT: LVEF<45% and Dec from BL ≥15% (n=546)        | 26  |  |  |  |
| EOT: LVEF ≥45% and Dec from BL ≥10% (n=546)       | 87  |  |  |  |
| D28FU: Inc/Dec from BL<10% or No Change (n=584)   | 472 |  |  |  |
| D28FU: LVEF<45% and Dec from BL ≥10%–<15% (n=584) | 4   |  |  |  |
| D28FU: LVEF<45% and Dec from BL ≥15% (n=584)      | 22  |  |  |  |
| D28FU: LVEF ≥45% and Dec from BL ≥10% (n=584)     | 86  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0

|                 |                                                                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0 <sup>[26]</sup> |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Clinical laboratory tests for hematology and coagulation parameters were performed at local laboratories. Laboratory toxicities were defined based on NCI-CTC v4.0 from Grades 1 (least severe) to 4 (most severe). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0–86.4) months.

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

|                                             |                                   |  |  |  |
|---------------------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>                     | Pertuzumab + Trastuzumab + Taxane |  |  |  |
| Subject group type                          | Reporting group                   |  |  |  |
| Number of subjects analysed                 | 1436                              |  |  |  |
| Units: Participants                         |                                   |  |  |  |
| Absolute Neutrophil Count: Normal to Normal | 844                               |  |  |  |

|                                               |      |  |  |  |
|-----------------------------------------------|------|--|--|--|
| Absolute Neutrophil Count: Normal to Grade 1  | 232  |  |  |  |
| Absolute Neutrophil Count: Normal to Grade 2  | 169  |  |  |  |
| Absolute Neutrophil Count: Normal to Grade 3  | 45   |  |  |  |
| Absolute Neutrophil Count: Normal to Grade 4  | 27   |  |  |  |
| Absolute Neutrophil Count: Normal to Missing  | 27   |  |  |  |
| Absolute Neutrophil Count: Grade 1 to Normal  | 3    |  |  |  |
| Absolute Neutrophil Count: Grade 1 to 1       | 11   |  |  |  |
| Absolute Neutrophil Count: Grade 1 to 2       | 14   |  |  |  |
| Absolute Neutrophil Count: Grade 1 to 3       | 3    |  |  |  |
| Absolute Neutrophil Count: Grade 2 to 1       | 2    |  |  |  |
| Absolute Neutrophil Count: Missing to Normal  | 21   |  |  |  |
| Absolute Neutrophil Count: Missing to Grade 1 | 2    |  |  |  |
| Absolute Neutrophil Count: Missing to Grade 2 | 3    |  |  |  |
| Absolute Neutrophil Count: Missing to Grade 4 | 1    |  |  |  |
| Absolute Neutrophil Count: Missing to Missing | 32   |  |  |  |
| Hemoglobin (High): Normal to Normal           | 1327 |  |  |  |
| Hemoglobin (High): Normal to Grade 1          | 29   |  |  |  |
| Hemoglobin (High): Normal to Grade 3          | 1    |  |  |  |
| Hemoglobin (High): Normal to Missing          | 26   |  |  |  |
| Hemoglobin (High): Grade 1 to Normal          | 28   |  |  |  |
| Hemoglobin (High): Grade 1 to 1               | 5    |  |  |  |
| Hemoglobin (High): Grade 1 to Missing         | 2    |  |  |  |
| Hemoglobin (High): Grade 2 to Normal          | 1    |  |  |  |
| Hemoglobin (High): Missing to Normal          | 14   |  |  |  |
| Hemoglobin (High): Missing to Missing         | 3    |  |  |  |
| Hemoglobin (Low): Normal to Normal            | 257  |  |  |  |
| Hemoglobin (Low): Normal to Grade 1           | 648  |  |  |  |
| Hemoglobin (Low): Normal to Grade 2           | 198  |  |  |  |
| Hemoglobin (Low): Normal to Grade 3           | 10   |  |  |  |
| Hemoglobin (Low): Normal to Missing           | 21   |  |  |  |
| Hemoglobin (Low): Grade 1 to Normal           | 2    |  |  |  |
| Hemoglobin (Low): Grade 1 to 1                | 109  |  |  |  |
| Hemoglobin (Low): Grade 1 to 2                | 128  |  |  |  |
| Hemoglobin (Low): Grade 1 to 3                | 12   |  |  |  |
| Hemoglobin (Low): Grade 1 to Missing          | 4    |  |  |  |
| Hemoglobin (Low): Grade 2 to 1                | 5    |  |  |  |
| Hemoglobin (Low): Grade 2 to 2                | 18   |  |  |  |
| Hemoglobin (Low): Grade 2 to 3                | 3    |  |  |  |
| Hemoglobin (Low): Grade 2 to Missing          | 3    |  |  |  |
| Hemoglobin (Low): Grade 3 to 1                | 1    |  |  |  |
| Hemoglobin (Low): Missing to Normal           | 3    |  |  |  |
| Hemoglobin (Low): Missing to Grade 1          | 7    |  |  |  |
| Hemoglobin (Low): Missing to Grade 2          | 4    |  |  |  |
| Hemoglobin (Low): Missing to Missing          | 3    |  |  |  |

|                                        |      |  |  |  |
|----------------------------------------|------|--|--|--|
| Lymphocytes (High): Normal to Normal   | 1251 |  |  |  |
| Lymphocytes (High): Normal to Grade 2  | 111  |  |  |  |
| Lymphocytes (High): Normal to Grade 3  | 8    |  |  |  |
| Lymphocytes (High): Normal to Missing  | 28   |  |  |  |
| Lymphocytes (High): Grade 2 to Normal  | 4    |  |  |  |
| Lymphocytes (High): Grade 2 to 2       | 10   |  |  |  |
| Lymphocytes (High): Grade 2 to 3       | 2    |  |  |  |
| Lymphocytes (High): Grade 3 to Normal  | 1    |  |  |  |
| Lymphocytes (High): Grade 3 to 3       | 2    |  |  |  |
| Lymphocytes (High): Missing to Normal  | 15   |  |  |  |
| Lymphocytes (High): Missing to Grade 2 | 2    |  |  |  |
| Lymphocytes (High): Missing to Missing | 2    |  |  |  |
| Lymphocytes (Low): Normal to Normal    | 565  |  |  |  |
| Lymphocytes (Low): Normal to Grade 1   | 255  |  |  |  |
| Lymphocytes (Low): Normal to Grade 2   | 210  |  |  |  |
| Lymphocytes (Low): Normal to Grade 3   | 76   |  |  |  |
| Lymphocytes (Low): Normal to Grade 4   | 18   |  |  |  |
| Lymphocytes (Low): Normal to Missing   | 19   |  |  |  |
| Lymphocytes (Low): Grade 1 to Normal   | 11   |  |  |  |
| Lymphocytes (Low): Grade 1 to 1        | 54   |  |  |  |
| Lymphocytes (Low): Grade 1 to 2        | 51   |  |  |  |
| Lymphocytes (Low): Grade 1 to 3        | 18   |  |  |  |
| Lymphocytes (Low): Grade 1 to 4        | 6    |  |  |  |
| Lymphocytes (Low): Grade 1 to Missing  | 5    |  |  |  |
| Lymphocytes (Low): Grade 2 to Normal   | 12   |  |  |  |
| Lymphocytes (Low): Grade 2 to 1        | 8    |  |  |  |
| Lymphocytes (Low): Grade 2 to 2        | 37   |  |  |  |
| Lymphocytes (Low): Grade 2 to 3        | 19   |  |  |  |
| Lymphocytes (Low): Grade 2 to 4        | 1    |  |  |  |
| Lymphocytes (Low): Grade 2 to Missing  | 2    |  |  |  |
| Lymphocytes (Low): Grade 3 to 1        | 3    |  |  |  |
| Lymphocytes (Low): Grade 3 to 2        | 8    |  |  |  |
| Lymphocytes (Low): Grade 3 to 3        | 14   |  |  |  |
| Lymphocytes (Low): Grade 3 to 4        | 2    |  |  |  |
| Lymphocytes (Low): Grade 3 to Missing  | 1    |  |  |  |
| Lymphocytes (Low): Grade 4 to 2        | 1    |  |  |  |
| Lymphocytes (Low): Grade 4 to 3        | 3    |  |  |  |
| Lymphocytes (Low): Grade 4 to 4        | 16   |  |  |  |
| Lymphocytes (Low): Grade 4 to Missing  | 1    |  |  |  |
| Lymphocytes (Low): Missing to Normal   | 11   |  |  |  |
| Lymphocytes (Low): Missing to Grade 1  | 3    |  |  |  |
| Lymphocytes (Low): Missing to Grade 2  | 3    |  |  |  |
| Lymphocytes (Low): Missing to Grade 3  | 1    |  |  |  |
| Lymphocytes (Low): Missing to Missing  | 2    |  |  |  |
| Platelet Count: Normal to Normal       | 1222 |  |  |  |
| Platelet Count: Normal to Grade 1      | 149  |  |  |  |
| Platelet Count: Normal to Grade 3      | 1    |  |  |  |
| Platelet Count: Normal to Grade 4      | 2    |  |  |  |
| Platelet Count: Normal to Missing      | 26   |  |  |  |
| Platelet Count: Grade 1 to Normal      | 15   |  |  |  |
| Platelet Count: Grade 1 to 1           | 16   |  |  |  |
| Platelet Count: Grade 1 to 2           | 1    |  |  |  |

|                                                   |      |  |  |  |
|---------------------------------------------------|------|--|--|--|
| Platelet Count: Grade 1 to Missing                | 2    |  |  |  |
| Platelet Count: Missing to Normal                 | 1    |  |  |  |
| Platelet Count: Missing to Grade 1                | 1    |  |  |  |
| White Blood Cells (High): Normal to Normal        | 1391 |  |  |  |
| White Blood Cells (High): Normal to Missing       | 29   |  |  |  |
| White Blood Cells (High): Missing to Normal       | 14   |  |  |  |
| White Blood Cells (High): Missing to Missing      | 2    |  |  |  |
| White Blood Cells (Low): Normal to Normal         | 702  |  |  |  |
| White Blood Cells (Low): Normal to Grade 1        | 392  |  |  |  |
| White Blood Cells (Low): Normal to Grade 2        | 190  |  |  |  |
| White Blood Cells (Low): Normal to Grade 3        | 29   |  |  |  |
| White Blood Cells (Low): Normal to Grade 4        | 6    |  |  |  |
| White Blood Cells (Low): Normal to Missing        | 29   |  |  |  |
| White Blood Cells (Low): Grade 1 to Normal        | 4    |  |  |  |
| White Blood Cells (Low): Grade 1 to 1             | 20   |  |  |  |
| White Blood Cells (Low): Grade 1 to 2             | 33   |  |  |  |
| White Blood Cells (Low): Grade 1 to 3             | 4    |  |  |  |
| White Blood Cells (Low): Grade 2 to Normal        | 2    |  |  |  |
| White Blood Cells (Low): Grade 2 to 1             | 4    |  |  |  |
| White Blood Cells (Low): Grade 2 to 2             | 3    |  |  |  |
| White Blood Cells (Low): Grade 3 to Normal        | 1    |  |  |  |
| White Blood Cells (Low): Grade 3 to 3             | 1    |  |  |  |
| White Blood Cells (Low): Missing to Normal        | 9    |  |  |  |
| White Blood Cells (Low): Missing to Grade 1       | 3    |  |  |  |
| White Blood Cells (Low): Missing to Grade 2       | 1    |  |  |  |
| White Blood Cells (Low): Missing to Grade 3       | 1    |  |  |  |
| White Blood Cells (Low): Missing to Missing       | 2    |  |  |  |
| International Normalized Ratio: Normal to Normal  | 17   |  |  |  |
| International Normalized Ratio: Normal to Grade 1 | 52   |  |  |  |
| International Normalized Ratio: Normal to Grade 2 | 1    |  |  |  |
| International Normalized Ratio: Normal to Missing | 3    |  |  |  |
| International Normalized Ratio: Grade 1 to Normal | 1    |  |  |  |
| International Normalized Ratio: Grade 2 to 3      | 1    |  |  |  |
| International Normalized Ratio: Missing to Normal | 424  |  |  |  |

|                                                    |     |  |  |  |
|----------------------------------------------------|-----|--|--|--|
| International Normalized Ratio: Missing to Grade 1 | 615 |  |  |  |
| International Normalized Ratio: Missing to Grade 2 | 23  |  |  |  |
| International Normalized Ratio: Missing to Grade 3 | 14  |  |  |  |
| International Normalized Ratio: Missing to Missing | 285 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria

|                 |                                                                                                                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Laboratory Abnormalities in Hematology and Coagulation Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria <sup>[27]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

Clinical laboratory tests for hematology and coagulation parameters were performed at local laboratories. Laboratory toxicities were defined based on local laboratory normal ranges (for parameters with NCI-CTC grade not defined). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

#### Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                   | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|------------------------------------|-----------------------------------|--|--|--|
| Subject group type                 | Reporting group                   |  |  |  |
| Number of subjects analysed        | 1436                              |  |  |  |
| Units: Participants                |                                   |  |  |  |
| Basophils (High): Normal to Normal | 1020                              |  |  |  |
| Basophils (High): Normal to Low    | 3                                 |  |  |  |
| Basophils (High): Normal to High   | 261                               |  |  |  |
| Basophils (High): Low to Normal    | 16                                |  |  |  |
| Basophils (High): Low to Low       | 1                                 |  |  |  |
| Basophils (High): Low to High      | 5                                 |  |  |  |
| Basophils (High): High to Normal   | 11                                |  |  |  |
| Basophils (High): High to High     | 38                                |  |  |  |

|                                        |      |  |  |  |
|----------------------------------------|------|--|--|--|
| Basophils (High): Missing to Normal    | 21   |  |  |  |
| Basophils (High): Missing to High      | 7    |  |  |  |
| Basophils (High): Missing to Missing   | 53   |  |  |  |
| Basophils (Low): Normal to Normal      | 1206 |  |  |  |
| Basophils (Low): Normal to Low         | 77   |  |  |  |
| Basophils (Low): Normal to High        | 1    |  |  |  |
| Basophils (Low): Low to Normal         | 3    |  |  |  |
| Basophils (Low): Low to Low            | 18   |  |  |  |
| Basophils (Low): Low to Missing        | 1    |  |  |  |
| Basophils (Low): High to Normal        | 36   |  |  |  |
| Basophils (Low): High to Low           | 5    |  |  |  |
| Basophils (Low): High to High          | 8    |  |  |  |
| Basophils (Low): Missing to Normal     | 40   |  |  |  |
| Basophils (Low): Missing to Low        | 3    |  |  |  |
| Basophils (Low): Missing to High       | 1    |  |  |  |
| Basophils (Low): Missing to Missing    | 37   |  |  |  |
| Eosinophils (High): Normal to Normal   | 904  |  |  |  |
| Eosinophils (High): Normal to Low      | 13   |  |  |  |
| Eosinophils (High): Normal to High     | 283  |  |  |  |
| Eosinophils (High): Low to Normal      | 66   |  |  |  |
| Eosinophils (High): Low to Low         | 13   |  |  |  |
| Eosinophils (High): Low to High        | 36   |  |  |  |
| Eosinophils (High): High to Normal     | 11   |  |  |  |
| Eosinophils (High): High to High       | 35   |  |  |  |
| Eosinophils (High): Missing to Normal  | 17   |  |  |  |
| Eosinophils (High): Missing to Low     | 1    |  |  |  |
| Eosinophils (High): Missing to High    | 7    |  |  |  |
| Eosinophils (High): Missing to Missing | 50   |  |  |  |
| Eosinophils (Low): Normal to Normal    | 810  |  |  |  |
| Eosinophils (Low): Normal to Low       | 390  |  |  |  |
| Eosinophils (Low): Low to Normal       | 13   |  |  |  |
| Eosinophils (Low): Low to Low          | 101  |  |  |  |
| Eosinophils (Low): Low to High         | 1    |  |  |  |
| Eosinophils (Low): High to Normal      | 28   |  |  |  |
| Eosinophils (Low): High to Low         | 13   |  |  |  |
| Eosinophils (Low): High to High        | 5    |  |  |  |
| Eosinophils (Low): Missing to Normal   | 37   |  |  |  |
| Eosinophils (Low): Missing to Low      | 10   |  |  |  |
| Eosinophils (Low): Missing to Missing  | 28   |  |  |  |
| Hematocrit (High): Normal to Normal    | 953  |  |  |  |
| Hematocrit (High): Normal to Low       | 47   |  |  |  |
| Hematocrit (High): Normal to High      | 58   |  |  |  |
| Hematocrit (High): Normal to Missing   | 4    |  |  |  |
| Hematocrit (High): Low to Normal       | 201  |  |  |  |
| Hematocrit (High): Low to Low          | 97   |  |  |  |
| Hematocrit (High): Low to High         | 10   |  |  |  |
| Hematocrit (High): Low to Missing      | 2    |  |  |  |
| Hematocrit (High): High to Normal      | 17   |  |  |  |
| Hematocrit (High): High to High        | 12   |  |  |  |
| Hematocrit (High): Missing to Normal   | 15   |  |  |  |
| Hematocrit (High): Missing to High     | 1    |  |  |  |
| Hematocrit (High): Missing to Missing  | 19   |  |  |  |

|                                            |     |  |  |  |
|--------------------------------------------|-----|--|--|--|
| Hematocrit (Low): Normal to Normal         | 223 |  |  |  |
| Hematocrit (Low): Normal to Low            | 837 |  |  |  |
| Hematocrit (Low): Normal to Missing        | 2   |  |  |  |
| Hematocrit (Low): Low to Normal            | 5   |  |  |  |
| Hematocrit (Low): Low to Low               | 305 |  |  |  |
| Hematocrit (Low): High to Normal           | 13  |  |  |  |
| Hematocrit (Low): High to Low              | 16  |  |  |  |
| Hematocrit (Low): Missing to Normal        | 3   |  |  |  |
| Hematocrit (Low): Missing to Low           | 12  |  |  |  |
| Hematocrit (Low): Missing to Missing       | 20  |  |  |  |
| Monocytes (High): Normal to Normal         | 802 |  |  |  |
| Monocytes (High): Normal to Low            | 3   |  |  |  |
| Monocytes (High): Normal to High           | 365 |  |  |  |
| Monocytes (High): Low to Normal            | 58  |  |  |  |
| Monocytes (High): Low to Low               | 6   |  |  |  |
| Monocytes (High): Low to High              | 17  |  |  |  |
| Monocytes (High): High to Normal           | 29  |  |  |  |
| Monocytes (High): High to Low              | 1   |  |  |  |
| Monocytes (High): High to High             | 82  |  |  |  |
| Monocytes (High): Missing to Normal        | 12  |  |  |  |
| Monocytes (High): Missing to High          | 8   |  |  |  |
| Monocytes (High): Missing to Missing       | 53  |  |  |  |
| Monocytes (Low): Normal to Normal          | 747 |  |  |  |
| Monocytes (Low): Normal to Low             | 420 |  |  |  |
| Monocytes (Low): Normal to High            | 3   |  |  |  |
| Monocytes (Low): Low to Normal             | 11  |  |  |  |
| Monocytes (Low): Low to Low                | 70  |  |  |  |
| Monocytes (Low): High to Normal            | 64  |  |  |  |
| Monocytes (Low): High to Low               | 40  |  |  |  |
| Monocytes (Low): High to High              | 8   |  |  |  |
| Monocytes (Low): Missing to Normal         | 13  |  |  |  |
| Monocytes (Low): Missing to Low            | 10  |  |  |  |
| Monocytes (Low): Missing to High           | 5   |  |  |  |
| Monocytes (Low): Missing to Missing        | 45  |  |  |  |
| Red Blood Cells (High): Normal to Normal   | 975 |  |  |  |
| Red Blood Cells (High): Normal to Low      | 31  |  |  |  |
| Red Blood Cells (High): Normal to High     | 111 |  |  |  |
| Red Blood Cells (High): Low to Normal      | 131 |  |  |  |
| Red Blood Cells (High): Low to Low         | 61  |  |  |  |
| Red Blood Cells (High): Low to High        | 15  |  |  |  |
| Red Blood Cells (High): High to Normal     | 22  |  |  |  |
| Red Blood Cells (High): High to High       | 45  |  |  |  |
| Red Blood Cells (High): Missing to Normal  | 18  |  |  |  |
| Red Blood Cells (High): Missing to Low     | 2   |  |  |  |
| Red Blood Cells (High): Missing to High    | 2   |  |  |  |
| Red Blood Cells (High): Missing to Missing | 23  |  |  |  |
| Red Blood Cells (Low): Normal to Normal    | 350 |  |  |  |
| Red Blood Cells (Low): Normal to Low       | 767 |  |  |  |
| Red Blood Cells (Low): Low to Normal       | 10  |  |  |  |

|                                           |      |  |  |  |
|-------------------------------------------|------|--|--|--|
| Red Blood Cells (Low): Low to Low         | 197  |  |  |  |
| Red Blood Cells (Low): High to Normal     | 44   |  |  |  |
| Red Blood Cells (Low): High to Low        | 21   |  |  |  |
| Red Blood Cells (Low): High to High       | 2    |  |  |  |
| Red Blood Cells (Low): Missing to Normal  | 6    |  |  |  |
| Red Blood Cells (Low): Missing to Low     | 16   |  |  |  |
| Red Blood Cells (Low): Missing to Missing | 23   |  |  |  |
| PTT (High): Normal to Normal              | 46   |  |  |  |
| PTT (High): Normal to Low                 | 1    |  |  |  |
| PTT (High): Normal to High                | 15   |  |  |  |
| PTT (High): Low to Normal                 | 19   |  |  |  |
| PTT (High): Low to Low                    | 1    |  |  |  |
| PTT (High): Low to High                   | 1    |  |  |  |
| PTT (High): High to High                  | 1    |  |  |  |
| PTT (High): Missing to Normal             | 19   |  |  |  |
| PTT (High): Missing to Low                | 5    |  |  |  |
| PTT (High): Missing to High               | 9    |  |  |  |
| PTT (High): Missing to Missing            | 1319 |  |  |  |
| PTT (Low): Normal to Normal               | 46   |  |  |  |
| PTT (Low): Normal to Low                  | 16   |  |  |  |
| PTT (Low): Low to Normal                  | 3    |  |  |  |
| PTT (Low): Low to Low                     | 18   |  |  |  |
| PTT (Low): High to Normal                 | 1    |  |  |  |
| PTT (Low): Missing to Normal              | 20   |  |  |  |
| PTT (Low): Missing to Low                 | 6    |  |  |  |
| PTT (Low): Missing to High                | 5    |  |  |  |
| PTT (Low): Missing to Missing             | 1321 |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0

|                 |                                                                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to NCI-CTC v4.0 <sup>[28]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

Clinical laboratory tests for biochemistry parameters were performed at local laboratories. Laboratory toxicities were defined based on NCI-CTC v4.0 from Grades 1 (least severe) to 4 (most severe). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                              | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|-----------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                            | Reporting group                         |  |  |  |
| Number of subjects analysed                   | 1436                                    |  |  |  |
| Units: Participants                           |                                         |  |  |  |
| Alanine Aminotransferase: Normal to Normal    | 610                                     |  |  |  |
| Alanine Aminotransferase: Normal to Grade 1   | 425                                     |  |  |  |
| Alanine Aminotransferase: Normal to Grade 2   | 26                                      |  |  |  |
| Alanine Aminotransferase: Normal to Grade 3   | 19                                      |  |  |  |
| Alanine Aminotransferase: Normal to Missing   | 25                                      |  |  |  |
| Alanine Aminotransferase: Grade 1 to Normal   | 75                                      |  |  |  |
| Alanine Aminotransferase: Grade 1 to 1        | 151                                     |  |  |  |
| Alanine Aminotransferase: Grade 1 to 2        | 26                                      |  |  |  |
| Alanine Aminotransferase: Grade 1 to 3        | 14                                      |  |  |  |
| Alanine Aminotransferase: Grade 1 to Missing  | 6                                       |  |  |  |
| Alanine Aminotransferase: Grade 2 to Normal   | 8                                       |  |  |  |
| Alanine Aminotransferase: Grade 2 to 1        | 28                                      |  |  |  |
| Alanine Aminotransferase: Grade 2 to 2        | 5                                       |  |  |  |
| Alanine Aminotransferase: Grade 2 to 3        | 1                                       |  |  |  |
| Alanine Aminotransferase: Grade 3 to 1        | 2                                       |  |  |  |
| Alanine Aminotransferase: Missing to Normal   | 7                                       |  |  |  |
| Alanine Aminotransferase: Missing to Grade 1  | 4                                       |  |  |  |
| Alanine Aminotransferase: Missing to Grade 2  | 1                                       |  |  |  |
| Alanine Aminotransferase: Missing to Missing  | 3                                       |  |  |  |
| Aspartate Aminotransferase: Normal to Normal  | 562                                     |  |  |  |
| Aspartate Aminotransferase: Normal to Grade 1 | 386                                     |  |  |  |
| Aspartate Aminotransferase: Normal to Grade 2 | 22                                      |  |  |  |
| Aspartate Aminotransferase: Normal to Grade 3 | 9                                       |  |  |  |
| Aspartate Aminotransferase: Normal to Missing | 15                                      |  |  |  |
| Aspartate Aminotransferase: Grade 1 to Normal | 120                                     |  |  |  |

|                                                |     |  |  |  |
|------------------------------------------------|-----|--|--|--|
| Aspartate Aminotransferase: Grade 1 to 1       | 187 |  |  |  |
| Aspartate Aminotransferase: Grade 1 to 2       | 24  |  |  |  |
| Aspartate Aminotransferase: Grade 1 to 3       | 9   |  |  |  |
| Aspartate Aminotransferase: Grade 1 to Missing | 14  |  |  |  |
| Aspartate Aminotransferase: Grade 2 to Normal  | 13  |  |  |  |
| Aspartate Aminotransferase: Grade 2 to 1       | 29  |  |  |  |
| Aspartate Aminotransferase: Grade 2 to 2       | 3   |  |  |  |
| Aspartate Aminotransferase: Grade 2 to Missing | 3   |  |  |  |
| Aspartate Aminotransferase: Grade 3 to Normal  | 2   |  |  |  |
| Aspartate Aminotransferase: Grade 3 to 1       | 7   |  |  |  |
| Aspartate Aminotransferase: Grade 3 to Missing | 1   |  |  |  |
| Aspartate Aminotransferase: Missing to Normal  | 13  |  |  |  |
| Aspartate Aminotransferase: Missing to Grade 1 | 9   |  |  |  |
| Aspartate Aminotransferase: Missing to Grade 2 | 2   |  |  |  |
| Aspartate Aminotransferase: Missing to Missing | 6   |  |  |  |
| Albumin: Normal to Normal                      | 785 |  |  |  |
| Albumin: Normal to Grade 1                     | 357 |  |  |  |
| Albumin: Normal to Grade 2                     | 86  |  |  |  |
| Albumin: Normal to Grade 3                     | 10  |  |  |  |
| Albumin: Normal to Missing                     | 23  |  |  |  |
| Albumin: Grade 1 to Normal                     | 13  |  |  |  |
| Albumin: Grade 1 to 1                          | 43  |  |  |  |
| Albumin: Grade 1 to 2                          | 35  |  |  |  |
| Albumin: Grade 1 to 3                          | 1   |  |  |  |
| Albumin: Grade 1 to Missing                    | 7   |  |  |  |
| Albumin: Grade 2 to Normal                     | 3   |  |  |  |
| Albumin: Grade 2 to 1                          | 5   |  |  |  |
| Albumin: Grade 2 to 2                          | 8   |  |  |  |
| Albumin: Grade 2 to 3                          | 2   |  |  |  |
| Albumin: Grade 2 to Missing                    | 2   |  |  |  |
| Albumin: Grade 3 to 2                          | 1   |  |  |  |
| Albumin: Grade 3 to Missing                    | 1   |  |  |  |
| Albumin: Missing to Normal                     | 28  |  |  |  |
| Albumin: Missing to Grade 1                    | 14  |  |  |  |
| Albumin: Missing to Grade 2                    | 6   |  |  |  |
| Albumin: Missing to Missing                    | 6   |  |  |  |
| Alkaline Phosphatase: Normal to Normal         | 605 |  |  |  |
| Alkaline Phosphatase: Normal to Grade 1        | 329 |  |  |  |
| Alkaline Phosphatase: Normal to Grade 2        | 14  |  |  |  |
| Alkaline Phosphatase: Normal to Grade 3        | 2   |  |  |  |

|                                          |      |  |  |  |
|------------------------------------------|------|--|--|--|
| Alkaline Phosphatase: Normal to Missing  | 18   |  |  |  |
| Alkaline Phosphatase: Grade 1 to Normal  | 44   |  |  |  |
| Alkaline Phosphatase: Grade 1 to 1       | 241  |  |  |  |
| Alkaline Phosphatase: Grade 1 to 2       | 72   |  |  |  |
| Alkaline Phosphatase: Grade 1 to 3       | 15   |  |  |  |
| Alkaline Phosphatase: Grade 1 to Missing | 6    |  |  |  |
| Alkaline Phosphatase: Grade 2 to Normal  | 2    |  |  |  |
| Alkaline Phosphatase: Grade 2 to 1       | 21   |  |  |  |
| Alkaline Phosphatase: Grade 2 to 2       | 24   |  |  |  |
| Alkaline Phosphatase: Grade 2 to 3       | 14   |  |  |  |
| Alkaline Phosphatase: Grade 2 to Missing | 8    |  |  |  |
| Alkaline Phosphatase: Grade 3 to 1       | 2    |  |  |  |
| Alkaline Phosphatase: Grade 3 to 2       | 1    |  |  |  |
| Alkaline Phosphatase: Grade 3 to 3       | 4    |  |  |  |
| Alkaline Phosphatase: Missing to Normal  | 7    |  |  |  |
| Alkaline Phosphatase: Missing to Grade 1 | 3    |  |  |  |
| Alkaline Phosphatase: Missing to Grade 3 | 1    |  |  |  |
| Alkaline Phosphatase: Missing to Missing | 3    |  |  |  |
| Calcium (High): Normal to Normal         | 1060 |  |  |  |
| Calcium (High): Normal to Grade 1        | 192  |  |  |  |
| Calcium (High): Normal to Grade 2        | 2    |  |  |  |
| Calcium (High): Normal to Grade 3        | 1    |  |  |  |
| Calcium (High): Normal to Grade 4        | 1    |  |  |  |
| Calcium (High): Normal to Missing        | 26   |  |  |  |
| Calcium (High): Grade 1 to Normal        | 47   |  |  |  |
| Calcium (High): Grade 1 to 1             | 47   |  |  |  |
| Calcium (High): Grade 1 to 2             | 1    |  |  |  |
| Calcium (High): Grade 1 to 3             | 1    |  |  |  |
| Calcium (High): Grade 1 to Missing       | 5    |  |  |  |
| Calcium (High): Grade 2 to Normal        | 1    |  |  |  |
| Calcium (High): Grade 2 to 1             | 1    |  |  |  |
| Calcium (High): Grade 2 to 2             | 1    |  |  |  |
| Calcium (High): Grade 3 to Normal        | 2    |  |  |  |
| Calcium (High): Grade 3 to 1             | 1    |  |  |  |
| Calcium (High): Grade 3 to 2             | 1    |  |  |  |
| Calcium (High): Grade 4 to Normal        | 1    |  |  |  |
| Calcium (High): Missing to Normal        | 32   |  |  |  |
| Calcium (High): Missing to Grade 1       | 3    |  |  |  |
| Calcium (High): Missing to Missing       | 10   |  |  |  |
| Calcium (Low): Normal to Normal          | 786  |  |  |  |
| Calcium (Low): Normal to Grade 1         | 378  |  |  |  |
| Calcium (Low): Normal to Grade 2         | 117  |  |  |  |
| Calcium (Low): Normal to Grade 3         | 18   |  |  |  |
| Calcium (Low): Normal to Missing         | 30   |  |  |  |
| Calcium (Low): Grade 1 to Normal         | 5    |  |  |  |
| Calcium (Low): Grade 1 to 1              | 31   |  |  |  |
| Calcium (Low): Grade 1 to 2              | 12   |  |  |  |
| Calcium (Low): Grade 1 to 3              | 2    |  |  |  |

|                                                      |     |  |  |  |
|------------------------------------------------------|-----|--|--|--|
| Calcium (Low): Grade 1 to Missing                    | 1   |  |  |  |
| Calcium (Low): Grade 2 to Normal                     | 5   |  |  |  |
| Calcium (Low): Grade 2 to 1                          | 1   |  |  |  |
| Calcium (Low): Grade 2 to 2                          | 4   |  |  |  |
| Calcium (Low): Grade 3 to 3                          | 1   |  |  |  |
| Calcium (Low): Missing to Normal                     | 20  |  |  |  |
| Calcium (Low): Missing to Grade 1                    | 11  |  |  |  |
| Calcium (Low): Missing to Grade 2                    | 4   |  |  |  |
| Calcium (Low): Missing to Missing                    | 10  |  |  |  |
| Creatinine: Normal to Normal                         | 176 |  |  |  |
| Creatinine: Normal to Grade 1                        | 960 |  |  |  |
| Creatinine: Normal to Grade 2                        | 175 |  |  |  |
| Creatinine: Normal to Grade 3                        | 5   |  |  |  |
| Creatinine: Normal to Grade 4                        | 5   |  |  |  |
| Creatinine: Normal to Missing                        | 26  |  |  |  |
| Creatinine: Grade 1 to Normal                        | 12  |  |  |  |
| Creatinine: Grade 1 to 1                             | 38  |  |  |  |
| Creatinine: Grade 1 to 2                             | 8   |  |  |  |
| Creatinine: Grade 1 to Missing                       | 3   |  |  |  |
| Creatinine: Grade 2 to 2                             | 3   |  |  |  |
| Creatinine: Grade 2 to 3                             | 1   |  |  |  |
| Creatinine: Grade 2 to Missing                       | 1   |  |  |  |
| Creatinine: Missing to Normal                        | 11  |  |  |  |
| Creatinine: Missing to Grade 1                       | 6   |  |  |  |
| Creatinine: Missing to Missing                       | 6   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Normal to Normal   | 498 |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Normal to Grade 1  | 227 |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Normal to Grade 2  | 39  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Normal to Grade 3  | 15  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Normal to Missing  | 12  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 1 to Normal  | 64  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 1 to 1       | 187 |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 1 to 2       | 75  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 1 to 3       | 20  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 1 to Missing | 7   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 2 to Normal  | 5   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 2 to 1       | 52  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 2 to 2       | 45  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 2 to 3       | 21  |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 2 to Missing | 5   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 3 to Normal  | 2   |  |  |  |

|                                                      |      |  |  |  |
|------------------------------------------------------|------|--|--|--|
| Gamma-Glutamyl Transpeptidase:<br>Grade 3 to 1       | 15   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 3 to 2       | 38   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 3 to 3       | 47   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Grade 3 to Missing | 4    |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Missing to Normal  | 14   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Missing to Grade 1 | 7    |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Missing to Grade 2 | 10   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Missing to Grade 3 | 18   |  |  |  |
| Gamma-Glutamyl Transpeptidase:<br>Missing to Missing | 9    |  |  |  |
| Glucose (High): Normal to Normal                     | 340  |  |  |  |
| Glucose (High): Normal to Grade 1                    | 534  |  |  |  |
| Glucose (High): Normal to Grade 2                    | 115  |  |  |  |
| Glucose (High): Normal to Missing                    | 21   |  |  |  |
| Glucose (High): Grade 1 to Normal                    | 28   |  |  |  |
| Glucose (High): Grade 1 to 1                         | 190  |  |  |  |
| Glucose (High): Grade 1 to 2                         | 74   |  |  |  |
| Glucose (High): Grade 1 to Missing                   | 9    |  |  |  |
| Glucose (High): Grade 2 to Normal                    | 2    |  |  |  |
| Glucose (High): Grade 2 to 1                         | 13   |  |  |  |
| Glucose (High): Grade 2 to 2                         | 10   |  |  |  |
| Glucose (High): Grade 2 to Missing                   | 3    |  |  |  |
| Glucose (High): Missing to Normal                    | 20   |  |  |  |
| Glucose (High): Missing to Grade 1                   | 30   |  |  |  |
| Glucose (High): Missing to Grade 2                   | 40   |  |  |  |
| Glucose (High): Missing to Missing                   | 7    |  |  |  |
| Glucose (Low): Normal to Normal                      | 1061 |  |  |  |
| Glucose (Low): Normal to Grade 1                     | 173  |  |  |  |
| Glucose (Low): Normal to Grade 2                     | 19   |  |  |  |
| Glucose (Low): Normal to Grade 3                     | 4    |  |  |  |
| Glucose (Low): Normal to Grade 4                     | 5    |  |  |  |
| Glucose (Low): Normal to Missing                     | 33   |  |  |  |
| Glucose (Low): Grade 1 to Normal                     | 8    |  |  |  |
| Glucose (Low): Grade 1 to 1                          | 24   |  |  |  |
| Glucose (Low): Grade 1 to 2                          | 3    |  |  |  |
| Glucose (Low): Grade 1 to 3                          | 1    |  |  |  |
| Glucose (Low): Grade 1 to 4                          | 1    |  |  |  |
| Glucose (Low): Grade 2 to Normal                     | 1    |  |  |  |
| Glucose (Low): Missing to Normal                     | 69   |  |  |  |
| Glucose (Low): Missing to Grade 1                    | 16   |  |  |  |
| Glucose (Low): Missing to Grade 2                    | 2    |  |  |  |
| Glucose (Low): Missing to Grade 3                    | 1    |  |  |  |
| Glucose (Low): Missing to Missing                    | 15   |  |  |  |
| Magnesium (High): Normal to Normal                   | 1100 |  |  |  |
| Magnesium (High): Normal to Grade 1                  | 122  |  |  |  |
| Magnesium (High): Normal to Grade 3                  | 38   |  |  |  |
| Magnesium (High): Normal to Grade 4                  | 6    |  |  |  |

|                                      |      |  |  |  |
|--------------------------------------|------|--|--|--|
| Magnesium (High): Normal to Missing  | 31   |  |  |  |
| Magnesium (High): Grade 1 to Normal  | 12   |  |  |  |
| Magnesium (High): Grade 1 to 1       | 7    |  |  |  |
| Magnesium (High): Grade 3 to Normal  | 2    |  |  |  |
| Magnesium (High): Grade 3 to 3       | 2    |  |  |  |
| Magnesium (High): Grade 4 to Normal  | 1    |  |  |  |
| Magnesium (High): Grade 4 to 4       | 1    |  |  |  |
| Magnesium (High): Missing to Normal  | 85   |  |  |  |
| Magnesium (High): Missing to Grade 1 | 12   |  |  |  |
| Magnesium (High): Missing to Grade 3 | 6    |  |  |  |
| Magnesium (High): Missing to Missing | 11   |  |  |  |
| Magnesium (Low): Normal to Normal    | 857  |  |  |  |
| Magnesium (Low): Normal to Grade 1   | 319  |  |  |  |
| Magnesium (Low): Normal to Grade 2   | 28   |  |  |  |
| Magnesium (Low): Normal to Grade 3   | 9    |  |  |  |
| Magnesium (Low): Normal to Grade 4   | 3    |  |  |  |
| Magnesium (Low): Normal to Missing   | 28   |  |  |  |
| Magnesium (Low): Grade 1 to Normal   | 9    |  |  |  |
| Magnesium (Low): Grade 1 to 1        | 55   |  |  |  |
| Magnesium (Low): Grade 1 to 2        | 7    |  |  |  |
| Magnesium (Low): Grade 1 to 3        | 3    |  |  |  |
| Magnesium (Low): Grade 1 to Missing  | 3    |  |  |  |
| Magnesium (Low): Grade 4 to 4        | 1    |  |  |  |
| Magnesium (Low): Missing to Normal   | 81   |  |  |  |
| Magnesium (Low): Missing to Grade 1  | 19   |  |  |  |
| Magnesium (Low): Missing to Grade 2  | 1    |  |  |  |
| Magnesium (Low): Missing to Grade 3  | 1    |  |  |  |
| Magnesium (Low): Missing to Grade 4  | 1    |  |  |  |
| Magnesium (Low): Missing to Missing  | 11   |  |  |  |
| Potassium (High): Normal to Normal   | 1051 |  |  |  |
| Potassium (High): Normal to Grade 1  | 183  |  |  |  |
| Potassium (High): Normal to Grade 2  | 81   |  |  |  |
| Potassium (High): Normal to Grade 3  | 18   |  |  |  |
| Potassium (High): Normal to Grade 4  | 8    |  |  |  |
| Potassium (High): Normal to Missing  | 26   |  |  |  |
| Potassium (High): Grade 1 to Normal  | 16   |  |  |  |
| Potassium (High): Grade 1 to 1       | 8    |  |  |  |
| Potassium (High): Grade 1 to 2       | 7    |  |  |  |
| Potassium (High): Grade 1 to 3       | 1    |  |  |  |
| Potassium (High): Grade 1 to Missing | 3    |  |  |  |
| Potassium (High): Grade 2 to Normal  | 2    |  |  |  |
| Potassium (High): Grade 2 to 1       | 1    |  |  |  |
| Potassium (High): Grade 2 to 2       | 1    |  |  |  |
| Potassium (High): Grade 4 to Normal  | 1    |  |  |  |
| Potassium (High): Missing to Normal  | 18   |  |  |  |
| Potassium (High): Missing to Grade 1 | 5    |  |  |  |
| Potassium (High): Missing to Grade 2 | 3    |  |  |  |
| Potassium (High): Missing to Missing | 3    |  |  |  |
| Potassium (Low): Normal to Normal    | 990  |  |  |  |
| Potassium (Low): Normal to Grade 2   | 367  |  |  |  |
| Potassium (Low): Normal to Missing   | 29   |  |  |  |
| Potassium (Low): Grade 2 to Normal   | 8    |  |  |  |

|                                     |      |  |  |  |
|-------------------------------------|------|--|--|--|
| Potassium (Low): Grade 2 to 2       | 13   |  |  |  |
| Potassium (Low): Missing to Normal  | 19   |  |  |  |
| Potassium (Low): Missing to Grade 2 | 7    |  |  |  |
| Potassium (Low): Missing to Missing | 3    |  |  |  |
| Sodium (High): Normal to Normal     | 1075 |  |  |  |
| Sodium (High): Normal to Grade 1    | 256  |  |  |  |
| Sodium (High): Normal to Grade 2    | 36   |  |  |  |
| Sodium (High): Normal to Grade 3    | 9    |  |  |  |
| Sodium (High): Normal to Grade 4    | 1    |  |  |  |
| Sodium (High): Normal to Missing    | 28   |  |  |  |
| Sodium (High): Grade 1 to Normal    | 3    |  |  |  |
| Sodium (High): Grade 1 to 1         | 6    |  |  |  |
| Sodium (High): Grade 1 to 2         | 3    |  |  |  |
| Sodium (High): Grade 1 to 3         | 1    |  |  |  |
| Sodium (High): Grade 2 to 2         | 2    |  |  |  |
| Sodium (High): Grade 2 to 3         | 1    |  |  |  |
| Sodium (High): Grade 3 to Normal    | 1    |  |  |  |
| Sodium (High): Grade 3 to Missing   | 1    |  |  |  |
| Sodium (High): Missing to Normal    | 11   |  |  |  |
| Sodium (High): Missing to Grade 1   | 1    |  |  |  |
| Sodium (High): Missing to Missing   | 1    |  |  |  |
| Sodium (Low): Normal to Normal      | 994  |  |  |  |
| Sodium (Low): Normal to Grade 1     | 298  |  |  |  |
| Sodium (Low): Normal to Grade 3     | 20   |  |  |  |
| Sodium (Low): Normal to Grade 4     | 15   |  |  |  |
| Sodium (Low): Normal to Missing     | 23   |  |  |  |
| Sodium (Low): Grade 1 to Normal     | 21   |  |  |  |
| Sodium (Low): Grade 1 to 1          | 36   |  |  |  |
| Sodium (Low): Grade 1 to 3          | 2    |  |  |  |
| Sodium (Low): Grade 1 to 4          | 1    |  |  |  |
| Sodium (Low): Grade 1 to Missing    | 6    |  |  |  |
| Sodium (Low): Grade 3 to Normal     | 1    |  |  |  |
| Sodium (Low): Grade 3 to 1          | 2    |  |  |  |
| Sodium (Low): Grade 3 to 3          | 1    |  |  |  |
| Sodium (Low): Grade 4 to Normal     | 2    |  |  |  |
| Sodium (Low): Grade 4 to 1          | 1    |  |  |  |
| Sodium (Low): Missing to Normal     | 6    |  |  |  |
| Sodium (Low): Missing to Grade 1    | 5    |  |  |  |
| Sodium (Low): Missing to Grade 3    | 1    |  |  |  |
| Sodium (Low): Missing to Missing    | 1    |  |  |  |
| Total Bilirubin: Normal to Normal   | 1231 |  |  |  |
| Total Bilirubin: Normal to Grade 1  | 88   |  |  |  |
| Total Bilirubin: Normal to Grade 2  | 35   |  |  |  |
| Total Bilirubin: Normal to Grade 3  | 2    |  |  |  |
| Total Bilirubin: Normal to Missing  | 28   |  |  |  |
| Total Bilirubin: Grade 1 to Normal  | 3    |  |  |  |
| Total Bilirubin: Grade 1 to 1       | 11   |  |  |  |
| Total Bilirubin: Grade 1 to 2       | 6    |  |  |  |
| Total Bilirubin: Grade 1 to Missing | 2    |  |  |  |
| Total Bilirubin: Grade 2 to 1       | 1    |  |  |  |
| Total Bilirubin: Grade 2 to 2       | 1    |  |  |  |
| Total Bilirubin: Grade 2 to Missing | 1    |  |  |  |

|                                     |     |  |  |  |
|-------------------------------------|-----|--|--|--|
| Total Bilirubin: Grade 3 to Normal  | 1   |  |  |  |
| Total Bilirubin: Missing to Normal  | 22  |  |  |  |
| Total Bilirubin: Missing to Grade 2 | 1   |  |  |  |
| Total Bilirubin: Missing to Missing | 3   |  |  |  |
| Uric Acid: Normal to Normal         | 933 |  |  |  |
| Uric Acid: Normal to Grade 1        | 190 |  |  |  |
| Uric Acid: Normal to Grade 4        | 8   |  |  |  |
| Uric Acid: Normal to Missing        | 20  |  |  |  |
| Uric Acid: Grade 1 to Normal        | 58  |  |  |  |
| Uric Acid: Grade 1 to 1             | 120 |  |  |  |
| Uric Acid: Grade 1 to 4             | 6   |  |  |  |
| Uric Acid: Grade 1 to Missing       | 11  |  |  |  |
| Uric Acid: Grade 4 to Normal        | 1   |  |  |  |
| Uric Acid: Grade 4 to 1             | 2   |  |  |  |
| Uric Acid: Grade 4 to 4             | 4   |  |  |  |
| Uric Acid: Grade 4 to Missing       | 1   |  |  |  |
| Uric Acid: Missing to Normal        | 57  |  |  |  |
| Uric Acid: Missing to Grade 1       | 13  |  |  |  |
| Uric Acid: Missing to Grade 4       | 2   |  |  |  |
| Uric Acid: Missing to Missing       | 10  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria

|                 |                                                                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Participants with Laboratory Abnormalities in Biochemistry Parameters: Shift From Baseline to the Worst Post-Baseline Grade According to Normal Range Criteria <sup>[29]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Clinical laboratory tests for biochemistry parameters were performed at local laboratories. Laboratory toxicities were defined based on local laboratory normal ranges (for parameters with NCI-CTC grade not defined). Some laboratory parameters are bi-dimensional (i.e. can be graded in both the low and high direction). These parameters were split and presented in both directions. Baseline was defined as the last non-missing measurement taken prior to the first dose of study treatment (including unscheduled assessments). Values from all visits, including unscheduled visits, were included in the derivation of the worst post-baseline grade. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: was clinically significant (per investigator); was accompanied by clinical symptoms; resulted in a change in study treatment; or resulted in a medical intervention or a change in concomitant therapy.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Predose for each treatment cycle (1 cycle is 3 weeks) from Baseline until 28 days after the last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

Notes:

[29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: There were no formal statistical hypothesis tests to be performed. All results were summarized by descriptive statistics.

| End point values                                   | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                 | Reporting group                         |  |  |  |
| Number of subjects analysed                        | 1436                                    |  |  |  |
| Units: Participants                                |                                         |  |  |  |
| Blood Urea Nitrogen (High): Normal to Normal       | 717                                     |  |  |  |
| Blood Urea Nitrogen (High): Normal to Low          | 5                                       |  |  |  |
| Blood Urea Nitrogen (High): Normal to High         | 402                                     |  |  |  |
| Blood Urea Nitrogen (High): Normal to Missing      | 2                                       |  |  |  |
| Blood Urea Nitrogen (High): Low to Normal          | 69                                      |  |  |  |
| Blood Urea Nitrogen (High): Low to Low             | 8                                       |  |  |  |
| Blood Urea Nitrogen (High): Low to High            | 12                                      |  |  |  |
| Blood Urea Nitrogen (High): High to Normal         | 23                                      |  |  |  |
| Blood Urea Nitrogen (High): High to High           | 98                                      |  |  |  |
| Blood Urea Nitrogen (High): Missing to Normal      | 42                                      |  |  |  |
| Blood Urea Nitrogen (High): Missing to High        | 19                                      |  |  |  |
| Blood Urea Nitrogen (High): Missing to Missing     | 39                                      |  |  |  |
| Blood Urea Nitrogen (Low): Normal to Normal        | 828                                     |  |  |  |
| Blood Urea Nitrogen (Low): Normal to Low           | 293                                     |  |  |  |
| Blood Urea Nitrogen (Low): Normal to High          | 3                                       |  |  |  |
| Blood Urea Nitrogen (Low): Normal to Missing       | 2                                       |  |  |  |
| Blood Urea Nitrogen (Low): Low to Normal           | 17                                      |  |  |  |
| Blood Urea Nitrogen (Low): Low to Low              | 72                                      |  |  |  |
| Blood Urea Nitrogen (Low): High to Normal          | 104                                     |  |  |  |
| Blood Urea Nitrogen (Low): High to Low             | 11                                      |  |  |  |
| Blood Urea Nitrogen (Low): High to High            | 6                                       |  |  |  |
| Blood Urea Nitrogen (Low): Missing to Normal       | 47                                      |  |  |  |
| Blood Urea Nitrogen (Low): Missing to Low          | 11                                      |  |  |  |
| Blood Urea Nitrogen (Low): Missing to High         | 3                                       |  |  |  |
| Blood Urea Nitrogen (Low): Missing to Missing      | 39                                      |  |  |  |
| Calc Creatinine Clearance (High): Normal to Normal | 540                                     |  |  |  |
| Calc Creatinine Clearance (High): Normal to Low    | 11                                      |  |  |  |
| Calc Creatinine Clearance (High): Normal to High   | 201                                     |  |  |  |
| Calc Creatinine Clearance(High): Normal to Missing | 2                                       |  |  |  |
| Calc Creatinine Clearance (High): Low to Normal    | 166                                     |  |  |  |

|                                                    |     |  |  |  |
|----------------------------------------------------|-----|--|--|--|
| Calc Creatinine Clearance (High): Low to Low       | 107 |  |  |  |
| Calc Creatinine Clearance (High): Low to High      | 34  |  |  |  |
| Calc Creatinine Clearance (High): Low to Missing   | 1   |  |  |  |
| Calc Creatinine Clearance (High): High to Normal   | 13  |  |  |  |
| Calc Creatinine Clearance (High): High to High     | 101 |  |  |  |
| Calc Creatinine Clearance(High): Missing to Normal | 46  |  |  |  |
| Calc Creatinine Clearance (High): Missing to Low   | 8   |  |  |  |
| Calc Creatinine Clearance (High): Missing to High  | 11  |  |  |  |
| Calc Creatinine Clearance(High):Missing to Missing | 195 |  |  |  |
| Calc Creatinine Clearance (Low): Normal to Normal  | 393 |  |  |  |
| Calc Creatinine Clearance (Low): Normal to Low     | 353 |  |  |  |
| Calc Creatinine Clearance (Low): Normal to High    | 8   |  |  |  |
| Calc Creatinine Clearance (Low): Low to Normal     | 12  |  |  |  |
| Calc Creatinine Clearance (Low): Low to Low        | 294 |  |  |  |
| Calc Creatinine Clearance (Low): Low to High       | 1   |  |  |  |
| Calc Creatinine Clearance (Low): Low to Missing    | 1   |  |  |  |
| Calc Creatinine Clearance (Low): High to Normal    | 61  |  |  |  |
| Calc Creatinine Clearance (Low): High to Low       | 36  |  |  |  |
| Calc Creatinine Clearance (Low): High to High      | 17  |  |  |  |
| Calc Creatinine Clearance (Low): Missing to Normal | 66  |  |  |  |
| Calc Creatinine Clearance (Low): Missing to Low    | 44  |  |  |  |
| Calc Creatinine Clearance (Low): Missing to High   | 17  |  |  |  |
| Calc Creatinine Clearance(Low): Missing to Missing | 133 |  |  |  |
| Chloride (High): Normal to Normal                  | 665 |  |  |  |
| Chloride (High): Normal to Low                     | 2   |  |  |  |
| Chloride (High): Normal to High                    | 508 |  |  |  |
| Chloride (High): Low to Normal                     | 54  |  |  |  |
| Chloride (High): Low to High                       | 13  |  |  |  |
| Chloride (High): High to Normal                    | 4   |  |  |  |
| Chloride (High): High to High                      | 58  |  |  |  |
| Chloride (High): Missing to Normal                 | 41  |  |  |  |
| Chloride (High): Missing to High                   | 32  |  |  |  |
| Chloride (High): Missing to Missing                | 59  |  |  |  |
| Chloride (Low): Normal to Normal                   | 971 |  |  |  |
| Chloride (Low): Normal to Low                      | 201 |  |  |  |
| Chloride (Low): Normal to High                     | 3   |  |  |  |

|                                                  |      |  |  |  |
|--------------------------------------------------|------|--|--|--|
| Chloride (Low): Low to Normal                    | 31   |  |  |  |
| Chloride (Low): Low to Low                       | 36   |  |  |  |
| Chloride (Low): High to Normal                   | 57   |  |  |  |
| Chloride (Low): High to Low                      | 4    |  |  |  |
| Chloride (Low): High to High                     | 1    |  |  |  |
| Chloride (Low): Missing to Normal                | 60   |  |  |  |
| Chloride (Low): Missing to Low                   | 13   |  |  |  |
| Chloride (Low): Missing to High                  | 1    |  |  |  |
| Chloride (Low): Missing to Missing               | 58   |  |  |  |
| Lactate Dehydrogenase (High): Normal to Normal   | 328  |  |  |  |
| Lactate Dehydrogenase (High): Normal to High     | 499  |  |  |  |
| Lactate Dehydrogenase (High): Low to Normal      | 10   |  |  |  |
| Lactate Dehydrogenase (High): Low to Low         | 1    |  |  |  |
| Lactate Dehydrogenase (High): Low to High        | 4    |  |  |  |
| Lactate Dehydrogenase (High): High to Normal     | 74   |  |  |  |
| Lactate Dehydrogenase (High): High to High       | 449  |  |  |  |
| Lactate Dehydrogenase (High): Missing to Normal  | 16   |  |  |  |
| Lactate Dehydrogenase (High): Missing to High    | 30   |  |  |  |
| Lactate Dehydrogenase (High): Missing to Missing | 25   |  |  |  |
| Lactate Dehydrogenase (Low): Normal to Normal    | 716  |  |  |  |
| Lactate Dehydrogenase (Low): Normal to Low       | 102  |  |  |  |
| Lactate Dehydrogenase (Low): Normal to High      | 9    |  |  |  |
| Lactate Dehydrogenase (Low): Low to Normal       | 5    |  |  |  |
| Lactate Dehydrogenase (Low): Low to Low          | 9    |  |  |  |
| Lactate Dehydrogenase (Low): Low to High         | 1    |  |  |  |
| Lactate Dehydrogenase (Low): High to Normal      | 426  |  |  |  |
| Lactate Dehydrogenase (Low): High to Low         | 31   |  |  |  |
| Lactate Dehydrogenase (Low): High to High        | 66   |  |  |  |
| Lactate Dehydrogenase (Low): Missing to Normal   | 39   |  |  |  |
| Lactate Dehydrogenase (Low): Missing to Low      | 3    |  |  |  |
| Lactate Dehydrogenase (Low): Missing to High     | 3    |  |  |  |
| Lactate Dehydrogenase (Low): Missing to Missing  | 26   |  |  |  |
| Total Protein (High): Normal to Normal           | 1091 |  |  |  |
| Total Protein (High): Normal to Low              | 20   |  |  |  |
| Total Protein (High): Normal to High             | 110  |  |  |  |
| Total Protein (High): Low to Normal              | 72   |  |  |  |

|                                          |     |  |  |  |
|------------------------------------------|-----|--|--|--|
| Total Protein (High): Low to Low         | 14  |  |  |  |
| Total Protein (High): High to Normal     | 28  |  |  |  |
| Total Protein (High): High to High       | 24  |  |  |  |
| Total Protein (High): Missing to Normal  | 38  |  |  |  |
| Total Protein (High): Missing to Low     | 3   |  |  |  |
| Total Protein (High): Missing to High    | 4   |  |  |  |
| Total Protein (High): Missing to Missing | 32  |  |  |  |
| Total Protein (Low): Normal to Normal    | 530 |  |  |  |
| Total Protein (Low): Normal to Low       | 691 |  |  |  |
| Total Protein (Low): Low to Normal       | 4   |  |  |  |
| Total Protein (Low): Low to Low          | 82  |  |  |  |
| Total Protein (Low): High to Normal      | 41  |  |  |  |
| Total Protein (Low): High to Low         | 11  |  |  |  |
| Total Protein (Low): Missing to Normal   | 23  |  |  |  |
| Total Protein (Low): Missing to Low      | 23  |  |  |  |
| Total Protein (Low): Missing to Missing  | 31  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-Free Survival, as Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

|                 |                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Progression-Free Survival, as Assessed by the Investigator Using Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

|                                  |                                   |  |  |  |
|----------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>          | Pertuzumab + Trastuzumab + Taxane |  |  |  |
| Subject group type               | Reporting group                   |  |  |  |
| Number of subjects analysed      | 1436                              |  |  |  |
| Units: Months                    |                                   |  |  |  |
| median (confidence interval 95%) | 20.67 (18.89 to 23.13)            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by Region of Enrollment: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Region of Enrollment: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Europe                 | Asia                   | North America          | South America          |
|----------------------------------|------------------------|------------------------|------------------------|------------------------|
| Subject group type               | Subject analysis set   | Subject analysis set   | Subject analysis set   | Subject analysis set   |
| Number of subjects analysed      | 1009                   | 177                    | 34                     | 121                    |
| Units: Months                    |                        |                        |                        |                        |
| median (confidence interval 95%) | 19.38 (17.51 to 21.75) | 23.79 (15.90 to 28.85) | 25.17 (14.42 to 29.44) | 22.37 (17.51 to 32.72) |

| End point values                 | Africa                 | Other (Australia)        |  |  |
|----------------------------------|------------------------|--------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set     |  |  |
| Number of subjects analysed      | 71                     | 24 <sup>[30]</sup>       |  |  |
| Units: Months                    |                        |                          |  |  |
| median (confidence interval 95%) | 22.83 (12.02 to 27.86) | 999999 (15.74 to 999999) |  |  |

Notes:

[30] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

## Statistical analyses

**Secondary: Subgroup Analysis by Age ( $\leq 65$  vs.  $> 65$  Years): Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1**

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Age ( $\leq 65$ vs. $> 65$ Years): Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Age $\leq 65$ Years    | Age $> 65$ Years       |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed      | 1167                   | 269                    |  |  |
| Units: Months                    |                        |                        |  |  |
| median (confidence interval 95%) | 21.98 (19.65 to 24.25) | 14.72 (12.22 to 19.55) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Subgroup Analysis by ECOG Performance Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1**

|                 |                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by ECOG Performance Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median

(full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | ECOG<br>Performance<br>Status 0 or 1 | ECOG<br>Performance<br>Status 2 |  |  |
|----------------------------------|--------------------------------------|---------------------------------|--|--|
| Subject group type               | Subject analysis set                 | Subject analysis set            |  |  |
| Number of subjects analysed      | 1371                                 | 63                              |  |  |
| Units: Months                    |                                      |                                 |  |  |
| median (confidence interval 95%) | 21.49 (19.45<br>to 23.98)            | 12.88 (8.67 to<br>15.90)        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Subgroup Analysis by Taxane Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                                        |
|-----------------|------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Taxane Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|------------------------------------------------------------------------------------------------------------------------|

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Docetaxel                 | Paclitaxel                | Nab-Paclitaxel            |  |
|----------------------------------|---------------------------|---------------------------|---------------------------|--|
| Subject group type               | Subject analysis set      | Subject analysis set      | Subject analysis set      |  |
| Number of subjects analysed      | 775                       | 588                       | 65                        |  |
| Units: Months                    |                           |                           |                           |  |
| median (confidence interval 95%) | 19.38 (16.92<br>to 22.11) | 23.23 (19.58<br>to 25.59) | 19.22 (11.70<br>to 37.09) |  |

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Subgroup Analysis by Visceral Disease at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1**

---

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Visceral Disease at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

---

| End point values                 | Visceral Disease       | Non-Visceral Disease   |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed      | 992                    | 444                    |  |  |
| Units: Months                    |                        |                        |  |  |
| median (confidence interval 95%) | 18.23 (16.13 to 20.57) | 27.24 (23.75 to 34.40) |  |  |

---

**Statistical analyses**

No statistical analyses for this end point

---

---

**Secondary: Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1**

---

|                 |                                                                                                                                     |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

---

| End point values                 | Prior<br>(Neo)Adjuvant<br>Chemotherapy | No Prior<br>(Neo)Adjuvant<br>Chemotherapy |  |  |
|----------------------------------|----------------------------------------|-------------------------------------------|--|--|
| Subject group type               | Subject analysis set                   | Subject analysis set                      |  |  |
| Number of subjects analysed      | 786                                    | 650                                       |  |  |
| Units: Months                    |                                        |                                           |  |  |
| median (confidence interval 95%) | 19.12 (16.59<br>to 21.49)              | 23.49 (20.57<br>to 25.63)                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Subgroup Analysis by Hormone Receptor Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Hormone Receptor Status at Baseline: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Hormone<br>Receptor<br>Positive | Hormone<br>Receptor<br>Negative | Hormone<br>Receptor<br>Status<br>Unknown |  |
|----------------------------------|---------------------------------|---------------------------------|------------------------------------------|--|
| Subject group type               | Subject analysis set            | Subject analysis set            | Subject analysis set                     |  |
| Number of subjects analysed      | 918                             | 512                             | 6                                        |  |
| Units: Months                    |                                 |                                 |                                          |  |
| median (confidence interval 95%) | 20.60 (18.53<br>to 23.82)       | 20.73 (17.05<br>to 23.79)       | 32.13 (11.63<br>to 61.57)                |  |

## Statistical analyses

**Secondary: Subgroup Analysis by Previous Trastuzumab Therapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1**

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Previous Trastuzumab Therapy: Progression-Free Survival, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Progression-free survival (PFS) was defined as the time between the date of enrollment and the date of first radiographically documented progressive disease assessment (by the investigator using RECIST v1.1) or death, whichever occurred first. PFS was analyzed using a Kaplan-Meier approach. Participants who had neither progressed nor died at the time of clinical cut-off or who were lost to follow-up were censored at the date of the last evaluable tumor assessment (response assessment with the latest end date); if no post-baseline assessments were available, such participants were censored at Day 1. If a participant missed 2 or more consecutive visits, then they were censored at the last evaluable visit prior to the missed visits. Tumor assessments were performed every 3 cycles (1 cycle is 3 weeks) for up to 36 months and at least every 12 cycles thereafter during treatment, and at least every 36 weeks post-treatment (if progression-free after 36 months), until disease progression.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

From date of enrollment until date of disease progression or death, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Previous Trastuzumab Therapy | No Previous Trastuzumab Therapy |  |  |
|----------------------------------|------------------------------|---------------------------------|--|--|
| Subject group type               | Subject analysis set         | Subject analysis set            |  |  |
| Number of subjects analysed      | 400                          | 1036                            |  |  |
| Units: Months                    |                              |                                 |  |  |
| median (confidence interval 95%) | 15.38 (13.67 to 19.02)       | 23.39 (20.67 to 25.00)          |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Overall Survival**

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

## End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|----------------------------------|-----------------------------------------|--|--|--|
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 1436                                    |  |  |  |
| Units: Months                    |                                         |  |  |  |
| median (confidence interval 95%) | 65.31 (60.88<br>to 70.87)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Subgroup Analysis by Region of Enrollment: Overall Survival

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Subgroup Analysis by Region of Enrollment: Overall Survival |
|-----------------|-------------------------------------------------------------|

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Europe                    | Asia                       | North America              | South America               |
|----------------------------------|---------------------------|----------------------------|----------------------------|-----------------------------|
| Subject group type               | Subject analysis set      | Subject analysis set       | Subject analysis set       | Subject analysis set        |
| Number of subjects analysed      | 1009                      | 177 <sup>[31]</sup>        | 34 <sup>[32]</sup>         | 121 <sup>[33]</sup>         |
| Units: Months                    |                           |                            |                            |                             |
| median (confidence interval 95%) | 66.56 (61.90<br>to 73.49) | 63.57 (47.57<br>to 999999) | 55.56 (41.49<br>to 999999) | 999999 (49.84<br>to 999999) |

Notes:

[31] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

[32] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

[33] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

| End point values                 | Africa                    | Other<br>(Australia)        |  |  |
|----------------------------------|---------------------------|-----------------------------|--|--|
| Subject group type               | Subject analysis set      | Subject analysis set        |  |  |
| Number of subjects analysed      | 71                        | 24 <sup>[34]</sup>          |  |  |
| Units: Months                    |                           |                             |  |  |
| median (confidence interval 95%) | 53.22 (33.35<br>to 63.87) | 999999 (44.16<br>to 999999) |  |  |

Notes:

[34] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by Age ( $\leq 65$ vs. $> 65$ Years): Overall Survival

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Age ( $\leq 65$ vs. $> 65$ Years): Overall Survival |
|-----------------|--------------------------------------------------------------------------|

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Age $\leq 65$ Years    | Age $> 65$ Years       |  |  |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set   |  |  |
| Number of subjects analysed      | 1167                   | 269                    |  |  |
| Units: Months                    |                        |                        |  |  |
| median (confidence interval 95%) | 70.01 (64.33 to 81.08) | 50.10 (41.26 to 53.98) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by ECOG Performance Status at Baseline: Overall Survival

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Subgroup Analysis by ECOG Performance Status at Baseline: Overall Survival |
|-----------------|----------------------------------------------------------------------------|

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was

| End point values                 | ECOG Performance Status 0 or 1 | ECOG Performance Status 2 |  |  |
|----------------------------------|--------------------------------|---------------------------|--|--|
| Subject group type               | Subject analysis set           | Subject analysis set      |  |  |
| Number of subjects analysed      | 1371                           | 63                        |  |  |
| Units: Months                    |                                |                           |  |  |
| median (confidence interval 95%) | 67.25 (63.44 to 76.52)         | 31.15 (20.50 to 39.13)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by Taxane Chemotherapy: Overall Survival

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | Subgroup Analysis by Taxane Chemotherapy: Overall Survival |
|-----------------|------------------------------------------------------------|

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Docetaxel              | Paclitaxel             | Nab-Paclitaxel          |  |
|----------------------------------|------------------------|------------------------|-------------------------|--|
| Subject group type               | Subject analysis set   | Subject analysis set   | Subject analysis set    |  |
| Number of subjects analysed      | 775                    | 588                    | 65 <sup>[35]</sup>      |  |
| Units: Months                    |                        |                        |                         |  |
| median (confidence interval 95%) | 66.53 (61.67 to 77.27) | 64.03 (56.61 to 72.25) | 70.87 (39.69 to 999999) |  |

Notes:

[35] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by Visceral Disease at Baseline: Overall Survival

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Subgroup Analysis by Visceral Disease at Baseline: Overall Survival |
|-----------------|---------------------------------------------------------------------|

**End point description:**

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Visceral Disease       | Non-Visceral Disease    |  |  |
|----------------------------------|------------------------|-------------------------|--|--|
| Subject group type               | Subject analysis set   | Subject analysis set    |  |  |
| Number of subjects analysed      | 992                    | 444 <sup>[36]</sup>     |  |  |
| Units: Months                    |                        |                         |  |  |
| median (confidence interval 95%) | 57.10 (52.40 to 63.44) | 81.08 (71.66 to 999999) |  |  |

**Notes:**

[36] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overall Survival**

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Prior (Neo)Adjuvant Chemotherapy: Overall Survival |
|-----------------|-------------------------------------------------------------------------|

**End point description:**

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Prior (Neo)Adjuvant Chemotherapy | No Prior (Neo)Adjuvant Chemotherapy |  |  |
|----------------------------------|----------------------------------|-------------------------------------|--|--|
| Subject group type               | Subject analysis set             | Subject analysis set                |  |  |
| Number of subjects analysed      | 786                              | 650 <sup>[37]</sup>                 |  |  |
| Units: Months                    |                                  |                                     |  |  |
| median (confidence interval 95%) | 57.10 (51.06 to 62.82)           | 79.80 (71.79 to 999999)             |  |  |

Notes:

[37] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by Hormone Receptor Status at Baseline: Overall Survival

|                 |                                                                            |
|-----------------|----------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Hormone Receptor Status at Baseline: Overall Survival |
|-----------------|----------------------------------------------------------------------------|

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Hormone Receptor Positive | Hormone Receptor Negative | Hormone Receptor Status Unknown |  |
|----------------------------------|---------------------------|---------------------------|---------------------------------|--|
| Subject group type               | Subject analysis set      | Subject analysis set      | Subject analysis set            |  |
| Number of subjects analysed      | 918                       | 512                       | 6 <sup>[38]</sup>               |  |
| Units: Months                    |                           |                           |                                 |  |
| median (confidence interval 95%) | 66.66 (62.39 to 77.27)    | 60.19 (52.34 to 67.71)    | 999999 (16.13 to 999999)        |  |

Notes:

[38] - '999999' means the median and 95% CI could not be calculated because not enough events had occurred.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by Previous Trastuzumab Therapy: Overall Survival

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Subgroup Analysis by Previous Trastuzumab Therapy: Overall Survival |
|-----------------|---------------------------------------------------------------------|

End point description:

Overall survival was defined as time from the date of enrollment until the date of death due to any cause. Overall survival was analyzed using a Kaplan-Meier approach. Participants who had not died were censored at the last date they were known to be alive. When it was not possible to confirm the full death date, partial death dates were imputed to: 01 June of that year if only the year was known, 15th of that month if only the month and year were known. If the imputed date was before the last known alive date, the last known alive date was used as the imputation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of enrollment until death due to any cause. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                 | Previous Trastuzumab Therapy | No Previous Trastuzumab Therapy |  |  |
|----------------------------------|------------------------------|---------------------------------|--|--|
| Subject group type               | Subject analysis set         | Subject analysis set            |  |  |
| Number of subjects analysed      | 400                          | 1036 <sup>[39]</sup>            |  |  |
| Units: Months                    |                              |                                 |  |  |
| median (confidence interval 95%) | 54.08 (48.66 to 60.75)       | 73.50 (65.61 to 999999)         |  |  |

Notes:

[39] - '999999' means the 95% CI could not be calculated because not enough events had occurred.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The overall response rate was defined as the percentage of participants with complete response (CR) or partial response (PR) as their best confirmed response ( $\geq 4$  weeks later), as assessed by the investigator using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to  $< 10$  millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Participants without post-baseline tumor assessments were considered non-responders.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                  | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type                | Reporting group                   |  |  |  |
| Number of subjects analysed       | 1198                              |  |  |  |
| Units: Percentage of participants |                                   |  |  |  |
| number (confidence interval 95%)  | 79.5 (77.07 to 81.72)             |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants by Best Overall Response as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants by Best Overall Response as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|-------------------------------------------------------------------------------------------------------|

End point description:

Best overall response (BOR) was defined as the best response recorded from the first dose of study treatment until disease progression/recurrence or death in the absence of disease progression. The hierarchy used to determine BOR: Complete Response (CR)>Partial Response (PR)>Stable Disease (SD)>Progressive Disease (PD)>Not Evaluable. Note that CR or PR was confirmed  $\geq 4$  weeks later. RECIST v1.1 responses are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to  $< 10$  millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum.; PD = At least 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study, and absolute increase of  $\geq 5$  mm.; SD = Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

|                                   |                                   |  |  |  |
|-----------------------------------|-----------------------------------|--|--|--|
| <b>End point values</b>           | Pertuzumab + Trastuzumab + Taxane |  |  |  |
| Subject group type                | Reporting group                   |  |  |  |
| Number of subjects analysed       | 1198 <sup>[40]</sup>              |  |  |  |
| Units: Percentage of participants |                                   |  |  |  |
| number (not applicable)           |                                   |  |  |  |
| Complete Response (Confirmed)     | 14.6                              |  |  |  |
| Partial Response (Confirmed)      | 64.9                              |  |  |  |
| Stable Disease                    | 15.3                              |  |  |  |
| Progressive Disease               | 4.2                               |  |  |  |
| Not Evaluable                     | 1.1                               |  |  |  |

Notes:

[40] - Only includes subjects with measurable disease at baseline.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Subgroup Analysis by Age ( $\leq 65$ vs. $> 65$ Years): Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Age ( $\leq 65$ vs. $> 65$ Years): Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The overall response rate was defined as the percentage of participants with complete response (CR) or partial response (PR) as their best confirmed response ( $\geq 4$  weeks later), as assessed by the investigator

using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Participants without post-baseline tumor assessments were considered non-responders.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                  | Age ≤65 Years         | Age >65 Years         |  |  |
|-----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                | Subject analysis set  | Subject analysis set  |  |  |
| Number of subjects analysed       | 968 <sup>[41]</sup>   | 230 <sup>[42]</sup>   |  |  |
| Units: Percentage of participants |                       |                       |  |  |
| number (confidence interval 95%)  | 81.7 (79.13 to 84.10) | 70.0 (63.63 to 75.85) |  |  |

Notes:

[41] - Only includes subjects with measurable disease at baseline.

[42] - Only includes subjects with measurable disease at baseline.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Subgroup Analysis by Taxane Chemotherapy: Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Subgroup Analysis by Taxane Chemotherapy: Overall Response Rate (Complete Response or Partial Response) Based on Best Overall Response (Confirmed) as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The overall response rate was defined as the percentage of participants with complete response (CR) or partial response (PR) as their best confirmed response (≥4 weeks later), as assessed by the investigator using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Participants without post-baseline tumor assessments were considered non-responders.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression or death. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                  | Docetaxel             | Paclitaxel            | Nab-Paclitaxel        |  |
|-----------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set  |  |
| Number of subjects analysed       | 657 <sup>[43]</sup>   | 481 <sup>[44]</sup>   | 53 <sup>[45]</sup>    |  |
| Units: Percentage of participants |                       |                       |                       |  |
| number (confidence interval 95%)  | 78.4 (75.04 to 81.48) | 82.1 (78.40 to 85.44) | 77.4 (63.79 to 87.72) |  |

Notes:

[43] - Only includes subjects with measurable disease at baseline and those who had received any taxane.

[44] - Only includes subjects with measurable disease at baseline and those who had received any taxane.

[45] - Only includes subjects with measurable disease at baseline and those who had received any taxane.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Benefit Rate (CR or PR, or SD for at Least 6 Months) Based on Best Overall Response as Assessed by the Investigator Using RECIST v.1.1

|                 |                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Clinical Benefit Rate (CR or PR, or SD for at Least 6 Months) Based on Best Overall Response as Assessed by the Investigator Using RECIST v.1.1 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The clinical benefit rate was defined as the percentage of participants whose best confirmed response ( $\geq 4$  weeks later) was a complete response (CR) or partial response (PR), or stable disease (SD) that lasted at least 6 months, as assessed by the investigator using RECIST v1.1 from the start of study treatment until disease progression/recurrence or death. Clinical benefit responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to  $< 10$  millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.; SD = Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD; at least 20% increase in sum of diameters of target lesions and absolute increase of  $\geq 5$  mm), taking as reference the smallest sum diameters while on study.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter, until disease progression. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

| End point values                  | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|-----------------------------------|-----------------------------------|--|--|--|
| Subject group type                | Reporting group                   |  |  |  |
| Number of subjects analysed       | 1198 <sup>[46]</sup>              |  |  |  |
| Units: Percentage of participants |                                   |  |  |  |
| number (confidence interval 95%)  | 86.2 (84.14 to 88.13)             |  |  |  |

Notes:

[46] - Only includes subjects with measurable disease at baseline.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Duration of Response as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|------------------------------------------------------------------------|

### End point description:

Duration of response (DOR) was defined as the time from when a confirmed best overall response of complete response (CR) or partial response (PR) was first documented to first documented disease progression or death from any cause (whichever occurred first). DOR was analyzed using a Kaplan-Meier approach. Participants who had not progressed or died after having had a confirmed response were censored at the date of their last tumor measurement. Response was assessed every 3 cycles (1 cycle is 3 weeks) up to 36 months, and at least every 12 cycles thereafter until event occurrence or end of study. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

### End point timeframe:

From date of first confirmed response (CR or PR) to first documented disease progression or death from any cause, whichever occurred first. The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

|                                  |                                         |  |  |  |
|----------------------------------|-----------------------------------------|--|--|--|
| <b>End point values</b>          | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 952 <sup>[47]</sup>                     |  |  |  |
| Units: Months                    |                                         |  |  |  |
| median (confidence interval 95%) | 20.01 (18.20<br>to 22.21)               |  |  |  |

### Notes:

[47] - Only includes subjects with measurable disease at baseline and a documented confirmed response.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response for Participants with Best Overall Response of Complete Response or Partial Response, as Assessed by the Investigator Using RECIST v1.1

|                 |                                                                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to Response for Participants with Best Overall Response of Complete Response or Partial Response, as Assessed by the Investigator Using RECIST v1.1 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

Time to response (TTR) was defined as the time from the first study treatment administration to the date of first confirmed response (CR or PR). TTR was analyzed using a Kaplan-Meier approach. Participants who did not have CR or PR were censored at the date of their last evaluable tumor assessment. Participants for whom no post-baseline tumor assessments were available were censored at Day 1. Responses according to RECIST v1.1 are defined as follows: CR = Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 millimetres (mm).; PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

### End point timeframe:

From date of first study treatment until date of first confirmed response (CR or PR). The median (full range) duration of follow-up was 68.73 (0.03-87.29) months.

|                                  |                                         |  |  |  |
|----------------------------------|-----------------------------------------|--|--|--|
| <b>End point values</b>          | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
| Subject group type               | Reporting group                         |  |  |  |
| Number of subjects analysed      | 1198                                    |  |  |  |
| Units: Months                    |                                         |  |  |  |
| median (confidence interval 95%) | 2.464 (2.398<br>to 2.497)               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) Questionnaire Total Score Over the Course of the Study

|                 |                                                                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in Functional Assessment of Cancer Therapy - Breast Cancer (FACT-B) Questionnaire Total Score Over the Course of the Study |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. Participants were given a series of statements in each subscale and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B total score, ranging from 0 to 148, was the sum of the scores for each subscale, provided that at least 80% of the items had been answered; a higher score indicated a better quality of life. If any of the 5 subscale scores were missing, the total score was also set to missing. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

|                                                   |                                         |  |  |  |
|---------------------------------------------------|-----------------------------------------|--|--|--|
| <b>End point values</b>                           | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
| Subject group type                                | Reporting group                         |  |  |  |
| Number of subjects analysed                       | 1429                                    |  |  |  |
| Units: Score on a scale                           |                                         |  |  |  |
| arithmetic mean (standard deviation)              |                                         |  |  |  |
| Baseline (BL): Absolute Value at Visit (n = 1306) | 99.87 (±<br>20.548)                     |  |  |  |
| Change from BL at Cycle 3 (n = 1158)              | 0.40 (±<br>15.526)                      |  |  |  |
| Change from BL at Cycle 6 (n = 1089)              | -1.93 (±<br>17.611)                     |  |  |  |
| Change from BL at Cycle 9 (n = 1006)              | 0.87 (±<br>17.211)                      |  |  |  |

|                                      |                  |  |  |  |
|--------------------------------------|------------------|--|--|--|
| Change from BL at Cycle 12 (n = 891) | 3.03 (± 17.426)  |  |  |  |
| Change from BL at Cycle 15 (n = 794) | 3.33 (± 18.764)  |  |  |  |
| Change from BL at Cycle 18 (n = 718) | 3.80 (± 18.689)  |  |  |  |
| Change from BL at Cycle 21 (n = 615) | 4.06 (± 18.175)  |  |  |  |
| Change from BL at Cycle 24 (n = 570) | 3.59 (± 19.570)  |  |  |  |
| Change from BL at Cycle 27 (n = 512) | 3.14 (± 20.311)  |  |  |  |
| Change from BL at Cycle 30 (n = 515) | 3.75 (± 18.877)  |  |  |  |
| Change from BL at Cycle 33 (n = 468) | 3.58 (± 20.586)  |  |  |  |
| Change from BL at Cycle 36 (n = 427) | 3.16 (± 18.838)  |  |  |  |
| Change from BL at Cycle 39 (n = 419) | 1.66 (± 19.791)  |  |  |  |
| Change from BL at Cycle 42 (n = 385) | 2.08 (± 20.658)  |  |  |  |
| Change from BL at Cycle 45 (n = 361) | 2.22 (± 20.811)  |  |  |  |
| Change from BL at Cycle 48 (n = 340) | 1.51 (± 21.268)  |  |  |  |
| Change from BL at Cycle 51 (n = 308) | 1.95 (± 20.221)  |  |  |  |
| Change from BL at Cycle 54 (n = 282) | 0.52 (± 20.784)  |  |  |  |
| Change from BL at Cycle 57 (n = 286) | 0.54 (± 20.014)  |  |  |  |
| Change from BL at Cycle 60 (n = 262) | 0.20 (± 21.207)  |  |  |  |
| Change from BL at Cycle 63 (n = 268) | 0.61 (± 21.475)  |  |  |  |
| Change from BL at Cycle 66 (n = 241) | 0.44 (± 20.633)  |  |  |  |
| Change from BL at Cycle 69 (n = 236) | -0.75 (± 21.419) |  |  |  |
| Change from BL at Cycle 72 (n = 219) | -1.16 (± 21.951) |  |  |  |
| Change from BL at Cycle 75 (n = 213) | -1.14 (± 21.132) |  |  |  |
| Change from BL at Cycle 78 (n = 207) | 0.11 (± 20.807)  |  |  |  |
| Change from BL at Cycle 81 (n = 192) | -1.03 (± 20.526) |  |  |  |
| Change from BL at Cycle 84 (n = 181) | -1.67 (± 21.030) |  |  |  |
| Change from BL at Cycle 87 (n = 174) | 0.62 (± 21.183)  |  |  |  |
| Change from BL at Cycle 90 (n = 147) | 0.00 (± 22.289)  |  |  |  |
| Change from BL at Cycle 93 (n = 129) | 0.99 (± 21.474)  |  |  |  |
| Change from BL at Cycle 96 (n = 106) | 2.36 (± 21.636)  |  |  |  |
| Change from BL at Cycle 99 (n = 85)  | 1.36 (± 23.195)  |  |  |  |
| Change from BL at Cycle 102 (n = 69) | 1.20 (± 21.262)  |  |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| Change from BL at Cycle 105 (n = 55)            | 3.13 (± 20.385)  |  |  |  |
| Change from BL at Cycle 108 (n = 44)            | 2.22 (± 23.617)  |  |  |  |
| Change from BL at Cycle 111 (n = 36)            | -0.48 (± 22.585) |  |  |  |
| Change from BL at Cycle 114 (n = 19)            | -4.42 (± 22.323) |  |  |  |
| Change from BL at Cycle 117 (n = 11)            | -4.96 (± 16.232) |  |  |  |
| Change from BL at Cycle 120 (n = 4)             | -8.64 (± 13.187) |  |  |  |
| Change from BL at Cycle 123 (n = 2)             | -20.94 (± 2.357) |  |  |  |
| Change from BL at End of Treatment (n = 454)    | -1.06 (± 19.923) |  |  |  |
| Change from BL at Day 28 of Follow-Up (n = 568) | -1.96 (± 21.201) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in FACT-B Questionnaire Physical Well-Being Subscale Score Over the Course of the Study

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in FACT-B Questionnaire Physical Well-Being Subscale Score Over the Course of the Study |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the physical well-being subscale, participants were given a series of 7 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B physical well-being subscale score, ranging from 0 to 28, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

| End point values                                  | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|---------------------------------------------------|-----------------------------------|--|--|--|
| Subject group type                                | Reporting group                   |  |  |  |
| Number of subjects analysed                       | 1429                              |  |  |  |
| Units: Score on a scale                           |                                   |  |  |  |
| arithmetic mean (standard deviation)              |                                   |  |  |  |
| Baseline (BL): Absolute Value at Visit (n = 1331) | 20.98 (± 6.044)                   |  |  |  |
| Change from BL at Cycle 3 (n = 1193)              | -1.13 (± 5.557)                   |  |  |  |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 6 (n = 1127) | -1.61 (± 5.994) |  |  |  |
| Change from BL at Cycle 9 (n = 1033) | -0.31 (± 5.604) |  |  |  |
| Change from BL at Cycle 12 (n = 919) | 0.51 (± 5.599)  |  |  |  |
| Change from BL at Cycle 15 (n = 816) | 0.51 (± 5.652)  |  |  |  |
| Change from BL at Cycle 18 (n = 734) | 0.69 (± 5.543)  |  |  |  |
| Change from BL at Cycle 21 (n = 631) | 0.73 (± 5.616)  |  |  |  |
| Change from BL at Cycle 24 (n = 581) | 0.61 (± 5.690)  |  |  |  |
| Change from BL at Cycle 27 (n = 526) | 0.47 (± 5.761)  |  |  |  |
| Change from BL at Cycle 30 (n = 523) | 0.71 (± 5.584)  |  |  |  |
| Change from BL at Cycle 33 (n = 483) | 0.56 (± 5.894)  |  |  |  |
| Change from BL at Cycle 36 (n = 437) | 0.39 (± 5.512)  |  |  |  |
| Change from BL at Cycle 39 (n = 429) | -0.04 (± 5.647) |  |  |  |
| Change from BL at Cycle 42 (n = 396) | 0.22 (± 5.604)  |  |  |  |
| Change from BL at Cycle 45 (n = 370) | 0.09 (± 5.698)  |  |  |  |
| Change from BL at Cycle 48 (n = 346) | 0.11 (± 5.564)  |  |  |  |
| Change from BL at Cycle 51 (n = 319) | 0.22 (± 5.280)  |  |  |  |
| Change from BL at Cycle 54 (n = 292) | -0.26 (± 5.765) |  |  |  |
| Change from BL at Cycle 57 (n = 296) | -0.35 (± 5.695) |  |  |  |
| Change from BL at Cycle 60 (n = 269) | -0.10 (± 5.630) |  |  |  |
| Change from BL at Cycle 63 (n = 275) | -0.20 (± 5.696) |  |  |  |
| Change from BL at Cycle 66 (n = 246) | 0.29 (± 5.338)  |  |  |  |
| Change from BL at Cycle 69 (n = 243) | -0.60 (± 5.579) |  |  |  |
| Change from BL at Cycle 72 (n = 224) | -0.35 (± 5.494) |  |  |  |
| Change from BL at Cycle 75 (n = 218) | -0.72 (± 5.507) |  |  |  |
| Change from BL at Cycle 78 (n = 213) | -0.44 (± 5.379) |  |  |  |
| Change from BL at Cycle 81 (n = 197) | -0.65 (± 5.029) |  |  |  |
| Change from BL at Cycle 84 (n = 186) | -0.81 (± 5.249) |  |  |  |
| Change from BL at Cycle 87 (n = 181) | -0.36 (± 5.391) |  |  |  |
| Change from BL at Cycle 90 (n = 153) | -0.66 (± 5.332) |  |  |  |
| Change from BL at Cycle 93 (n = 134) | -0.42 (± 5.788) |  |  |  |
| Change from BL at Cycle 96 (n = 110) | -0.28 (± 5.178) |  |  |  |
| Change from BL at Cycle 99 (n = 88)  | -0.21 (± 5.474) |  |  |  |
| Change from BL at Cycle 102 (n = 72) | -0.80 (± 5.269) |  |  |  |
| Change from BL at Cycle 105 (n = 57) | -0.07 (± 5.133) |  |  |  |
| Change from BL at Cycle 108 (n = 45) | 0.07 (± 5.775)  |  |  |  |
| Change from BL at Cycle 111 (n = 37) | 0.38 (± 5.309)  |  |  |  |
| Change from BL at Cycle 114 (n = 20) | -1.70 (± 4.950) |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 117 (n = 12)            | -1.83 (± 3.474) |  |  |  |
| Change from BL at Cycle 120 (n = 4)             | -2.38 (± 3.092) |  |  |  |
| Change from BL at Cycle 123 (n = 2)             | -5.58 (± 2.946) |  |  |  |
| Change from BL at End of Treatment (n = 465)    | -0.73 (± 6.366) |  |  |  |
| Change from BL at Day 28 of Follow-Up (n = 583) | -0.95 (± 6.393) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in FACT-B Questionnaire Social Well-Being Subscale Score Over the Course of the Study

|                 |                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in FACT-B Questionnaire Social Well-Being Subscale Score Over the Course of the Study |
|-----------------|------------------------------------------------------------------------------------------------------------|

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the social well-being subscale, participants were given a series of 7 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B social well-being subscale score, ranging from 0 to 28, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

| End point values                                  | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|---------------------------------------------------|-----------------------------------|--|--|--|
| Subject group type                                | Reporting group                   |  |  |  |
| Number of subjects analysed                       | 1429                              |  |  |  |
| Units: Score on a scale                           |                                   |  |  |  |
| arithmetic mean (standard deviation)              |                                   |  |  |  |
| Baseline (BL): Absolute Value at Visit (n = 1329) | 22.24 (± 4.993)                   |  |  |  |
| Change from BL at Cycle 3 (n = 1189)              | -0.41 (± 4.145)                   |  |  |  |
| Change from BL at Cycle 6 (n = 1118)              | -1.09 (± 4.320)                   |  |  |  |
| Change from BL at Cycle 9 (n = 1032)              | -1.02 (± 4.728)                   |  |  |  |
| Change from BL at Cycle 12 (n = 921)              | -1.19 (± 4.846)                   |  |  |  |
| Change from BL at Cycle 15 (n = 812)              | -1.28 (± 4.949)                   |  |  |  |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 18 (n = 733) | -1.19 (± 4.986) |  |  |  |
| Change from BL at Cycle 21 (n = 630) | -1.24 (± 4.881) |  |  |  |
| Change from BL at Cycle 24 (n = 580) | -1.26 (± 4.856) |  |  |  |
| Change from BL at Cycle 27 (n = 525) | -1.48 (± 4.994) |  |  |  |
| Change from BL at Cycle 30 (n = 523) | -1.18 (± 5.107) |  |  |  |
| Change from BL at Cycle 33 (n = 482) | -1.45 (± 4.852) |  |  |  |
| Change from BL at Cycle 36 (n = 437) | -1.54 (± 4.953) |  |  |  |
| Change from BL at Cycle 39 (n = 430) | -1.77 (± 5.066) |  |  |  |
| Change from BL at Cycle 42 (n = 394) | -1.73 (± 5.154) |  |  |  |
| Change from BL at Cycle 45 (n = 370) | -1.50 (± 5.238) |  |  |  |
| Change from BL at Cycle 48 (n = 345) | -1.84 (± 5.475) |  |  |  |
| Change from BL at Cycle 51 (n = 318) | -2.01 (± 5.657) |  |  |  |
| Change from BL at Cycle 54 (n = 293) | -1.77 (± 5.236) |  |  |  |
| Change from BL at Cycle 57 (n = 297) | -1.88 (± 5.117) |  |  |  |
| Change from BL at Cycle 60 (n = 270) | -2.01 (± 5.528) |  |  |  |
| Change from BL at Cycle 63 (n = 277) | -2.18 (± 5.278) |  |  |  |
| Change from BL at Cycle 66 (n = 246) | -2.19 (± 5.586) |  |  |  |
| Change from BL at Cycle 69 (n = 243) | -2.24 (± 5.434) |  |  |  |
| Change from BL at Cycle 72 (n = 224) | -2.49 (± 5.846) |  |  |  |
| Change from BL at Cycle 75 (n = 219) | -2.40 (± 5.777) |  |  |  |
| Change from BL at Cycle 78 (n = 213) | -2.33 (± 5.676) |  |  |  |
| Change from BL at Cycle 81 (n = 197) | -2.53 (± 5.609) |  |  |  |
| Change from BL at Cycle 84 (n = 187) | -2.96 (± 5.624) |  |  |  |
| Change from BL at Cycle 87 (n = 181) | -2.29 (± 5.487) |  |  |  |
| Change from BL at Cycle 90 (n = 152) | -2.38 (± 5.355) |  |  |  |
| Change from BL at Cycle 93 (n = 134) | -1.97 (± 5.102) |  |  |  |
| Change from BL at Cycle 96 (n = 110) | -1.94 (± 4.831) |  |  |  |
| Change from BL at Cycle 99 (n = 89)  | -2.07 (± 5.316) |  |  |  |
| Change from BL at Cycle 102 (n = 73) | -1.70 (± 4.258) |  |  |  |
| Change from BL at Cycle 105 (n = 58) | -1.76 (± 4.074) |  |  |  |
| Change from BL at Cycle 108 (n = 46) | -1.75 (± 3.387) |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 111 (n = 38)            | -1.94 (± 3.663) |  |  |  |
| Change from BL at Cycle 114 (n = 20)            | -2.31 (± 3.386) |  |  |  |
| Change from BL at Cycle 117 (n = 12)            | -1.83 (± 3.600) |  |  |  |
| Change from BL at Cycle 120 (n = 4)             | -2.85 (± 5.485) |  |  |  |
| Change from BL at Cycle 123 (n = 2)             | -1.92 (± 2.946) |  |  |  |
| Change from BL at End of Treatment (n = 461)    | -1.29 (± 4.911) |  |  |  |
| Change from BL at Day 28 of Follow-Up (n = 581) | -1.61 (± 5.080) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in FACT-B Questionnaire Emotional Well-Being Subscale Score Over the Course of the Study

|                 |                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in FACT-B Questionnaire Emotional Well-Being Subscale Score Over the Course of the Study |
|-----------------|---------------------------------------------------------------------------------------------------------------|

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the emotional well-being subscale, participants were given a series of 6 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B emotional well-being subscale score, ranging from 0 to 24, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

| End point values                                  | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|---------------------------------------------------|-----------------------------------|--|--|--|
| Subject group type                                | Reporting group                   |  |  |  |
| Number of subjects analysed                       | 1429                              |  |  |  |
| Units: Score on a scale                           |                                   |  |  |  |
| arithmetic mean (standard deviation)              |                                   |  |  |  |
| Baseline (BL): Absolute Value at Visit (n = 1333) | 15.08 (± 4.990)                   |  |  |  |
| Change from BL at Cycle 3 (n = 1194)              | 1.69 (± 4.219)                    |  |  |  |
| Change from BL at Cycle 6 (n = 1124)              | 1.53 (± 4.526)                    |  |  |  |
| Change from BL at Cycle 9 (n = 1032)              | 1.64 (± 4.624)                    |  |  |  |
| Change from BL at Cycle 12 (n = 916)              | 2.02 (± 4.686)                    |  |  |  |
| Change from BL at Cycle 15 (n = 811)              | 1.98 (± 4.778)                    |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 18 (n = 731)            | 2.03 (± 4.861)  |  |  |  |
| Change from BL at Cycle 21 (n = 628)            | 2.17 (± 4.877)  |  |  |  |
| Change from BL at Cycle 24 (n = 581)            | 2.19 (± 5.040)  |  |  |  |
| Change from BL at Cycle 27 (n = 523)            | 2.21 (± 5.171)  |  |  |  |
| Change from BL at Cycle 30 (n = 523)            | 2.17 (± 4.763)  |  |  |  |
| Change from BL at Cycle 33 (n = 478)            | 2.21 (± 5.275)  |  |  |  |
| Change from BL at Cycle 36 (n = 435)            | 2.32 (± 5.130)  |  |  |  |
| Change from BL at Cycle 39 (n = 430)            | 1.99 (± 5.115)  |  |  |  |
| Change from BL at Cycle 42 (n = 394)            | 1.96 (± 5.451)  |  |  |  |
| Change from BL at Cycle 45 (n = 367)            | 2.25 (± 5.367)  |  |  |  |
| Change from BL at Cycle 48 (n = 343)            | 1.82 (± 5.414)  |  |  |  |
| Change from BL at Cycle 51 (n = 317)            | 2.32 (± 5.311)  |  |  |  |
| Change from BL at Cycle 54 (n = 288)            | 1.84 (± 5.325)  |  |  |  |
| Change from BL at Cycle 57 (n = 293)            | 1.80 (± 5.256)  |  |  |  |
| Change from BL at Cycle 60 (n = 268)            | 1.59 (± 5.462)  |  |  |  |
| Change from BL at Cycle 63 (n = 274)            | 1.70 (± 5.336)  |  |  |  |
| Change from BL at Cycle 66 (n = 246)            | 1.52 (± 5.074)  |  |  |  |
| Change from BL at Cycle 69 (n = 243)            | 1.83 (± 5.351)  |  |  |  |
| Change from BL at Cycle 72 (n = 223)            | 1.56 (± 5.421)  |  |  |  |
| Change from BL at Cycle 75 (n = 217)            | 1.58 (± 5.308)  |  |  |  |
| Change from BL at Cycle 78 (n = 210)            | 1.72 (± 5.463)  |  |  |  |
| Change from BL at Cycle 81 (n = 196)            | 2.01 (± 5.750)  |  |  |  |
| Change from BL at Cycle 84 (n = 185)            | 2.06 (± 5.384)  |  |  |  |
| Change from BL at Cycle 87 (n = 180)            | 1.97 (± 5.558)  |  |  |  |
| Change from BL at Cycle 90 (n = 151)            | 2.08 (± 5.686)  |  |  |  |
| Change from BL at Cycle 93 (n = 134)            | 2.17 (± 5.388)  |  |  |  |
| Change from BL at Cycle 96 (n = 109)            | 2.40 (± 5.769)  |  |  |  |
| Change from BL at Cycle 99 (n = 88)             | 2.30 (± 6.041)  |  |  |  |
| Change from BL at Cycle 102 (n = 71)            | 2.07 (± 5.949)  |  |  |  |
| Change from BL at Cycle 105 (n = 58)            | 2.58 (± 5.902)  |  |  |  |
| Change from BL at Cycle 108 (n = 46)            | 2.34 (± 6.721)  |  |  |  |
| Change from BL at Cycle 111 (n = 38)            | 1.19 (± 7.241)  |  |  |  |
| Change from BL at Cycle 114 (n = 20)            | 1.55 (± 7.944)  |  |  |  |
| Change from BL at Cycle 117 (n = 12)            | 1.33 (± 4.185)  |  |  |  |
| Change from BL at Cycle 120 (n = 4)             | 0.75 (± 2.217)  |  |  |  |
| Change from BL at Cycle 123 (n = 2)             | -0.50 (± 2.121) |  |  |  |
| Change from BL at End of Treatment (n = 465)    | 0.30 (± 5.001)  |  |  |  |
| Change from BL at Day 28 of Follow-Up (n = 585) | 0.37 (± 5.193)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in FACT-B Questionnaire Functional Well-Being Subscale Score Over the Course of the Study

|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in FACT-B Questionnaire Functional Well-Being Subscale Score Over the Course of the Study |
|-----------------|----------------------------------------------------------------------------------------------------------------|

# End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the functional well-being subscale, participants were given a series of 7 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B functional well-being subscale score, ranging from 0 to 28, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

# End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

| End point values                                  | Pertuzumab + Trastuzumab + Taxane |  |  |  |
|---------------------------------------------------|-----------------------------------|--|--|--|
| Subject group type                                | Reporting group                   |  |  |  |
| Number of subjects analysed                       | 1429                              |  |  |  |
| Units: Score on a scale                           |                                   |  |  |  |
| arithmetic mean (standard deviation)              |                                   |  |  |  |
| Baseline (BL): Absolute Value at Visit (n = 1335) | 16.65 (± 6.096)                   |  |  |  |
| Change from BL at Cycle 3 (n = 1192)              | -0.47 (± 4.961)                   |  |  |  |
| Change from BL at Cycle 6 (n = 1125)              | -0.79 (± 5.437)                   |  |  |  |
| Change from BL at Cycle 9 (n = 1032)              | -0.11 (± 5.572)                   |  |  |  |
| Change from BL at Cycle 12 (n = 915)              | 0.46 (± 5.577)                    |  |  |  |
| Change from BL at Cycle 15 (n = 814)              | 0.78 (± 5.758)                    |  |  |  |
| Change from BL at Cycle 18 (n = 732)              | 0.83 (± 5.797)                    |  |  |  |
| Change from BL at Cycle 21 (n = 629)              | 0.89 (± 5.804)                    |  |  |  |
| Change from BL at Cycle 24 (n = 583)              | 0.53 (± 5.903)                    |  |  |  |
| Change from BL at Cycle 27 (n = 523)              | 0.71 (± 6.064)                    |  |  |  |
| Change from BL at Cycle 30 (n = 524)              | 0.60 (± 5.961)                    |  |  |  |
| Change from BL at Cycle 33 (n = 478)              | 0.67 (± 6.209)                    |  |  |  |
| Change from BL at Cycle 36 (n = 436)              | 0.52 (± 5.687)                    |  |  |  |
| Change from BL at Cycle 39 (n = 430)              | 0.26 (± 5.927)                    |  |  |  |
| Change from BL at Cycle 42 (n = 393)              | 0.31 (± 6.038)                    |  |  |  |
| Change from BL at Cycle 45 (n = 368)              | 0.34 (± 6.049)                    |  |  |  |
| Change from BL at Cycle 48 (n = 344)              | 0.28 (± 6.227)                    |  |  |  |
| Change from BL at Cycle 51 (n = 319)              | 0.23 (± 5.931)                    |  |  |  |
| Change from BL at Cycle 54 (n = 289)              | -0.06 (± 6.090)                   |  |  |  |
| Change from BL at Cycle 57 (n = 294)              | 0.21 (± 5.925)                    |  |  |  |
| Change from BL at Cycle 60 (n = 268)              | 0.01 (± 6.100)                    |  |  |  |
| Change from BL at Cycle 63 (n = 275)              | -0.06 (± 6.178)                   |  |  |  |
| Change from BL at Cycle 66 (n = 247)              | -0.07 (± 6.264)                   |  |  |  |
| Change from BL at Cycle 69 (n = 243)              | -0.47 (± 6.476)                   |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 72 (n = 224)            | -0.50 (± 6.378) |  |  |  |
| Change from BL at Cycle 75 (n = 217)            | -0.40 (± 6.391) |  |  |  |
| Change from BL at Cycle 78 (n = 211)            | -0.18 (± 6.197) |  |  |  |
| Change from BL at Cycle 81 (n = 197)            | -0.29 (± 6.046) |  |  |  |
| Change from BL at Cycle 84 (n = 186)            | -0.48 (± 6.022) |  |  |  |
| Change from BL at Cycle 87 (n = 180)            | -0.08 (± 6.250) |  |  |  |
| Change from BL at Cycle 90 (n = 152)            | 0.16 (± 6.587)  |  |  |  |
| Change from BL at Cycle 93 (n = 135)            | 0.58 (± 6.161)  |  |  |  |
| Change from BL at Cycle 96 (n = 111)            | 1.27 (± 6.663)  |  |  |  |
| Change from BL at Cycle 99 (n = 89)             | 0.46 (± 6.651)  |  |  |  |
| Change from BL at Cycle 102 (n = 73)            | 0.96 (± 6.327)  |  |  |  |
| Change from BL at Cycle 105 (n = 59)            | 1.14 (± 5.922)  |  |  |  |
| Change from BL at Cycle 108 (n = 46)            | 1.42 (± 6.902)  |  |  |  |
| Change from BL at Cycle 111 (n = 38)            | 0.32 (± 6.507)  |  |  |  |
| Change from BL at Cycle 114 (n = 20)            | -0.25 (± 6.439) |  |  |  |
| Change from BL at Cycle 117 (n = 12)            | -0.58 (± 5.316) |  |  |  |
| Change from BL at Cycle 120 (n = 4)             | -2.00 (± 3.916) |  |  |  |
| Change from BL at Cycle 123 (n = 2)             | -5.00 (± 2.828) |  |  |  |
| Change from BL at End of Treatment (n = 463)    | -0.50 (± 6.132) |  |  |  |
| Change from BL at Day 28 of Follow-Up (n = 586) | -0.70 (± 6.558) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in FACT-B Questionnaire Breast Cancer Subscale Score Over the Course of the Study

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in FACT-B Questionnaire Breast Cancer Subscale Score Over the Course of the Study |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

The FACT-B questionnaire (version 4) was administered only to female participants to assess quality of life in five subscales: physical, social, emotional, and functional well-being, and breast cancer. For the breast cancer subscale, participants were given a series of 10 statements and were asked to rate how true each statement was for them during the past 7 days on a 5-point scale ranging from 0 (not at all) to 4 (very much). The calculated FACT-B breast cancer subscale score, ranging from 0 to 40, was the sum of the scores for each statement only if at least 50% of items had been answered; the higher the score, the better the quality of life. Baseline was defined as the last non-missing measurement taken prior to first dose of study treatment (including unscheduled assessments). Post-baseline values were summarized for planned visits only.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, every 3 cycles (1 cycle is 3 weeks) during treatment period, and 28 days post-treatment safety follow-up. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

| End point values                                  | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |  |
|---------------------------------------------------|-----------------------------------------|--|--|--|
| Subject group type                                | Reporting group                         |  |  |  |
| Number of subjects analysed                       | 1429                                    |  |  |  |
| Units: Score on a scale                           |                                         |  |  |  |
| arithmetic mean (standard deviation)              |                                         |  |  |  |
| Baseline (BL): Absolute Value at Visit (n = 1326) | 24.98 (± 6.296)                         |  |  |  |
| Change from BL at Cycle 3 (n = 1181)              | 0.48 (± 5.101)                          |  |  |  |
| Change from BL at Cycle 6 (n = 1117)              | -0.11 (± 5.759)                         |  |  |  |
| Change from BL at Cycle 9 (n = 1027)              | 0.52 (± 5.633)                          |  |  |  |
| Change from BL at Cycle 12 (n = 910)              | 0.89 (± 5.770)                          |  |  |  |
| Change from BL at Cycle 15 (n = 808)              | 1.16 (± 6.180)                          |  |  |  |
| Change from BL at Cycle 18 (n = 729)              | 1.30 (± 6.043)                          |  |  |  |
| Change from BL at Cycle 21 (n = 625)              | 1.30 (± 5.898)                          |  |  |  |
| Change from BL at Cycle 24 (n = 580)              | 1.39 (± 6.231)                          |  |  |  |
| Change from BL at Cycle 27 (n = 520)              | 1.17 (± 6.043)                          |  |  |  |
| Change from BL at Cycle 30 (n = 521)              | 1.34 (± 5.968)                          |  |  |  |
| Change from BL at Cycle 33 (n = 477)              | 1.34 (± 6.113)                          |  |  |  |
| Change from BL at Cycle 36 (n = 435)              | 1.33 (± 6.030)                          |  |  |  |
| Change from BL at Cycle 39 (n = 427)              | 1.12 (± 6.210)                          |  |  |  |
| Change from BL at Cycle 42 (n = 393)              | 1.11 (± 6.499)                          |  |  |  |
| Change from BL at Cycle 45 (n = 366)              | 1.13 (± 6.414)                          |  |  |  |
| Change from BL at Cycle 48 (n = 343)              | 1.00 (± 6.679)                          |  |  |  |
| Change from BL at Cycle 51 (n = 316)              | 0.99 (± 6.430)                          |  |  |  |
| Change from BL at Cycle 54 (n = 291)              | 0.76 (± 6.555)                          |  |  |  |
| Change from BL at Cycle 57 (n = 294)              | 0.70 (± 6.355)                          |  |  |  |
| Change from BL at Cycle 60 (n = 267)              | 0.80 (± 6.586)                          |  |  |  |
| Change from BL at Cycle 63 (n = 274)              | 1.32 (± 6.960)                          |  |  |  |
| Change from BL at Cycle 66 (n = 246)              | 0.74 (± 6.822)                          |  |  |  |
| Change from BL at Cycle 69 (n = 241)              | 0.54 (± 6.532)                          |  |  |  |
| Change from BL at Cycle 72 (n = 223)              | 0.50 (± 7.142)                          |  |  |  |
| Change from BL at Cycle 75 (n = 216)              | 0.85 (± 6.925)                          |  |  |  |
| Change from BL at Cycle 78 (n = 210)              | 1.22 (± 6.899)                          |  |  |  |
| Change from BL at Cycle 81 (n = 196)              | 0.27 (± 7.100)                          |  |  |  |
| Change from BL at Cycle 84 (n = 184)              | 0.55 (± 6.690)                          |  |  |  |
| Change from BL at Cycle 87 (n = 178)              | 1.17 (± 6.882)                          |  |  |  |
| Change from BL at Cycle 90 (n = 150)              | 0.51 (± 7.313)                          |  |  |  |
| Change from BL at Cycle 93 (n = 132)              | 0.30 (± 7.163)                          |  |  |  |
| Change from BL at Cycle 96 (n = 110)              | 0.65 (± 6.240)                          |  |  |  |
| Change from BL at Cycle 99 (n = 87)               | 1.19 (± 6.957)                          |  |  |  |
| Change from BL at Cycle 102 (n = 72)              | 0.56 (± 6.189)                          |  |  |  |
| Change from BL at Cycle 105 (n = 58)              | 0.68 (± 6.399)                          |  |  |  |
| Change from BL at Cycle 108 (n = 45)              | 0.19 (± 6.982)                          |  |  |  |
| Change from BL at Cycle 111 (n = 36)              | 0.01 (± 6.814)                          |  |  |  |
| Change from BL at Cycle 114 (n = 19)              | -1.67 (± 5.963)                         |  |  |  |

|                                                 |                 |  |  |  |
|-------------------------------------------------|-----------------|--|--|--|
| Change from BL at Cycle 117 (n = 11)            | -1.56 (± 5.842) |  |  |  |
| Change from BL at Cycle 120 (n = 4)             | -2.17 (± 6.055) |  |  |  |
| Change from BL at Cycle 123 (n = 2)             | -7.94 (± 7.307) |  |  |  |
| Change from BL at End of Treatment (n = 459)    | 0.88 (± 6.574)  |  |  |  |
| Change from BL at Day 28 of Follow-Up (n = 576) | 0.66 (± 6.477)  |  |  |  |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline until 28 days after last dose of study treatment. The median (full range) duration of exposure to any study treatment was 16.2 (0.0-86.4) months.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Pertuzumab + Trastuzumab + Taxane |
|-----------------------|-----------------------------------|

Reporting group description:

Participants received pertuzumab and trastuzumab intravenously (IV) plus taxane chemotherapy once of every 3 weeks per treatment cycle until predefined study end, unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurred first. Taxane chemotherapy was docetaxel, paclitaxel, or nab-paclitaxel, per the investigator's choice.

| Serious adverse events                                              | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |
|---------------------------------------------------------------------|-----------------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                         |  |  |
| subjects affected / exposed                                         | 535 / 1436<br>(37.26%)                  |  |  |
| number of deaths (all causes)                                       | 658                                     |  |  |
| number of deaths resulting from adverse events                      |                                         |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                         |  |  |
| Colon cancer                                                        |                                         |  |  |
| subjects affected / exposed                                         | 2 / 1436 (0.14%)                        |  |  |
| occurrences causally related to treatment / all                     | 0 / 2                                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                   |  |  |
| B-cell type acute leukemia                                          |                                         |  |  |
| subjects affected / exposed                                         | 1 / 1436 (0.07%)                        |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                   |  |  |
| Breast neoplasm                                                     |                                         |  |  |
| subjects affected / exposed                                         | 1 / 1436 (0.07%)                        |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                   |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                   |  |  |
| Bronchial carcinoma                                                 |                                         |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cancer pain                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Endometrial cancer                              |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal stromal tumour                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lentigo maligna                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lobular breast carcinoma in situ                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lung neoplasm                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metastatic squamous cell carcinoma              |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neuroendocrine tumour of the lung               |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Papillary thyroid cancer                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rectal adenocarcinoma                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal cancer                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Squamous cell carcinoma                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Thyroid cancer                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tumour embolism                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Vascular disorders                              |                  |  |  |
| Hypertensive crisis                             |                  |  |  |
| subjects affected / exposed                     | 4 / 1436 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Deep vein thrombosis                            |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematoma                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypertension                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypotension                                     |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Circulatory collapse                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Jugular vein thrombosis                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lymphoedema                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral ischaemia                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Subclavian vein thrombosis                      |                  |  |  |

|                                                      |                   |  |  |
|------------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                          | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Superior vena cava syndrome                          |                   |  |  |
| subjects affected / exposed                          | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Thrombosis                                           |                   |  |  |
| subjects affected / exposed                          | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Surgical and medical procedures                      |                   |  |  |
| Internal fixation of fracture                        |                   |  |  |
| subjects affected / exposed                          | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Pregnancy, puerperium and perinatal conditions       |                   |  |  |
| Abortion spontaneous                                 |                   |  |  |
| subjects affected / exposed                          | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all      | 1 / 2             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Abortion                                             |                   |  |  |
| subjects affected / exposed                          | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all      | 0 / 1             |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| General disorders and administration site conditions |                   |  |  |
| Pyrexia                                              |                   |  |  |
| subjects affected / exposed                          | 18 / 1436 (1.25%) |  |  |
| occurrences causally related to treatment / all      | 7 / 21            |  |  |
| deaths causally related to treatment / all           | 0 / 0             |  |  |
| Asthenia                                             |                   |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| subjects affected / exposed                     | 6 / 1436 (0.42%) |  |  |  |
| occurrences causally related to treatment / all | 4 / 6            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| General physical health deterioration           |                  |  |  |  |
| subjects affected / exposed                     | 5 / 1436 (0.35%) |  |  |  |
| occurrences causally related to treatment / all | 3 / 7            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Death                                           |                  |  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |  |
| deaths causally related to treatment / all      | 1 / 3            |  |  |  |
| Fatigue                                         |                  |  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Chills                                          |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Mucosal inflammation                            |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Catheter site inflammation                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Chest pain                                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Device related thrombosis                       |                  |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Drug intolerance                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Inflammatory pain                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Influenza like illness                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infusion site extravasation                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Malaise                                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nodule                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Systemic inflammatory response syndrome         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Immune system disorders                         |                  |  |  |
| Drug hypersensitivity                           |                  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 20 / 1436 (1.39%) |  |  |
| occurrences causally related to treatment / all | 4 / 20            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Hypersensitivity                                |                   |  |  |
| subjects affected / exposed                     | 5 / 1436 (0.35%)  |  |  |
| occurrences causally related to treatment / all | 1 / 5             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Reproductive system and breast disorders        |                   |  |  |
| Breast haematoma                                |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Ovarian cyst                                    |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Uterine prolapse                                |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Respiratory, thoracic and mediastinal disorders |                   |  |  |
| Dyspnoea                                        |                   |  |  |
| subjects affected / exposed                     | 16 / 1436 (1.11%) |  |  |
| occurrences causally related to treatment / all | 1 / 16            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pulmonary embolism                              |                   |  |  |
| subjects affected / exposed                     | 11 / 1436 (0.77%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pleural effusion                                |                   |  |  |
| subjects affected / exposed                     | 6 / 1436 (0.42%)  |  |  |
| occurrences causally related to treatment / all | 0 / 8             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| Lung disorder                                   |                  |  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pneumothorax                                    |                  |  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Asthma                                          |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pneumonitis                                     |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Respiratory failure                             |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Acute respiratory distress syndrome             |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Aspiration                                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |  |
| Chronic obstructive pulmonary disease           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Cough                                           |                  |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Interstitial lung disease                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pleuritic pain                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumothorax spontaneous                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Psychiatric disorders                           |                  |  |  |
| Agitation                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Depression                                      |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anxiety                                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anxiety disorder                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Confusional state                               |                  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Delirium                                        |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Psychiatric decompensation                      |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Psychotic disorder                              |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Product issues                                  |                   |  |  |
| Device breakage                                 |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Device loosening                                |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Investigations                                  |                   |  |  |
| Ejection fraction decreased                     |                   |  |  |
| subjects affected / exposed                     | 18 / 1436 (1.25%) |  |  |
| occurrences causally related to treatment / all | 17 / 19           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Neutrophil count decreased                      |                   |  |  |
| subjects affected / exposed                     | 11 / 1436 (0.77%) |  |  |
| occurrences causally related to treatment / all | 10 / 18           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| White blood cell count decreased                |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Blood creatinine increased                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Computerised tomogram abdomen abnormal          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gamma-glutamyltransferase increased             |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Platelet count decreased                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Weight decreased                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Injury, poisoning and procedural complications  |                  |  |  |
| Femur fracture                                  |                  |  |  |
| subjects affected / exposed                     | 8 / 1436 (0.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infusion related reaction                       |                  |  |  |
| subjects affected / exposed                     | 8 / 1436 (0.56%) |  |  |
| occurrences causally related to treatment / all | 4 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| Ankle fracture                                  |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Femoral neck fracture                           |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Hip fracture                                    |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Post procedural haemorrhage                     |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Rib fracture                                    |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Carbon monoxide poisoning                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Chemical burns of eye                           |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Fall                                            |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Foot fracture                                   |                  |  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Fractured sacrum                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Humerus fracture                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Inflammation of wound                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Injury                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Limb injury                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lower limb injury                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Multiple fractures                              |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Overdose                                        |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Radiation injury                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Radius fracture                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal fracture                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Toxicity to various agents                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ulna fracture                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Upper limb fracture                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Wound                                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac disorders                               |                  |  |  |
| Cardiac failure                                 |                  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 12 / 1436 (0.84%) |  |  |
| occurrences causally related to treatment / all | 12 / 13           |  |  |
| deaths causally related to treatment / all      | 1 / 1             |  |  |
| Atrial fibrillation                             |                   |  |  |
| subjects affected / exposed                     | 8 / 1436 (0.56%)  |  |  |
| occurrences causally related to treatment / all | 4 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Atrial thrombosis                               |                   |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Cardiac arrest                                  |                   |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 2             |  |  |
| Cardiac failure congestive                      |                   |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 1 / 1             |  |  |
| Left ventricular dysfunction                    |                   |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 2 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pericardial effusion                            |                   |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Supraventricular tachycardia                    |                   |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Acute coronary syndrome                         |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac failure chronic                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardiac tamponade                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cardio-respiratory arrest                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Cardiovascular insufficiency                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intracardiac mass                               |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Left ventricular failure                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Mitral valve disease                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Myocardial infarction                           |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Right ventricular failure                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Sinus node dysfunction                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tachycardia                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nervous system disorders                        |                  |  |  |
| Ischaemic stroke                                |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Seizure                                         |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Aphasia                                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ataxia                                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cauda equina syndrome                           |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cerebral haemorrhage                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cerebral infarction                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cerebrovascular disorder                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cognitive disorder                              |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Generalised tonic-clonic seizure                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Headache                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic encephalopathy                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Hypoaesthesia                                   |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Intracranial pressure increased                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Loss of consciousness                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neuropsychiatric lupus                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peripheral sensory neuropathy                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Presyncope                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Progressive supranuclear palsy                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Restless legs syndrome                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Spinal cord compression                         |                  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Transient global amnesia                        |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Transverse sinus thrombosis                     |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Tremor                                          |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Trigeminal neuralgia                            |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Blood and lymphatic system disorders            |                   |  |  |
| Febrile neutropenia                             |                   |  |  |
| subjects affected / exposed                     | 71 / 1436 (4.94%) |  |  |
| occurrences causally related to treatment / all | 21 / 75           |  |  |
| deaths causally related to treatment / all      | 1 / 1             |  |  |
| Neutropenia                                     |                   |  |  |
| subjects affected / exposed                     | 47 / 1436 (3.27%) |  |  |
| occurrences causally related to treatment / all | 5 / 56            |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Anaemia                                         |                   |  |  |
| subjects affected / exposed                     | 8 / 1436 (0.56%)  |  |  |
| occurrences causally related to treatment / all | 2 / 8             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Leukopenia                                      |                   |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 2 / 1436 (0.14%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Febrile bone marrow aplasia                     |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Bone marrow failure                             |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Thrombocytopenia                                |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Eye disorders                                   |                   |  |  |
| Cataract                                        |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Glaucoma                                        |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Retinal detachment                              |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Gastrointestinal disorders                      |                   |  |  |
| Diarrhoea                                       |                   |  |  |
| subjects affected / exposed                     | 36 / 1436 (2.51%) |  |  |
| occurrences causally related to treatment / all | 16 / 43           |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Vomiting                                        |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 7 / 1436 (0.49%) |  |  |
| occurrences causally related to treatment / all | 2 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Colitis                                         |                  |  |  |
| subjects affected / exposed                     | 4 / 1436 (0.28%) |  |  |
| occurrences causally related to treatment / all | 3 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal pain                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastritis                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Rectal haemorrhage                              |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Anal fistula                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abdominal pain upper                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Crohn's disease                                 |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Food poisoning                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastric ulcer perforation                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haematemesis                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Ileal stenosis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Large intestinal obstruction                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Large intestine polyp                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lower gastrointestinal haemorrhage              |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oesophageal stenosis                            |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pancreatitis chronic                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Small intestinal obstruction                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Stomatitis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatobiliary disorders                         |                  |  |  |
| Cholecystitis                                   |                  |  |  |
| subjects affected / exposed                     | 4 / 1436 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cholecystitis acute                             |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cholangitis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cholangitis sclerosing                          |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cholestasis                                     |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatic failure                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 1 / 1            |  |  |
| Hepatocellular injury                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Liver injury                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin and subcutaneous tissue disorders          |                  |  |  |
| Angioedema                                      |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pemphigus                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Rash                                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Skin ulcer                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal and urinary disorders                     |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| Acute kidney injury                             |                  |  |  |
| subjects affected / exposed                     | 7 / 1436 (0.49%) |  |  |
| occurrences causally related to treatment / all | 3 / 8            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal failure                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cystitis haemorrhagic                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hydronephrosis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nephrolithiasis                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Renal impairment                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Urinary tract obstruction                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Endocrine disorders                             |                  |  |  |
| Hypogonadism                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Musculoskeletal and connective tissue           |                  |  |  |

|                                                 |                  |  |  |  |
|-------------------------------------------------|------------------|--|--|--|
| disorders                                       |                  |  |  |  |
| Osteonecrosis of jaw                            |                  |  |  |  |
| subjects affected / exposed                     | 7 / 1436 (0.49%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 9            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Osteoarthritis                                  |                  |  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Arthritis                                       |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Bone pain                                       |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Pain in extremity                               |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Spinal osteoarthritis                           |                  |  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Arthralgia                                      |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Back pain                                       |                  |  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |  |
| Fracture pain                                   |                  |  |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Intervertebral disc protrusion                  |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Musculoskeletal chest pain                      |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Musculoskeletal pain                            |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Myalgia                                         |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Neck pain                                       |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Pathological fracture                           |                   |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Infections and infestations                     |                   |  |  |
| Pneumonia                                       |                   |  |  |
| subjects affected / exposed                     | 26 / 1436 (1.81%) |  |  |
| occurrences causally related to treatment / all | 4 / 30            |  |  |
| deaths causally related to treatment / all      | 0 / 4             |  |  |
| Cellulitis                                      |                   |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 15 / 1436 (1.04%) |  |  |
| occurrences causally related to treatment / all | 4 / 19            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Urinary tract infection                         |                   |  |  |
| subjects affected / exposed                     | 15 / 1436 (1.04%) |  |  |
| occurrences causally related to treatment / all | 3 / 15            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Neutropenic sepsis                              |                   |  |  |
| subjects affected / exposed                     | 10 / 1436 (0.70%) |  |  |
| occurrences causally related to treatment / all | 1 / 10            |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Sepsis                                          |                   |  |  |
| subjects affected / exposed                     | 10 / 1436 (0.70%) |  |  |
| occurrences causally related to treatment / all | 0 / 11            |  |  |
| deaths causally related to treatment / all      | 0 / 3             |  |  |
| Vascular device infection                       |                   |  |  |
| subjects affected / exposed                     | 9 / 1436 (0.63%)  |  |  |
| occurrences causally related to treatment / all | 0 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Device related infection                        |                   |  |  |
| subjects affected / exposed                     | 8 / 1436 (0.56%)  |  |  |
| occurrences causally related to treatment / all | 1 / 9             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Respiratory tract infection                     |                   |  |  |
| subjects affected / exposed                     | 7 / 1436 (0.49%)  |  |  |
| occurrences causally related to treatment / all | 1 / 7             |  |  |
| deaths causally related to treatment / all      | 0 / 1             |  |  |
| Erysipelas                                      |                   |  |  |
| subjects affected / exposed                     | 6 / 1436 (0.42%)  |  |  |
| occurrences causally related to treatment / all | 3 / 8             |  |  |
| deaths causally related to treatment / all      | 0 / 0             |  |  |
| Upper respiratory tract infection               |                   |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 6 / 1436 (0.42%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Influenza                                       |                  |  |  |
| subjects affected / exposed                     | 5 / 1436 (0.35%) |  |  |
| occurrences causally related to treatment / all | 0 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lower respiratory tract infection               |                  |  |  |
| subjects affected / exposed                     | 5 / 1436 (0.35%) |  |  |
| occurrences causally related to treatment / all | 1 / 5            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastroenteritis                                 |                  |  |  |
| subjects affected / exposed                     | 4 / 1436 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Arthritis bacterial                             |                  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Herpes zoster                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyelonephritis                                  |                  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Viral infection                                 |                  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 1 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bacteraemia                                     |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Diverticulitis                                  |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 2 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Extradural abscess                              |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastroenteritis viral                           |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Infection                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Neutropenic infection                           |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 1 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Staphylococcal infection                        |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Wound infection                                 |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Abscess limb                                    |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bacterial pyelonephritis                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Biliary sepsis                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Bronchitis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Catheter site infection                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Clostridial infection                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Clostridium colitis                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Clostridium difficile colitis                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Clostridium difficile infection                 |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Cystitis                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Device related sepsis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Dysentery                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enteritis infectious                            |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Enterocolitis bacterial                         |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gangrene                                        |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gastrointestinal infection                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hepatitis C                                     |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Herpes zoster disseminated                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Large intestine infection                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Localised infection                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Lung abscess                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Meningitis                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Nasopharyngitis                                 |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Necrotising fasciitis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Oesophageal candidiasis                         |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Osteomyelitis                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Paronychia                                      |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Peritonitis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Pharyngitis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumocystis jirovecii pneumonia                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pneumonia bacterial                             |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Post procedural infection                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pseudomonal sepsis                              |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pyomyositis                                     |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Salmonellosis                                   |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Septic shock                                    |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Sinusitis                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Sinusitis fungal                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Soft tissue infection                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 2 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Staphylococcal sepsis                           |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 1 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Tooth infection                                 |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Varicella                                       |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Metabolism and nutrition disorders              |                  |  |  |
| Dehydration                                     |                  |  |  |
| subjects affected / exposed                     | 4 / 1436 (0.28%) |  |  |
| occurrences causally related to treatment / all | 1 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyponatraemia                                   |                  |  |  |
| subjects affected / exposed                     | 4 / 1436 (0.28%) |  |  |
| occurrences causally related to treatment / all | 0 / 6            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypocalcaemia                                   |                  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypophosphataemia                               |                  |  |  |
| subjects affected / exposed                     | 3 / 1436 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 3            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoglycaemia                                   |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Hypokalaemia                                    |                  |  |  |
| subjects affected / exposed                     | 2 / 1436 (0.14%) |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Gout                                            |                  |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperglycaemia                                  |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoalbuminaemia                                |                  |  |  |
| subjects affected / exposed                     | 1 / 1436 (0.07%) |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | Pertuzumab +<br>Trastuzumab +<br>Taxane |  |  |
|-------------------------------------------------------|-----------------------------------------|--|--|
| Total subjects affected by non-serious adverse events |                                         |  |  |
| subjects affected / exposed                           | 1394 / 1436<br>(97.08%)                 |  |  |
| Vascular disorders                                    |                                         |  |  |
| Hypertension                                          |                                         |  |  |
| subjects affected / exposed                           | 152 / 1436<br>(10.58%)                  |  |  |
| occurrences (all)                                     | 217                                     |  |  |
| Hot flush                                             |                                         |  |  |
| subjects affected / exposed                           | 129 / 1436 (8.98%)                      |  |  |
| occurrences (all)                                     | 165                                     |  |  |
| Lymphoedema                                           |                                         |  |  |
| subjects affected / exposed                           | 98 / 1436 (6.82%)                       |  |  |
| occurrences (all)                                     | 121                                     |  |  |
| General disorders and administration site conditions  |                                         |  |  |
| Fatigue                                               |                                         |  |  |
| subjects affected / exposed                           | 457 / 1436<br>(31.82%)                  |  |  |
| occurrences (all)                                     | 829                                     |  |  |
| Asthenia                                              |                                         |  |  |

|                                                 |                        |  |  |
|-------------------------------------------------|------------------------|--|--|
| subjects affected / exposed                     | 426 / 1436<br>(29.67%) |  |  |
| occurrences (all)                               | 1123                   |  |  |
| Mucosal inflammation                            |                        |  |  |
| subjects affected / exposed                     | 287 / 1436<br>(19.99%) |  |  |
| occurrences (all)                               | 490                    |  |  |
| Pyrexia                                         |                        |  |  |
| subjects affected / exposed                     | 258 / 1436<br>(17.97%) |  |  |
| occurrences (all)                               | 387                    |  |  |
| Oedema peripheral                               |                        |  |  |
| subjects affected / exposed                     | 257 / 1436<br>(17.90%) |  |  |
| occurrences (all)                               | 344                    |  |  |
| Influenza like illness                          |                        |  |  |
| subjects affected / exposed                     | 96 / 1436 (6.69%)      |  |  |
| occurrences (all)                               | 136                    |  |  |
| Pain                                            |                        |  |  |
| subjects affected / exposed                     | 81 / 1436 (5.64%)      |  |  |
| occurrences (all)                               | 114                    |  |  |
| Chills                                          |                        |  |  |
| subjects affected / exposed                     | 75 / 1436 (5.22%)      |  |  |
| occurrences (all)                               | 84                     |  |  |
| Chest pain                                      |                        |  |  |
| subjects affected / exposed                     | 74 / 1436 (5.15%)      |  |  |
| occurrences (all)                               | 86                     |  |  |
| Respiratory, thoracic and mediastinal disorders |                        |  |  |
| Cough                                           |                        |  |  |
| subjects affected / exposed                     | 271 / 1436<br>(18.87%) |  |  |
| occurrences (all)                               | 410                    |  |  |
| Epistaxis                                       |                        |  |  |
| subjects affected / exposed                     | 263 / 1436<br>(18.31%) |  |  |
| occurrences (all)                               | 360                    |  |  |
| Dyspnoea                                        |                        |  |  |
| subjects affected / exposed                     | 195 / 1436<br>(13.58%) |  |  |
| occurrences (all)                               | 260                    |  |  |
| Oropharyngeal pain                              |                        |  |  |

|                             |                     |  |  |
|-----------------------------|---------------------|--|--|
| subjects affected / exposed | 124 / 1436 (8.64%)  |  |  |
| occurrences (all)           | 156                 |  |  |
| Rhinorrhoea                 |                     |  |  |
| subjects affected / exposed | 100 / 1436 (6.96%)  |  |  |
| occurrences (all)           | 135                 |  |  |
| Psychiatric disorders       |                     |  |  |
| Insomnia                    |                     |  |  |
| subjects affected / exposed | 157 / 1436 (10.93%) |  |  |
| occurrences (all)           | 183                 |  |  |
| Depression                  |                     |  |  |
| subjects affected / exposed | 78 / 1436 (5.43%)   |  |  |
| occurrences (all)           | 94                  |  |  |
| Anxiety                     |                     |  |  |
| subjects affected / exposed | 75 / 1436 (5.22%)   |  |  |
| occurrences (all)           | 87                  |  |  |
| Investigations              |                     |  |  |
| Ejection fraction decreased |                     |  |  |
| subjects affected / exposed | 157 / 1436 (10.93%) |  |  |
| occurrences (all)           | 215                 |  |  |
| Weight decreased            |                     |  |  |
| subjects affected / exposed | 98 / 1436 (6.82%)   |  |  |
| occurrences (all)           | 115                 |  |  |
| Nervous system disorders    |                     |  |  |
| Headache                    |                     |  |  |
| subjects affected / exposed | 328 / 1436 (22.84%) |  |  |
| occurrences (all)           | 542                 |  |  |
| Neuropathy peripheral       |                     |  |  |
| subjects affected / exposed | 328 / 1436 (22.84%) |  |  |
| occurrences (all)           | 537                 |  |  |
| Paraesthesia                |                     |  |  |
| subjects affected / exposed | 221 / 1436 (15.39%) |  |  |
| occurrences (all)           | 366                 |  |  |
| Dizziness                   |                     |  |  |
| subjects affected / exposed | 205 / 1436 (14.28%) |  |  |
| occurrences (all)           | 271                 |  |  |

|                                                                                   |                                |  |  |
|-----------------------------------------------------------------------------------|--------------------------------|--|--|
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                     | 141 / 1436 (9.82%)<br>193      |  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 120 / 1436 (8.36%)<br>158      |  |  |
| Taste disorder<br>subjects affected / exposed<br>occurrences (all)                | 75 / 1436 (5.22%)<br>92        |  |  |
| Neurotoxicity<br>subjects affected / exposed<br>occurrences (all)                 | 72 / 1436 (5.01%)<br>118       |  |  |
| Blood and lymphatic system disorders                                              |                                |  |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                       | 312 / 1436<br>(21.73%)<br>521  |  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                   | 222 / 1436<br>(15.46%)<br>439  |  |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                    | 84 / 1436 (5.85%)<br>162       |  |  |
| Eye disorders                                                                     |                                |  |  |
| Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)         | 169 / 1436<br>(11.77%)<br>220  |  |  |
| Gastrointestinal disorders                                                        |                                |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                     | 974 / 1436<br>(67.83%)<br>2753 |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                        | 512 / 1436<br>(35.65%)<br>918  |  |  |
| Vomiting                                                                          |                                |  |  |

|                                        |                        |  |  |
|----------------------------------------|------------------------|--|--|
| subjects affected / exposed            | 340 / 1436<br>(23.68%) |  |  |
| occurrences (all)                      | 531                    |  |  |
| Constipation                           |                        |  |  |
| subjects affected / exposed            | 235 / 1436<br>(16.36%) |  |  |
| occurrences (all)                      | 347                    |  |  |
| Stomatitis                             |                        |  |  |
| subjects affected / exposed            | 210 / 1436<br>(14.62%) |  |  |
| occurrences (all)                      | 326                    |  |  |
| Abdominal pain                         |                        |  |  |
| subjects affected / exposed            | 206 / 1436<br>(14.35%) |  |  |
| occurrences (all)                      | 314                    |  |  |
| Abdominal pain upper                   |                        |  |  |
| subjects affected / exposed            | 149 / 1436<br>(10.38%) |  |  |
| occurrences (all)                      | 187                    |  |  |
| Dyspepsia                              |                        |  |  |
| subjects affected / exposed            | 141 / 1436 (9.82%)     |  |  |
| occurrences (all)                      | 170                    |  |  |
| Haemorrhoids                           |                        |  |  |
| subjects affected / exposed            | 79 / 1436 (5.50%)      |  |  |
| occurrences (all)                      | 92                     |  |  |
| Skin and subcutaneous tissue disorders |                        |  |  |
| Alopecia                               |                        |  |  |
| subjects affected / exposed            | 693 / 1436<br>(48.26%) |  |  |
| occurrences (all)                      | 813                    |  |  |
| Rash                                   |                        |  |  |
| subjects affected / exposed            | 365 / 1436<br>(25.42%) |  |  |
| occurrences (all)                      | 596                    |  |  |
| Pruritus                               |                        |  |  |
| subjects affected / exposed            | 292 / 1436<br>(20.33%) |  |  |
| occurrences (all)                      | 466                    |  |  |
| Dry skin                               |                        |  |  |
| subjects affected / exposed            | 167 / 1436<br>(11.63%) |  |  |
| occurrences (all)                      | 208                    |  |  |
| Nail disorder                          |                        |  |  |

|                                                    |                        |  |  |
|----------------------------------------------------|------------------------|--|--|
| subjects affected / exposed                        | 163 / 1436<br>(11.35%) |  |  |
| occurrences (all)                                  | 197                    |  |  |
| Erythema                                           |                        |  |  |
| subjects affected / exposed                        | 137 / 1436 (9.54%)     |  |  |
| occurrences (all)                                  | 183                    |  |  |
| Onycholysis                                        |                        |  |  |
| subjects affected / exposed                        | 118 / 1436 (8.22%)     |  |  |
| occurrences (all)                                  | 179                    |  |  |
| Palmar-plantar erythrodysaesthesia<br>syndrome     |                        |  |  |
| subjects affected / exposed                        | 75 / 1436 (5.22%)      |  |  |
| occurrences (all)                                  | 94                     |  |  |
| Musculoskeletal and connective tissue<br>disorders |                        |  |  |
| Arthralgia                                         |                        |  |  |
| subjects affected / exposed                        | 328 / 1436<br>(22.84%) |  |  |
| occurrences (all)                                  | 550                    |  |  |
| Myalgia                                            |                        |  |  |
| subjects affected / exposed                        | 284 / 1436<br>(19.78%) |  |  |
| occurrences (all)                                  | 476                    |  |  |
| Back pain                                          |                        |  |  |
| subjects affected / exposed                        | 220 / 1436<br>(15.32%) |  |  |
| occurrences (all)                                  | 289                    |  |  |
| Muscle spasms                                      |                        |  |  |
| subjects affected / exposed                        | 196 / 1436<br>(13.65%) |  |  |
| occurrences (all)                                  | 292                    |  |  |
| Pain in extremity                                  |                        |  |  |
| subjects affected / exposed                        | 195 / 1436<br>(13.58%) |  |  |
| occurrences (all)                                  | 248                    |  |  |
| Bone pain                                          |                        |  |  |
| subjects affected / exposed                        | 135 / 1436 (9.40%)     |  |  |
| occurrences (all)                                  | 185                    |  |  |
| Musculoskeletal pain                               |                        |  |  |
| subjects affected / exposed                        | 128 / 1436 (8.91%)     |  |  |
| occurrences (all)                                  | 157                    |  |  |
| Infections and infestations                        |                        |  |  |

|                                                                                                              |                               |  |  |
|--------------------------------------------------------------------------------------------------------------|-------------------------------|--|--|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                          | 183 / 1436<br>(12.74%)<br>309 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                  | 180 / 1436<br>(12.53%)<br>294 |  |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 164 / 1436<br>(11.42%)<br>269 |  |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                                                | 110 / 1436 (7.66%)<br>155     |  |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                                           | 99 / 1436 (6.89%)<br>125      |  |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                                                 | 93 / 1436 (6.48%)<br>117      |  |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 274 / 1436<br>(19.08%)<br>447 |  |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                                             | 76 / 1436 (5.29%)<br>122      |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 02 January 2012  | Version 2. Key changes included the following: • Change of inclusion criteria to allow inclusion of patients with a baseline LVEF of at least 50%. • Exclusion of patients with alkaline phosphatase levels $> 2.5 \times$ the ULN ( $> 5 \times$ ULN in patients with liver metastases, or $>10 \times$ ULN in patients with bone metastases). • Update of background and rationale to include efficacy and safety data from CLEOPATRA. • Change the definition of time to response from the time from the date of randomization to the date of first CR or PR to the time from date of enrolment to date of first CR or PR. • Update of criteria for elevated liver function tests. • Update of safety analyses to include all enrolled patients.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 30 August 2012   | Version 3. Key changes included the following: • Redefinition of the end of study to 45 months after the last patient has been enrolled into the study or all patients in the study have withdrawn consent, or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first. • Inclusion of patients who, prior to study entry had received up to two lines of hormonal therapies for metastatic or locally recurrent disease, one of which may have been in combination with everolimus. • Inclusion of patients with central nervous system (CNS) metastases if they were stable in the 3 months prior to screening after receiving local therapy but without anti-HER2 therapy. • Reduction of the time from major surgery to randomization from 28 days to 14 days based on recommendation from the Steering Committee for the PERTAIN study. • Reduction in the time from receipt of intravenous (IV) antibiotics prior to randomization from 14 days to 7 days based on recommendation from the PERTAIN Steering Committee. • Increase of the flexibility in the timing and order of administration of study medications. • Increase of the number of interim analyses from 3 to 5 planned analyses. • Update of the study rationale to include the latest CLEOPATRA study OS results. • Extension of the interval duration for the scheduling of tumor assessments after 36 months. • Increase of the defined timeline for scheduling of tumor assessments (excluding electrocardiogram [ECG]) to within 7 days of the scheduled visit. • Removal of the requirement for HER2 status to be measured within 28 days of enrolment if a previous result is available. • Update of the timeframe for reporting of SAEs. • Update of the Schedule of Assessments (SoA) to increase the number of days within which visits could occur before/after scheduled treatment day from $\pm 3$ to $\pm 7$ days. |
| 09 May 2014      | Version 4. Key changes included the following: • Updated guidance on the recommended pregnancy follow-up for trastuzumab and pregnancy testing technique. • Update of the study background to include CLEOPATRA OS results and US approval for neoadjuvant treatment. • Addition of an annual review of safety data by the iDMC following completion of enrollment. • Change in timing of follow-up visits to approximately every 3 months. • Inclusion of analysis of adverse event of special interest (AESI) and description of baseline covariates to be explored for ORR assessment. • Update to permit radiotherapy of brain metastases.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 20 November 2015 | Version 5. Key changes included the following: • Extension of the follow-up period of the study from 45 months to at least 60 months after the last patient had been enrolled into the study or all patients in the study had withdrawn consent, or died, whichever occurred first. • Update of the definition for abnormal liver function test (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] elevations) SAEs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 November 2018 | Version 6. Key changes included the following: • Reduction in the frequency of imaging procedures for response assessments in long-term responders from every six cycles (approximately 4.5 months) in patients who remained progression free after 36 months to at least every 12 cycles following discussions at the iDMC meeting on 28 June 2018. • Reduction in the frequency of iDMC meetings from annually to approximately once per year. • Update of the policy on post-trial access to pertuzumab. |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

---

## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported