# Clinical trial results:
# A Phase III, Randomized, Multicenter, Open-Label, Two-Arm Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab in Combination With Chemotherapy in Patients With HER2-Positive Early Breast Cancer

## Summary

| | |
|---|---|
| EudraCT number | 2017-004897-32 |
| Trial protocol | GB DE ES BE CZ PL IT |
| Global end of trial date | 02 June 2023 |

**Results information**

| | |
|---|---|
| Result version number | v3 |
| This version publication date | 01 June 2024 |
| First version publication date | 10 July 2020 |
| Version creation reason | |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | WO40324 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03493854 |
| 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 | 02 June 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 02 June 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trough concentration (Ctrough) of pertuzumab by subcutaneous (SC) injection within the pertuzumab and trastuzumab fixed-dose combination (FDC) SC compared with pertuzumab by intravenous (IV) infusion.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 June 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 8 |
| Country: Number of subjects enrolled | Belgium: 17 |
| Country: Number of subjects enrolled | Brazil: 27 |
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | Czechia: 3 |
| Country: Number of subjects enrolled | France: 27 |
| Country: Number of subjects enrolled | Germany: 29 |
| Country: Number of subjects enrolled | Italy: 35 |
| Country: Number of subjects enrolled | Japan: 41 |
| Country: Number of subjects enrolled | Korea, Republic of: 35 |
| Country: Number of subjects enrolled | Mexico: 21 |
| Country: Number of subjects enrolled | Poland: 61 |
| Country: Number of subjects enrolled | Russian Federation: 64 |
| Country: Number of subjects enrolled | Spain: 49 |
| Country: Number of subjects enrolled | Taiwan: 19 |
| Country: Number of subjects enrolled | Thailand: 9 |

| | |
|---|---|
| Country: Number of subjects enrolled | Ukraine: 21 |
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Country: Number of subjects enrolled | United States: 5 |
| Worldwide total number of subjects | 500 |
| EEA total number of subjects | 221 |

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) | 441 |
| From 65 to 84 years | 59 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 607 patients were screened, 500 of whom were randomized.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy |

Arm description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab was given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Pertuzumab |
| Investigational medicinal product code | RO4368451 |
| Other name | Pertuzumab IV; Perjeta |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Pertuzumab is administered as a fixed non-weight-based dose of 840-milligram (mg) intravenous (IV) loading dose and then 420-mg IV maintenance dose once every 3 weeks (Q3W).

| | |
|---|---|
| Investigational medicinal product name | Trastuzumab SC |
| Investigational medicinal product code | |
| Other name | Trastuzumab and hyaluronidase-oysk; Herceptin Hylecta |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

After surgery (from Cycle 9 onwards), participants in Arm A will be allowed to switch from trastuzumab intravenous (IV) to trastuzumab subcutaneous (SC), at the discretion of the investigator, in the countries where trastuzumab SC is routinely used. For participants who switch, a fixed dose of 600 mg trastuzumab SC (irrespective of the patient’s weight) will be administered in the adjuvant phase.

| | |
|---|---|
| Investigational medicinal product name | Trastuzumab IV |
| Investigational medicinal product code | RO0452317 |
| Other name | Herceptin |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab is administered as an 8-milligram per kilogram (mg/kg) intravenous (IV) loading dose and then 6-mg/kg IV maintenance dose once every 3 weeks (Q3W).

| **Arm title** | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|

Arm description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Fixed dose combination of pertuzumab and trastuzumab |
| Investigational medicinal product code | RO7198574 |
| Other name | PH FDC SC |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The fixed-dose combinatinon (FDC) of pertuzumab and trastuzumab is administered subcutaneously (SC) at a fixed non-weight-based dose. A loading dose of 1200 mg SC pertuzumab and 600 mg SC trastuzumab is then followed by a maintenance dose of 600 mg SC pertuzumab and 600 mg SC trastuzumab once every 3 weeks (Q3W).

| **Number of subjects in period 1** | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|---|
| Started | 252 | 248 |
| Received at Least One Dose of Study Drug | 252 | 248 |
| Completed Neoadjuvant Phase | 242 | 234 |
| Completed Surgery | 239 | 234 |
| Completed Adjuvant Treatment Phase | 209 [1] | 217 [2] |
| Started Treatment-Free Follow-Up | 247 | 241 |
| Completed | 223 | 219 |
| Not completed | 29 | 29 |
| Consent withdrawn by subject | 13 | 15 |
| Death | 12 | 13 |
| Lost to follow-up | 4 | 1 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number of subjects represents those who completed adjuvant treatment. Subjects who withdrew prematurely from treatment remained in the study by entering into the follow-up period.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number of subjects represents those who completed adjuvant treatment. Subjects who withdrew prematurely from treatment remained in the study by entering into the follow-up period.

## Baseline characteristics

### Reporting groups

| Reporting group title | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy |
|---|---|

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab was given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

| Reporting group title | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

| Reporting group values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | Total |
|---|---|---|---|
| Number of subjects | 252 | 248 | 500 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 219 | 222 | 441 |
| From 65-84 years | 33 | 26 | 59 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: Years | | | |
| arithmetic mean | 50.3 | 51.7 | |
| standard deviation | ± 10.8 | ± 10.7 | - |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 250 | 248 | 498 |
| Male | 2 | 0 | 2 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 32 | 42 | 74 |
| Not Hispanic or Latino | 200 | 189 | 389 |

| | | | |
|---|---|---|---|
| Unknown or Not Reported | 20 | 17 | 37 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| American Indian or Alaska Native | 10 | 10 | 20 |
| Asian | 54 | 51 | 105 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 3 | 3 | 6 |
| White | 164 | 165 | 329 |
| More than one race | 2 | 3 | 5 |
| Unknown or Not Reported | 19 | 16 | 35 |
| Randomization Stratification Factors: Hormone Receptor Status | | | |
| Hormone receptor status was based on central assessment of participant samples for estrogen receptor (ER) and progesterone receptor (PgR) negativity or positivity. | | | |
| Units: Subjects | | | |
| ER Negative and PgR Negative | 97 | 96 | 193 |
| ER Positive and PgR Positive | 155 | 151 | 306 |
| Unknown | 0 | 1 | 1 |
| Randomization Stratification Factors: Clinical Stage at Presentation<br>Units: Subjects | | | |
| Stage II-IIIA | 201 | 198 | 399 |
| Stage IIIB-IIIC | 51 | 50 | 101 |
| Randomization Stratification Factors: Neoadjuvant Chemotherapy Regimen | | | |
| AC = doxorubicin plus cyclophosphamide; ddAC = dose-dense doxorubicin plus cyclophosphamide | | | |
| Units: Subjects | | | |
| ddAC Followed by Paclitaxel | 120 | 120 | 240 |
| AC Followed by Docetaxel | 132 | 128 | 260 |

## End points

### End points reporting groups

| Reporting group title | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy |
|---|---|

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab was given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

| Reporting group title | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

### Primary: Trough Serum Concentration (Ctrough) of Pertuzumab During Cycle 7 (Pre-Dose Cycle 8)

| End point title | Trough Serum Concentration (Ctrough) of Pertuzumab During Cycle 7 (Pre-Dose Cycle 8) |
|---|---|

End point description:

The observed pertuzumab trough serum concentration (Ctrough) at Cycle 7 was assessed following 3 cycles of pertuzumab IV and trastuzumab IV or the fixed-dose combination (FDC) of pertuzumab and trastuzumab SC. The Per Protocol Pharmacokinetics (PK) analysis population includes all enrolled participants who adhered to the protocol. Exclusions from the Per Protocol PK analysis population were made for the following reasons: participants were missing the Ctrough pre-dose Cycle 8 PK sample, participants with a Ctrough sample collected with at least 2 days deviation from the planned date on Day 21 (i.e., before Day 19 or after Day 23), participants given a dose amount that deviated from the planned dose by >20% within 3 cycles (from Cycle 5), participants with a dose delay of more than 7 days, a subcutaneous injection site other than thigh was used, if the Cycle 8 pre-dose and post-dose samples were switched, and an assay error impacting Ctrough measurement.

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

End point timeframe:

Pre-dose on Cycle 8, Day 1 (up to 21 weeks)

| **End point values** | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203[1] | 206[2] | | |
| Units: micrograms per millilitre (µg/mL) | | | | |
| geometric mean (geometric coefficient | 72.4 (± 34.1) | 88.7 (± 33.6) | | |

| of variation) |
|---|

Notes:

[1] - Per Protocol PK analysis population

[2] - Per Protocol PK analysis population

### Statistical analyses

| **Statistical analysis title** | Non-inferiority of Ctrough Pertuzumab SC vs. IV |
|---|---|

Statistical analysis description:

The null hypothesis was that the pertuzumab Arm A SC dose is inferior to the pertuzumab Arm B IV dose (i.e., the CtroughSC/CtroughIV geometric mean ratio of the SC dose of pertuzumab relative to the IV dose is not greater than 0.8).

| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v<br>Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|
| Number of subjects included in analysis | 409 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.14 |
| upper limit | 1.31 |

## Secondary: Ctrough of Trastuzumab During Cycle 7 (Pre-Dose Cycle 8)

| End point title | Ctrough of Trastuzumab During Cycle 7 (Pre-Dose Cycle 8) |
|---|---|

End point description:

The observed trastuzumab trough serum concentration (Ctrough) at Cycle 7 was assessed following 3 cycles of pertuzumab IV and trastuzumab IV or the fixed-dose combination (FDC) of pertuzumab and trastuzumab SC. The Per Protocol Pharmacokinetics (PK) analysis population includes all enrolled participants who adhered to the protocol. Exclusions from the Per Protocol PK analysis population were made for the following reasons: participants were missing the Ctrough pre-dose Cycle 8 PK sample, participants with a Ctrough sample collected with at least 2 days deviation from the planned date on Day 21 (i.e., before Day 19 or after Day 23), participants given a dose amount that deviated from the planned dose by >20% within 3 cycles (from Cycle 5), participants with a dose delay of more than 7 days, a subcutaneous injection site other than thigh was used, if the Cycle 8 pre-dose and post-dose samples were switched, and an assay error impacting Ctrough measurement.

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

End point timeframe:

Pre-dose on Cycle 8, Day 1 (up to 21 weeks)

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 203[3] | 206[4] | | |
| Units: micrograms per milllilitre (µg/mL) | | | | |
| geometric mean (geometric coefficient of variation) | 43.2 (± 34.7) | 57.5 (± 37.0) | | |

Notes:

[3] - Per Protocol PK analysis population

[4] - Per Protocol PK analysis population

### Statistical analyses

| Statistical analysis title | Non-inferiority of Ctrough Trastuzumab SC vs. IV |
|---|---|

Statistical analysis description:

The null hypothesis was that the trastuzumab Arm B SC dose is inferior to the Arm A trastuzumab IV dose (i.e., the CtroughSC/CtroughIV geometric mean ratio of the SC dose of trastuzumab relative to the IV dose is not greater than 0.8).

| | |
|---|---|
| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
| Number of subjects included in analysis | 409 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 1.33 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.24 |
| upper limit | 1.43 |

## Secondary: Percentage of Participants with Total Pathological Complete Response (tpCR), According to Local Pathologist Assessment

| End point title | Percentage of Participants with Total Pathological Complete Response (tpCR), According to Local Pathologist Assessment |
|---|---|

End point description:

Total pCR (tpCR) was defined as eradication of invasive disease in the breast and axilla; that is, ypT0/is ypN0, according to the local pathologists' assessment. Pathologic response to therapy was determined at the time of surgery. The tpCR rate is the percentage of participants in the ITT population who achieved a tpCR. Participants with missing data for tpCR (i.e., do not undergo surgery or have an invalid pCR assessment) were included in the analysis and classified as non-responders. Rates of tpCR were calculated in each treatment arm and were assessed using the difference between the Arm B: Pertuzumab and Trastuzumab FDC SC and the Arm A: Pertuzumab IV and Trastuzumab IV tpCR rates and corresponding 95% Clopper-Pearson confidence intervals (CIs). The difference between the tpCR rates along with corresponding 95% Hauck-Anderson CIs were calculated. The lower bound of the CI will reliably reflect the largest tpCR difference that can be considered unlikely.

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

End point timeframe:

Following completion of surgery (up to 33 weeks)

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 59.5 (53.2 to 65.6) | 59.7 (53.3 to 65.8) | | |

**Statistical analyses**

| Statistical analysis title | Difference in tpCR Rates SC vs. IV |
|---|---|
| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
| Number of subjects included in analysis | 500 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Difference in tpCR Rate |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.67 |
| upper limit | 8.97 |

## Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Invasive Disease-Free Survival (iDFS; Excluding Second Primary Non-Breast Cancer [SPNBC]) Criteria

| End point title | Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Invasive Disease-Free Survival (iDFS; Excluding Second Primary Non-Breast Cancer [SPNBC]) Criteria |
|---|---|

End point description:

iDFS (excluding SPNBC) is defined as the time from the first date of no disease (i.e., the date of primary surgery) to the first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence; ipsilateral local-regional invasive breast cancer reccurrence; distant recurrence; contralateral invasive breast cancer; or death attributable to any cause. Ipsilateral or contralateral in situ disease and SPNBC (including in situ carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or relapse. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

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

End point timeframe:

At 1, 2, 3, and 4 years

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239[5] | 234[6] | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n = 219, 222) | 96.07 (93.55 to 98.59) | 97.37 (95.30 to 99.45) | | |
| 2 Years (n = 208, 205) | 92.98 (89.66 to 96.30) | 90.75 (86.98 to 94.52) | | |
| 3 Years (n = 194, 199) | 90.71 (86.93 to 94.50) | 89.86 (85.93 to 93.79) | | |
| 4 Years (n = 31, 23) | 89.60 (85.54 to 93.65) | 88.50 (84.34 to 92.66) | | |

Notes:

[5] - The analysis includes subjects who completed surgery.

[6] - The analysis includes subjects who completed surgery.

### Statistical analyses

| Statistical analysis title | iDFS - Log Rank |
|---|---|
| Statistical analysis description: Descriptive analysis only | |
| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
| Number of subjects included in analysis | 473 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5216 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 2.11 |

## Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to iDFS (Including SPNBC) Criteria

| End point title | Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to iDFS (Including SPNBC) Criteria |
|---|---|

End point description:

Invasive disease-free survival (iDFS) including second primary non-breast cancer (SPNBC) is defined as the time from the first date of no disease (i.e., the date of primary surgery) to the first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence; ipsilateral local-regional

invasive breast cancer reccurrence; distant recurrence; contralateral invasive breast cancer; or death attributable to any cause. It also includes SPNBC as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

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

End point timeframe:

At 1, 2, 3, and 4 years

| **End point values** | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 239[7] | 234[8] | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n = 218, 221) | 95.63 (92.99 to 98.28) | 96.94 (94.70 to 99.17) | | |
| 2 Years (n = 206, 202) | 92.10 (88.60 to 95.60) | 89.44 (85.44 to 93.43) | | |
| 3 Years (n = 191, 196) | 89.39 (85.37 to 93.40) | 88.54 (84.40 to 92.69) | | |
| 4 Years (n = 31, 23) | 88.27 (84.01 to 92.53) | 87.64 (83.35 to 91.93) | | |

Notes:

[7] - The analysis includes subjects who completed surgery.

[8] - The analysis includes subjects who completed surgery.

## Statistical analyses

| **Statistical analysis title** | iDFS (+SPNBC) - Log Rank |
|---|---|

Statistical analysis description:

Descriptive analysis only

| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|
| Number of subjects included in analysis | 473 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5992 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.15 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.97 |

## Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Event-Free Survival (EFS; Excluding SPNBC) Criteria

| End point title | Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Event-Free Survival (EFS; Excluding SPNBC) Criteria |
|---|---|

End point description:

Event-free survival (EFS) excluding second primary non-breast cancer (SPNBC) is defined as the time from enrollment to the first occurrence of one of the following events: breast cancer progression; breast cancer recurrence; or death from any cause. Ipsilateral or contralateral in situ disease and SPNBC (including in situ carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or relapse. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

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

End point timeframe:

At 1, 2, 3, and 4 years

| **End point values** | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n = 237, 235) | 96.79 (94.60 to 98.98) | 97.95 (96.18 to 99.73) | | |
| 2 Years (n = 224, 218) | 92.29 (88.96 to 95.62) | 91.67 (88.17 to 95.16) | | |
| 3 Years (n = 212, 209) | 89.77 (85.96 to 93.57) | 88.29 (84.21 to 92.37) | | |
| 4 Years (n = 191, 198) | 88.47 (84.44 to 92.49) | 86.57 (82.24 to 90.90) | | |

### Statistical analyses

| **Statistical analysis title** | EFS - Log Rank |
|---|---|

Statistical analysis description:

Descriptive analysis only

| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|
| Number of subjects included in analysis | 500 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4844 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.2 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.98 |

## Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to EFS (Including SPNBC) Criteria

| End point title | Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to EFS (Including SPNBC) Criteria |
|---|---|

End point description:

Event-free survival (EFS) including second primary non-breast cancer (SPNBC) is defined as the time from enrollment to the first occurrence of one of the following events: breast cancer progression; breast cancer recurrence; or death from any cause. It also includes SPNBC as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site). The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

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

End point timeframe:

At 1, 2, 3, and 4 years

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n = 236, 234) | 96.38 (94.06 to 98.70) | 97.54 (95.59 to 99.48) | | |
| 2 Years (n = 222, 215) | 91.47 (87.98 to 94.96) | 90.41 (86.69 to 94.14) | | |
| 3 Years (n = 209, 206) | 88.53 (84.52 to 92.53) | 87.04 (82.78 to 91.30) | | |
| 4 Years (n = 188, 196) | 87.22 (83.02 to 91.43) | 85.75 (81.31 to 90.18) | | |

### Statistical analyses

| Statistical analysis title | EFS (+SPNBC) - Log Rank |
|---|---|

Statistical analysis description:

Descriptive analysis only

| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 500 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5474 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.88 |

## Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Distant Recurrence-Free Interval (DRFI) Criteria

| | |
|---|---|
| End point title | Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Distant Recurrence-Free Interval (DRFI) Criteria |

End point description:

The distant recurrence-free interval (DRFI) is defined as the time between randomization and the date of distant breast cancer recurrence. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

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

End point timeframe:

At 1, 2, 3, and 4 years

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n = 244, 239) | 99.59 (98.80 to 100.00) | 99.58 (98.77 to 100.00) | | |
| 2 Years (n = 231, 224) | 95.88 (93.39 to 98.38) | 95.37 (92.70 to 98.04) | | |
| 3 Years (n = 221, 216) | 93.77 (90.72 to 96.82) | 93.23 (90.02 to 96.43) | | |
| 4 Years (n = 212, 210) | 92.49 (89.15 to 95.83) | 91.92 (88.44 to 95.41) | | |

## Statistical analyses

| Statistical analysis title | DRFI - Log Rank |
|---|---|
| Statistical analysis description:<br>Descriptive analysis only | |
| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v<br>Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
| Number of subjects included in analysis | 500 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.6291 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 2.24 |

## Secondary: Kaplan-Meier Estimate of the Percentage of Participants in Overall Survival

| End point title | Kaplan-Meier Estimate of the Percentage of Participants in Overall Survival |
|---|---|
| End point description:<br>Overall survival is defined as the time from randomization to death from any cause. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event. | |
| End point type | Secondary |
| End point timeframe:<br>At 1, 2, 3, and 4 years | |

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| 1 Year (n = 245, 240) | 99.60 (98.82 to 100.00) | 99.19 (98.06 to 100.00) | | |
| 2 Years (n = 241, 230) | 98.38 (96.80 to 99.95) | 96.68 (94.42 to 98.94) | | |
| 3 Years (n = 232, 226) | 96.73 (94.50 to 98.96) | 95.83 (93.30 to 98.36) | | |
| 4 Years (n = 223, 221) | 95.47 (92.86 to 98.09) | 94.13 (91.14 to 97.11) | | |

### Statistical analyses

| **Statistical analysis title** | OS - Log Rank |
|---|---|
| Comparison groups | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |
| Number of subjects included in analysis | 500 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.5609 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 2.72 |

## Secondary: Summary of the Number of Participants With at Least One Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0), Over the Course of the Entire Study

| End point title | Summary of the Number of Participants With at Least One Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0), Over the Course of the Entire Study |
|---|---|

End point description:

The adverse event (AE) severity grading scale for the NCI CTCAE v4.0 was used for assessing AE severity. Any AEs that were not specifically listed in the NCI CTCAE, v4.0 were graded per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 3 = severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

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

End point timeframe:

From Baseline until end of study (up to 5.5 years)

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Participants | | | | |
| Any Adverse Event (AE): Any Grade | 251 | 248 | | |
| AE with Fatal Outcome (Grade 5) | 2 | 2 | | |
| Any AE: Grades 3 to 5 | 149 | 132 | | |
| Serious AE | 52 | 49 | | |
| Related Serious AE | 29 | 29 | | |
| Anaphylaxis and Hypersensitivity AEs, Any Grade | 3 | 3 | | |
| Anaphylaxis and Hypersensitivity AEs, Grade ≥3 | 1 | 0 | | |
| Infusion/Admin.-Rel. Reactions in 24 hrs, Any Gr. | 39 | 54 | | |
| Infusion/Admin.-Rel. Reactions in 24 hrs, Gr. ≥3 | 3 | 0 | | |
| Serious Rash/Skin Reactions, Any Grade | 0 | 1 | | |
| Serious Rash/Skin Reactions, Grade ≥3 | 0 | 0 | | |
| Diarrhoea, Any Grade | 149 | 153 | | |
| Diarrhoea, Grade ≥3 | 13 | 16 | | |
| Cardiac Dysfunction, Any Grade | 65 | 52 | | |
| Cardiac Dysfunction, Grade ≥3 | 12 | 3 | | |
| Interstitial Lung Disease, Any Grade | 3 | 5 | | |
| Interstitial Lung Disease, Grade ≥3 | 0 | 0 | | |
| Neutropenia/Febrile Neutropenia, Any Grade | 142 | 123 | | |
| Neutropenia/Febrile Neutropenia, Grade ≥3 | 92 | 82 | | |
| Serious Mucositis, Any Grade | 3 | 3 | | |
| Serious Mucositis, Grade ≥3 | 3 | 2 | | |
| Pregnancy- and Neonatal-Related AEs, Any Grade | 0 | 0 | | |
| AE Leading to Study Drug Discontinuation | 32 | 22 | | |
| AE Leading to Anti-HER2 Therapy Discontinuation | 15 | 12 | | |
| AE Leading to Any Chemo. Drug Discontinuation | 23 | 14 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With a Primary Cardiac Event During the Neoadjuvant Phase

| End point title | Number of Participants With a Primary Cardiac Event During the Neoadjuvant Phase |
|---|---|

End point description:

A primary cardiac event is defined as the occurrence of either of the following events: - Incidence of a symptomatic ejection fraction decrease (heart failure) of New York Heart Association (NYHA) Class III or IV and a drop in left ventricular ejection fraction (LVEF) of at least 10-percentage points from baseline and to below 50%; or - Cardiac death, defined as: Definite cardiac death (due to heart failure, myocardial infarction, or documented primary arrhythmia); or, Probable cardiac death (sudden unexpected death within 24 hours of a definite or probable cardiac event [e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia] without documented etiology).

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

End point timeframe:

From first dose of study treatment until the completion of neoadjuvant therapy (24 weeks)

| **End point values** | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Participants | | | | |
| Any Primary Cardiac Event | 0 | 2 | | |
| Heart Failure and Significant LVEF Decline | 0 | 1 | | |
| Cardiac Death (Definite or Probable) | 0 | 1 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With a Secondary Cardiac Event During the Neoadjuvant Phase

| End point title | Number of Participants With a Secondary Cardiac Event During the Neoadjuvant Phase |
|---|---|

End point description:

A secondary cardiac event is defined as asymptomatic or mildly symptomatic Left Ventricular Systolic Dysfunction (LVSD) of NYHA Class II, defined as a left ventricular ejection fraction (LVEF) decrease of at least 10-percentage points below the baseline measurement to an absolute LVEF value of <50% confirmed by a second assessment within approximately 3 weeks

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

End point timeframe:

From first dose of study treatment until the completion of neoadjuvant therapy (24 weeks)

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Participants | | | | |
| Any Secondary Cardiac Event | 4 | 1 | | |
| Identified by Initial LVEF Assessments | 4 | 1 | | |
| Confirmed by Second LVEF Assessment | 1 | 1 | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With a Primary Cardiac Event During the Adjuvant Phase

| End point title | Number of Participants With a Primary Cardiac Event During the Adjuvant Phase |
|---|---|

End point description:

A primary cardiac event is defined as the occurrence of either of the following events: - Incidence of a symptomatic ejection fraction decrease (heart failure) of New York Heart Association (NYHA) Class III or IV and a drop in left ventricular ejection fraction (LVEF) of at least 10-percentage points from baseline and to below 50%; or - Cardiac death, defined as: Definite cardiac death (due to heart failure, myocardial infarction, or documented primary arrhythmia); or, Probable cardiac death (sudden unexpected death within 24 hours of a definite or probable cardiac event [e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia] without documented etiology).

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

End point timeframe:

From surgery until 28 days after the last dose of adjuvant treatment (42 weeks)

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Participants | | | | |
| Any Primary Cardiac Event | 1 | 2 | | |
| Heart Failure and Significant LVEF Decline | 1 | 2 | | |
| Cardiac Death (Definite or Probable) | 1 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With a Secondary Cardiac Event During the Adjuvant

| End point title | Number of Participants With a Secondary Cardiac Event During the Adjuvant |
|---|---|

End point description:

A secondary cardiac event is defined as asymptomatic or mildly symptomatic Left Ventricular Systolic Dysfunction (LVSD) of NYHA Class II, defined as a left ventricular ejection fraction (LVEF) decrease of at least 10-percentage points below the baseline measurement to an absolute LVEF value of <50% confirmed by a second assessment within approximately 3 weeks.

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

End point timeframe:

From surgery until 28 days after the last dose of adjuvant treatment (42 weeks)

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Participants | | | | |
| Any Secondary Cardiac Event | 15 | 8 | | |
| Identified by Initial LVEF Assessment | 15 | 8 | | |
| Confirmed by Second LVEF Assessment | 0 | 0 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Laboratory Test Abnormalities at the Highest NCI CTCAE v4 Grade Post-Baseline Over the Course of the Entire Study

| End point title | Number of Participants with Laboratory Test Abnormalities at the Highest NCI CTCAE v4 Grade Post-Baseline Over the Course of the Entire Study |
|---|---|

End point description:

Clinical laboratory tests were performed at local laboratories; any abnormal values (High or Low) were based on local laboratory normal ranges. Laboratory abnormalities are presented by the highest (worst) severity grade (according to NCI-CTCAE v4.0) post-baseline. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: clinically significant (per investigator); accompanied by clinical symptoms; resulted in a change in study treatment; or required a medical intervention or a change in concomitant therapy. For a participant with multiple post-baseline abnormalities, only the highest (worst) grade for a given laboratory test is reported. 'Any Grade' indicates the total number of participants with a post-baseline abnormality of any grade for the specified test.

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

End point timeframe:

From first dose of study treatment until 28 days after last dose of study treatment (up to 1 year, 5 months)

| End point values | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 248 | | |
| Units: Participants | | | | |
| Albumin, Low - Any Grade (n=251,247) | 50 | 39 | | |
| Albumin, Low - Grade 1 (n=251,247) | 41 | 34 | | |
| Albumin, Low - Grade 2 (n=251,247) | 8 | 5 | | |
| Albumin, Low - Grade 3 (n=251,247) | 1 | 0 | | |
| Alkaline Phosphatase, High - Any Grade (n=234,225) | 80 | 71 | | |
| Alkaline Phosphatase, High - Grade 1 (n=234,225) | 78 | 70 | | |
| Alkaline Phosphatase, High - Grade 2 (n=234,225) | 2 | 1 | | |
| SGPT/ALT, High - Any Grade | 172 | 149 | | |
| SGPT/ALT, High - Grade 1 | 145 | 132 | | |
| SGPT/ALT, High - Grade 2 | 18 | 13 | | |
| SGPT/ALT, High - Grade 3 | 9 | 4 | | |
| SGOT/AST, High - Any Grade | 149 | 130 | | |
| SGOT/AST, High - Grade 1 | 137 | 125 | | |
| SGOT/AST, High - Grade 2 | 7 | 3 | | |
| SGOT/AST, High - Grade 3 | 5 | 2 | | |
| Creatinine, High - Any Grade | 225 | 217 | | |
| Creatinine, High - Grade 1 | 214 | 204 | | |
| Creatinine, High - Grade 2 | 9 | 13 | | |
| Creatinine, High - Grade 3 | 2 | 0 | | |
| Glucose, Low - Any Grade (n=251,247) | 23 | 22 | | |
| Glucose, Low - Grade 1 (n=251,247) | 20 | 22 | | |
| Glucose, Low - Grade 2 (n=251,247) | 3 | 0 | | |
| Glucose, High - Any Grade (n=251,247) | 3 | 4 | | |
| Glucose, High - Grade 3 (n=251,247) | 3 | 4 | | |
| Hemoglobin, Low - Any Grade | 233 | 223 | | |
| Hemoglobin, Low - Grade 1 | 129 | 139 | | |
| Hemoglobin, Low - Grade 2 | 93 | 77 | | |
| Hemoglobin, Low - Grade 3 | 11 | 7 | | |
| Hemoglobin, High - Any Grade | 12 | 6 | | |
| Hemoglobin, High - Grade 1 | 12 | 6 | | |
| Lymphocytes, Abs., Low -Any Grade (n=163,167) | 144 | 150 | | |
| Lymphocytes, Abs., Low - Grade 1 (n=163,167) | 23 | 22 | | |
| Lymphocytes, Abs., Low - Grade 2 (n=163,167) | 59 | 68 | | |
| Lymphocytes, Abs., Low - Grade 3 (n=163,167) | 55 | 56 | | |
| Lymphocytes, Abs., Low - Grade 4 (n=163,167) | 7 | 4 | | |

| | | | | |
|---|---|---|---|---|
| Lymphocytes, Abs., High - Any Grade (n=163,167) | 4 | 3 | | |
| Lymphocytes, Abs., High - Grade 2 (n=163,167) | 4 | 3 | | |
| Neutrophils, Total,Abs., Low -Any Grade(n=163,167) | 110 | 114 | | |
| Neutrophils, Total,Abs., Low - Grade 1(n=163,167) | 27 | 42 | | |
| Neutrophils, Total,Abs., Low - Grade 2(n=163,167) | 30 | 23 | | |
| Neutrophils, Total,Abs., Low - Grade 3(n=163,167) | 17 | 24 | | |
| Neutrophils, Total,Abs., Low - Grade 4(n=163,167) | 36 | 25 | | |
| Platelets, Low - Any Grade | 72 | 67 | | |
| Platelets, Low - Grade 1 | 68 | 65 | | |
| Platelets, Low - Grade 2 | 3 | 2 | | |
| Platelets, Low - Grade 3 | 1 | 0 | | |
| Potassium, Low - Any Grade | 45 | 41 | | |
| Potassium, Low - Grade 2 | 38 | 28 | | |
| Potassium, Low - Grade 3 | 6 | 11 | | |
| Potassium, Low - Grade 4 | 1 | 2 | | |
| Potassium, High - Any Grade | 24 | 32 | | |
| Potassium, High - Grade 1 | 17 | 26 | | |
| Potassium, High - Grade 2 | 7 | 3 | | |
| Potassium, High - Grade 3 | 0 | 2 | | |
| Potassium, High - Grade 4 | 0 | 1 | | |
| Sodium, Low - Any Grade | 27 | 33 | | |
| Sodium, Low - Grade 1 | 22 | 32 | | |
| Sodium, Low - Grade 3 | 4 | 0 | | |
| Sodium, Low - Grade 4 | 1 | 1 | | |
| Sodium, High - Any Grade | 25 | 16 | | |
| Sodium, High - Grade 1 | 19 | 13 | | |
| Sodium, High - Grade 2 | 4 | 1 | | |
| Sodium, High - Grade 3 | 0 | 1 | | |
| Sodium, High - Grade 4 | 2 | 1 | | |
| Bilirubin, High - Any Grade | 24 | 22 | | |
| Bilirubin, High - Grade 1 | 16 | 17 | | |
| Bilirubin, High - Grade 2 | 7 | 5 | | |
| Bilirubin, High - Grade 3 | 1 | 0 | | |
| Total Leukocyte Count, Low - Any Grade | 199 | 203 | | |
| Total Leukocyte Count, Low - Grade 1 | 57 | 64 | | |
| Total Leukocyte Count, Low - Grade 2 | 81 | 78 | | |
| Total Leukocyte Count, Low - Grade 3 | 41 | 43 | | |
| Total Leukocyte Count, Low - Grade 4 | 20 | 18 | | |
| Total Leukocyte Count, High - Any Grade | 0 | 1 | | |
| Total Leukocyte Count, High - Grade 1 | 0 | 1 | | |

**Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs): From first dose of study treatment until 28 days after last dose of study treatment (up to 1 year, 5 months); All-cause mortality: From first dose of study treatment until end of follow-up (up to 4 years, 11.5 months)

Adverse event reporting additional description:

After initiation of study drug, all AEs were reported until 28 days after the last dose of study drug. After this period, only drug-related serious AEs, heart failure, pregnancies, and malignancies were reported.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy |

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

| | |
|---|---|
| Reporting group title | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy |

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab were given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

| Serious adverse events | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 49 / 248 (19.76%) | 52 / 252 (20.63%) | |
| number of deaths (all causes) | 14 | 12 | |
| number of deaths resulting from adverse events | 2 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Angiosarcoma | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clear cell renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endometrial cancer | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thyroid cancer | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer stage I | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iliac artery occlusion | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 3 / 252 (1.19%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lithiasis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|---|---|---|
| Intermenstrual bleeding | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast haematoma | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast inflammation | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 248 (0.81%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium test positive | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Flap necrosis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haematoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 2 / 252 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 248 (1.61%) | 6 / 252 (2.38%) | |
| occurrences causally related to treatment / all | 5 / 5 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Seizure | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 9 / 248 (3.63%) | 10 / 252 (3.97%) | |
| occurrences causally related to treatment / all | 9 / 9 | 10 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 3 / 252 (1.19%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 2 / 252 (0.79%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal incontinence | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal toxicity | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Periostitis | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 3 / 252 (1.19%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mastitis | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 2 / 252 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 2 / 252 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 3 / 248 (1.21%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngopharyngitis | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 248 (0.81%) | 2 / 252 (0.79%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative abscess | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 248 (0.40%) | 0 / 252 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 248 (0.00%) | 1 / 252 (0.40%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy | Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 248 / 248 (100.00%) | 251 / 252 (99.60%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 248 (4.84%) | 16 / 252 (6.35%) | |
| occurrences (all) | 13 | 19 | |
| Hot flush | | | |
| subjects affected / exposed | 41 / 248 (16.53%) | 39 / 252 (15.48%) | |
| occurrences (all) | 44 | 44 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 79 / 248 (31.85%) | 84 / 252 (33.33%) | |
| occurrences (all) | 160 | 142 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 39 / 248 (15.73%) | 49 / 252 (19.44%) | |
| occurrences (all) | 53 | 66 | |
| Oedema | | | |
| subjects affected / exposed | 6 / 248 (2.42%) | 13 / 252 (5.16%) | |
| occurrences (all) | 6 | 13 | |
| Pyrexia | | | |
| subjects affected / exposed | 32 / 248 (12.90%) | 41 / 252 (16.27%) | |
| occurrences (all) | 41 | 56 | |
| Fatigue | | | |
| subjects affected / exposed | 71 / 248 (28.63%) | 62 / 252 (24.60%) | |
| occurrences (all) | 113 | 114 | |
| Injection site reaction | | | |
| subjects affected / exposed | 40 / 248 (16.13%) | 2 / 252 (0.79%) | |
| occurrences (all) | 174 | 2 | |
| Influenza like illness | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 11 / 252 (4.37%) | |
| occurrences (all) | 21 | 17 | |

| | | | |
|---|---|---|---|
| Oedema peripheral | | | |
| subjects affected / exposed | 23 / 248 (9.27%) | 26 / 252 (10.32%) | |
| occurrences (all) | 25 | 28 | |
| Malaise | | | |
| subjects affected / exposed | 14 / 248 (5.65%) | 16 / 252 (6.35%) | |
| occurrences (all) | 20 | 20 | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 13 / 252 (5.16%) | |
| occurrences (all) | 17 | 13 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 31 / 248 (12.50%) | 37 / 252 (14.68%) | |
| occurrences (all) | 36 | 43 | |
| Dyspnoea | | | |
| subjects affected / exposed | 29 / 248 (11.69%) | 15 / 252 (5.95%) | |
| occurrences (all) | 32 | 18 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 14 / 252 (5.56%) | |
| occurrences (all) | 16 | 21 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 17 / 248 (6.85%) | 13 / 252 (5.16%) | |
| occurrences (all) | 22 | 15 | |
| Cough | | | |
| subjects affected / exposed | 41 / 248 (16.53%) | 40 / 252 (15.87%) | |
| occurrences (all) | 44 | 43 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 44 / 248 (17.74%) | 35 / 252 (13.89%) | |
| occurrences (all) | 50 | 45 | |
| Anxiety | | | |
| subjects affected / exposed | 15 / 248 (6.05%) | 8 / 252 (3.17%) | |
| occurrences (all) | 17 | 8 | |
| Investigations | | | |
| Neutrophil count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 40 / 248 (16.13%) | 54 / 252 (21.43%) | |
| occurrences (all) | 97 | 141 | |
| Weight decreased | | | |
| subjects affected / exposed | 26 / 248 (10.48%) | 15 / 252 (5.95%) | |
| occurrences (all) | 27 | 16 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 16 / 248 (6.45%) | 24 / 252 (9.52%) | |
| occurrences (all) | 17 | 28 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 29 / 248 (11.69%) | 40 / 252 (15.87%) | |
| occurrences (all) | 37 | 54 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 19 / 248 (7.66%) | 35 / 252 (13.89%) | |
| occurrences (all) | 58 | 108 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 39 / 248 (15.73%) | 50 / 252 (19.84%) | |
| occurrences (all) | 50 | 61 | |
| Injury, poisoning and procedural complications | | | |
| Radiation skin injury | | | |
| subjects affected / exposed | 50 / 248 (20.16%) | 54 / 252 (21.43%) | |
| occurrences (all) | 51 | 55 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 9 / 248 (3.63%) | 36 / 252 (14.29%) | |
| occurrences (all) | 9 | 53 | |
| Procedural pain | | | |
| subjects affected / exposed | 29 / 248 (11.69%) | 25 / 252 (9.92%) | |
| occurrences (all) | 31 | 26 | |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 42 / 248 (16.94%) | 40 / 252 (15.87%) | |
| occurrences (all) | 45 | 44 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 33 / 248 (13.31%) | 40 / 252 (15.87%) | |
| occurrences (all) | 38 | 53 | |
| Paraesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 25 / 248 (10.08%) | 23 / 252 (9.13%) | |
| occurrences (all) | 30 | 26 | |
| Dysgeusia | | | |
| subjects affected / exposed | 43 / 248 (17.34%) | 35 / 252 (13.89%) | |
| occurrences (all) | 53 | 45 | |
| Dizziness | | | |
| subjects affected / exposed | 34 / 248 (13.71%) | 32 / 252 (12.70%) | |
| occurrences (all) | 39 | 39 | |
| Headache | | | |
| subjects affected / exposed | 45 / 248 (18.15%) | 68 / 252 (26.98%) | |
| occurrences (all) | 72 | 84 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 90 / 248 (36.29%) | 109 / 252 (43.25%) | |
| occurrences (all) | 117 | 148 | |
| Leukopenia | | | |
| subjects affected / exposed | 25 / 248 (10.08%) | 36 / 252 (14.29%) | |
| occurrences (all) | 42 | 58 | |
| Neutropenia | | | |
| subjects affected / exposed | 58 / 248 (23.39%) | 64 / 252 (25.40%) | |
| occurrences (all) | 109 | 119 | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 14 / 248 (5.65%) | 9 / 252 (3.57%) | |
| occurrences (all) | 14 | 11 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 14 / 248 (5.65%) | 14 / 252 (5.56%) | |
| occurrences (all) | 15 | 15 | |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 35 / 248 (14.11%) | 31 / 252 (12.30%) | |
| occurrences (all) | 42 | 34 | |
| Stomatitis | | | |
| subjects affected / exposed | 63 / 248 (25.40%) | 61 / 252 (24.21%) | |
| occurrences (all) | 85 | 90 | |
| Abdominal pain upper | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 20 / 248 (8.06%) | 21 / 252 (8.33%) | |
| occurrences (all) | 31 | 25 | |
| Vomiting | | | |
| subjects affected / exposed | 50 / 248 (20.16%) | 50 / 252 (19.84%) | |
| occurrences (all) | 71 | 73 | |
| Abdominal pain | | | |
| subjects affected / exposed | 22 / 248 (8.87%) | 15 / 252 (5.95%) | |
| occurrences (all) | 29 | 17 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 22 / 248 (8.87%) | 11 / 252 (4.37%) | |
| occurrences (all) | 22 | 11 | |
| Diarrhoea | | | |
| subjects affected / exposed | 152 / 248 (61.29%) | 148 / 252 (58.73%) | |
| occurrences (all) | 293 | 309 | |
| Nausea | | | |
| subjects affected / exposed | 151 / 248 (60.89%) | 157 / 252 (62.30%) | |
| occurrences (all) | 308 | 327 | |
| Constipation | | | |
| subjects affected / exposed | 57 / 248 (22.98%) | 54 / 252 (21.43%) | |
| occurrences (all) | 75 | 79 | |
| Gastritis | | | |
| subjects affected / exposed | 13 / 248 (5.24%) | 5 / 252 (1.98%) | |
| occurrences (all) | 14 | 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Onycholysis | | | |
| subjects affected / exposed | 11 / 248 (4.44%) | 13 / 252 (5.16%) | |
| occurrences (all) | 11 | 13 | |
| Dry skin | | | |
| subjects affected / exposed | 38 / 248 (15.32%) | 34 / 252 (13.49%) | |
| occurrences (all) | 43 | 39 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 17 / 248 (6.85%) | 13 / 252 (5.16%) | |
| occurrences (all) | 17 | 13 | |
| Alopecia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 196 / 248 (79.03%) | 184 / 252 (73.02%) | |
| occurrences (all) | 196 | 188 | |
| Rash | | | |
| subjects affected / exposed | 46 / 248 (18.55%) | 56 / 252 (22.22%) | |
| occurrences (all) | 56 | 75 | |
| Pruritus | | | |
| subjects affected / exposed | 29 / 248 (11.69%) | 25 / 252 (9.92%) | |
| occurrences (all) | 35 | 29 | |
| Nail disorder | | | |
| subjects affected / exposed | 16 / 248 (6.45%) | 17 / 252 (6.75%) | |
| occurrences (all) | 18 | 17 | |
| Nail discolouration | | | |
| subjects affected / exposed | 23 / 248 (9.27%) | 17 / 252 (6.75%) | |
| occurrences (all) | 23 | 17 | |
| Dermatitis | | | |
| subjects affected / exposed | 19 / 248 (7.66%) | 14 / 252 (5.56%) | |
| occurrences (all) | 20 | 14 | |
| Erythema | | | |
| subjects affected / exposed | 22 / 248 (8.87%) | 14 / 252 (5.56%) | |
| occurrences (all) | 26 | 14 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 22 / 248 (8.87%) | 25 / 252 (9.92%) | |
| occurrences (all) | 26 | 30 | |
| Back pain | | | |
| subjects affected / exposed | 25 / 248 (10.08%) | 15 / 252 (5.95%) | |
| occurrences (all) | 32 | 20 | |
| Myalgia | | | |
| subjects affected / exposed | 67 / 248 (27.02%) | 52 / 252 (20.63%) | |
| occurrences (all) | 80 | 63 | |
| Muscle spasms | | | |
| subjects affected / exposed | 21 / 248 (8.47%) | 18 / 252 (7.14%) | |
| occurrences (all) | 23 | 20 | |
| Musculoskeletal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 248 (3.23%) | 13 / 252 (5.16%) | |
| occurrences (all) | 9 | 18 | |
| Bone pain | | | |
| subjects affected / exposed | 20 / 248 (8.06%) | 13 / 252 (5.16%) | |
| occurrences (all) | 24 | 19 | |
| Arthralgia | | | |
| subjects affected / exposed | 71 / 248 (28.63%) | 82 / 252 (32.54%) | |
| occurrences (all) | 91 | 106 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 18 / 248 (7.26%) | 16 / 252 (6.35%) | |
| occurrences (all) | 22 | 20 | |
| Paronychia | | | |
| subjects affected / exposed | 20 / 248 (8.06%) | 12 / 252 (4.76%) | |
| occurrences (all) | 21 | 14 | |
| Rhinitis | | | |
| subjects affected / exposed | 14 / 248 (5.65%) | 13 / 252 (5.16%) | |
| occurrences (all) | 15 | 17 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 34 / 248 (13.71%) | 24 / 252 (9.52%) | |
| occurrences (all) | 43 | 37 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 33 / 248 (13.31%) | 36 / 252 (14.29%) | |
| occurrences (all) | 40 | 39 | |
| Cystitis | | | |
| subjects affected / exposed | 8 / 248 (3.23%) | 13 / 252 (5.16%) | |
| occurrences (all) | 8 | 14 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 16 / 248 (6.45%) | 22 / 252 (8.73%) | |
| occurrences (all) | 17 | 24 | |
| Decreased appetite | | | |
| subjects affected / exposed | 43 / 248 (17.34%) | 51 / 252 (20.24%) | |
| occurrences (all) | 50 | 70 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 12 October 2018 | Protocol version 2 provided additional clarifications and corrected inconsistencies regarding the inclusion criteria, observation periods following IMPs administration, management of hypersensitivity, tumor staging, PK sampling process, reasons for discontinuation, and LVEF assessments. None of these updates constituted a major change to the protocol. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported