



Clinical trial results:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial To Evaluate the Efficacy And Safety Of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2007-002997-72 |
| Trial protocol | FI DE GB ES FR IT LV |
| Global end of trial date | 23 November 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 18 December 2019 |
| First version publication date | 06 August 2015 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | TOC4129g/WO20698 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00567190 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, 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 | 23 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 May 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare progression-free survival (PFS) based on tumor assessments by an independent review facility (IRF) between participants in two treatment arms: Placebo + Trastuzumab + Docetaxel vs. Pertuzumab + Trastuzumab + Docetaxel.

Protection of trial subjects:

This study was conducted in full conformance with the principles of the Declaration of Helsinki and its subsequent amendments or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the participant. The study adhered to the principles outlined in the Guideline for Good Clinical Practice ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the participant. In other countries where guidelines for good clinical practice existed, the sponsor and the investigators were to strictly ensure adherence to the stated provisions. For each potential participant, written informed consent was obtained prior to the performance of any study related procedures and after the aims, methods, anticipated benefits, and potential hazards of the study were adequately explained. The protocol and any accompanying material provided to the participant (such as participant information sheets or descriptions of the study used to obtain informed consent) were approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) before starting the study. Protocol amendments were also approved by IECs/IRBs.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------------------------|
| Actual start date of recruitment | 12 February 2008 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Regulatory reason, Efficacy |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Brazil: 100 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | Argentina: 13 |
| Country: Number of subjects enrolled | China: 13 |
| Country: Number of subjects enrolled | Costa Rica: 6 |
| Country: Number of subjects enrolled | Croatia: 4 |
| Country: Number of subjects enrolled | Ecuador: 1 |
| Country: Number of subjects enrolled | Finland: 5 |
| Country: Number of subjects enrolled | France: 24 |
| Country: Number of subjects enrolled | Germany: 44 |
| Country: Number of subjects enrolled | Guatemala: 5 |

| | |
|--------------------------------------|---|
| Country: Number of subjects enrolled | Hong Kong: 5 |
| Country: Number of subjects enrolled | Italy: 24 |
| Country: Number of subjects enrolled | Japan: 53 |
| Country: Number of subjects enrolled | Latvia: 6 |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 3 |
| Country: Number of subjects enrolled | Mexico: 6 |
| Country: Number of subjects enrolled | Philippines: 30 |
| Country: Number of subjects enrolled | Poland: 33 |
| Country: Number of subjects enrolled | Russian Federation: 71 |
| Country: Number of subjects enrolled | Singapore: 20 |
| Country: Number of subjects enrolled | Korea, Republic of: 94 |
| Country: Number of subjects enrolled | Spain: 58 |
| Country: Number of subjects enrolled | Thailand: 38 |
| Country: Number of subjects enrolled | United Kingdom: 34 |
| Country: Number of subjects enrolled | United States: 116 |
| Worldwide total number of subjects | 808 |
| EEA total number of subjects | 232 |

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) | 681 |
| From 65 to 84 years | 126 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1196 patients were screened for the study, of whom a total of 808 subjects were randomized to one of the two treatment arms.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Assessor |

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Pertuzumab + Trastuzumab + Docetaxel |

Arm description:

Subjects randomized to this arm received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m²) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

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

Dosage and administration details:

Pertuzumab was administered as an intravenous (IV) loading dose of 840 milligrams (mg) at Cycle 1 then at a dose of 420 mg at all subsequent cycles (1 cycle was 21 days) until investigator-assessed radiographic or clinical evidence of progressive disease (PD), unacceptable toxicity, or withdrawal of consent.

| | |
|--|---|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | Herclon, Herceptin |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab was administered as an IV loading dose of 8 mg/kg at Cycle 1 and at a dose of 6 mg/kg at all subsequent cycles (1 cycle was 21 days) until investigator-assessed radiographic or clinical evidence of PD, unacceptable toxicity, or withdrawal of consent.

| | |
|--|---|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | Taxotere, Docecad, Docefrez |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel was administered as an IV dose of 75 milligrams per square metre of body surface area

(mg/m²) for at least 6 cycles (1 cycle was 21 days). For subjects who tolerated at least one cycle without any significant toxicity, the docetaxel dose was increased to 100 mg/m² at the investigator's discretion. On or prior to Cycle 6, docetaxel was only discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician.

| | |
|------------------|-----------------------------------|
| Arm title | Placebo + Trastuzumab + Docetaxel |
|------------------|-----------------------------------|

Arm description:

Subjects randomized to this arm received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m² IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The placebo formulation was equivalent to pertuzumab without the active agent. Subjects received placebo IV at each treatment cycle (once every 3 weeks) until investigator-assessed radiographic or clinical evidence of PD, unacceptable toxicity, or withdrawal of consent.

| | |
|--|---|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | Herclon, Herceptin |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Trastuzumab was administered as an IV loading dose of 8 mg/kg at Cycle 1 and at a dose of 6 mg/kg at all subsequent cycles (1 cycle was 21 days) until investigator-assessed radiographic or clinical evidence of PD, unacceptable toxicity, or withdrawal of consent.

| | |
|--|---|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | Taxotere, Docecad, Docefrez |
| Pharmaceutical forms | Concentrate and solvent for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel was administered as an IV dose of 75 milligrams per square metre of body surface area (mg/m²) for at least 6 cycles (1 cycle was 21 days). For subjects who tolerated at least one cycle without any significant toxicity, the docetaxel dose was increased to 100 mg/m² at the investigator's discretion. On or prior to Cycle 6, docetaxel was only discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician.

| Number of subjects in period 1 | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel |
|--|---|--|
| Started | 402 | 406 |
| Did Not Receive Any Study Treatment | 2 ^[1] | 2 ^[2] |
| Received At Least One Dose of Pertuzumab | 399 | 9 ^[3] |
| Received Placebo at Every Cycle | 1 ^[4] | 395 |

| | | |
|---------------------------------------|-----|-----|
| Completed | 119 | 73 |
| Not completed | 283 | 333 |
| Withdrew Consent or Lost to Follow-up | 48 | 53 |
| Death | 235 | 280 |

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: A total of 2 subjects randomized to the Pertuzumab arm withdrew from the study before receiving any study treatment.

[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: A total of 2 subjects randomized to the Placebo arm withdrew from the study before receiving any study treatment.

[3] - 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: A total of 9 subjects randomized to the Placebo arm actually received at least one dose of pertuzumab in error.

[4] - 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: One subject randomized to the Pertuzumab arm actually received placebo in error at every treatment cycle.

Baseline characteristics

Reporting groups

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

Reporting group description:

Subjects randomized to this arm received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m²) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo + Trastuzumab + Docetaxel |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects randomized to this arm received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m² IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| Reporting group values | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel | Total |
|---|--|---|-------|
| Number of subjects | 402 | 406 | 808 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 342 | 339 | 681 |
| From 65 to 84 years | 60 | 66 | 126 |
| 85 years and over | 0 | 1 | 1 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 53.4 | 53.5 | |
| standard deviation | ± 10.94 | ± 11.35 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 402 | 404 | 806 |
| Male | 0 | 2 | 2 |
| Region | | | |
| Units: Subjects | | | |
| Asia | 125 | 128 | 253 |
| Europe | 154 | 152 | 306 |
| North America | 67 | 68 | 135 |
| South America | 56 | 58 | 114 |
| Prior Treatment Status | | | |
| Units: Subjects | | | |
| Adjuvant or Neo-Adjuvant Therapy | 184 | 192 | 376 |
| De Novo | 218 | 214 | 432 |
| Independent-Review Facility (IRF)- Determined Disease Status at Screening | | | |
| A subject was deemed to have measurable disease if they had at least 1 target lesion at screening. Target lesions (maximum of 5 per organ and 10 in total) were selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging | | | |

techniques or clinically). Any subjects with non-target lesions only were deemed to have non-measurable disease. The IRF did not evaluate baseline tumor assessments for any subject without a post-baseline tumor assessment.

| Units: Subjects | | | |
|------------------------|-----|-----|-----|
| Measurable Disease | 343 | 336 | 679 |
| Non-Measurable Disease | 44 | 43 | 87 |
| Not Evaluated | 15 | 27 | 42 |

End points

End points reporting groups

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

Reporting group description:

Subjects randomized to this arm received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m²) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo + Trastuzumab + Docetaxel |
|-----------------------|-----------------------------------|

Reporting group description:

Subjects randomized to this arm received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m² IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | Placebo + Trastuzumab + Docetaxel |
|----------------------------|-----------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

This is the placebo safety population, which includes subjects who received study treatment with placebo at every cycle. Subjects received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m² IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| | |
|----------------------------|--------------------------------------|
| Subject analysis set title | Pertuzumab + Trastuzumab + Docetaxel |
|----------------------------|--------------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

This is the pertuzumab safety population, which includes subjects who received at least one dose of study treatment with pertuzumab. Subjects received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m²) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| | |
|----------------------------|--------------------------------------|
| Subject analysis set title | Crossover From Placebo to Pertuzumab |
|----------------------------|--------------------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Fifty of 406 subjects (12.3%) randomized to the placebo treatment group whose disease had not progressed crossed over to an open-label pertuzumab treatment group between July 2012 and November 2018. Subjects received pertuzumab administered as an IV loading dose of 840 mg at cycle 1 then 420 mg IV every q3w. Trastuzumab and docetaxel doses continued in accordance with the pre-crossover placebo treatment regimens and according to dosing specifications indicated in the study protocol. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

Primary: Progression-Free Survival (PFS) Determined by an Independent Review Facility

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|-----------------|--|
| End point title | Progression-Free Survival (PFS) Determined by an Independent Review Facility |
|-----------------|--|

End point description:

PFS was defined as the time from randomization to first documented radiographical progressive disease (PD), as determined by an independent review facility (IRF) using RECIST version 1.0, or death from any cause (within 18 weeks of last tumor assessment), whichever occurred first (Kaplan-Meier method). For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum of the LD recorded since treatment started or the appearance of ≥ 1 new lesion. For non-target lesions, PD was defined as the appearance of ≥ 1 new lesion or unequivocal progression of existing lesions. Subjects without IRF-determined PD or who had not died within 18 weeks of their last IRF-determined, progression-free tumor assessment were censored at the date of the last IRF-reviewed, evaluable tumor assessment. Subjects with no post-baseline tumor assessment and who had not died within 18 weeks of baseline were censored at 1 day.

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

End point timeframe:

Tumor assessments every 9 weeks from randomization to IRF-determined PD or death from any cause, whichever occurred first, up to the primary completion date (up to 3 years, 3 months)

| End point values | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel | | |
|----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 402 ^[1] | 406 ^[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.5 (15 to 23) | 12.4 (10 to 13) | | |

Notes:

[1] - Intent-to-Treat (ITT) Population: all randomized subjects were included.

[2] - ITT Population: all randomized subjects were included.

Statistical analyses

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|----------------------------|-------------------------|
| Statistical analysis title | PFS by IRF - Stratified |
|----------------------------|-------------------------|

Statistical analysis description:

The null hypothesis (H0) was that the survival distributions of PFS in the two treatments arms (pertuzumab vs. placebo) are the same. The alternative hypothesis (H1) was that the survival distribution of PFS in the experimental arm (pertuzumab) and control arm (placebo) are different.

| | |
|---|--|
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.0001 ^[4] |
| Method | Log Rank (stratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.75 |

Notes:

[3] - Hazard ratio is comparing Pertuzumab arm with Placebo arm.

[4] - Stratified by prior treatment status and region. Tested at two-sided 5% significance level.

| | |
|---|--|
| Statistical analysis title | PFS by IRF - Unstratified |
| Statistical analysis description: | |
| The null hypothesis (H0) was that the survival distributions of PFS in the two treatments arms (pertuzumab vs. placebo) are the same. The alternative hypothesis (H1) was that the survival distribution of PFS in the experimental arm (pertuzumab) and control arm (placebo) are different. | |
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | < 0.0001 ^[6] |
| Method | Log Rank (unstratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 0.76 |

Notes:

[5] - Hazard ratio is comparing Pertuzumab arm with Placebo arm.

[6] - Unstratified and tested at two-sided 5% significance level

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall survival (OS) was defined as time from randomization to death from any cause, using Kaplan-Meier methodology. Survival data was collected every 18 weeks during the post-treatment follow-up period until death, loss to follow-up, or withdrawal of consent; immediately prior to final OS analysis data cutoff, every subject on study was contacted to confirm current status. Those who were alive, lost to follow up, or withdrew consent were censored at the latest date they participated in the study; those without post-baseline data were censored at 1 day. OS analyses were planned to take place at the primary completion date (First Interim OS Analysis), after 385 deaths (Event-Driven Final OS Analysis), and at the end of study (End-of-Study OS Analysis). A second interim OS analysis was planned due to a formal request from the EMA. '99999' indicates median and/or 95% confidence interval values could not be determined because they were larger than the maximum follow-up time at analysis. | |
| End point type | Secondary |

End point timeframe:

From randomization (first subject enrolled date: 12-Feb-2008) to death from any cause, up to each respective data analysis cut-off date (First: 13-May-2011; Second: 14-May-2012; Event-Driven Final: 11-Feb-2014; End-of-Study: 23-Nov-2018)

| | | | | |
|----------------------------------|--------------------------------------|-----------------------------------|--|--|
| End point values | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 402 ^[7] | 406 ^[8] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |

| | | | | |
|--|------------------------|---------------------|--|--|
| End-of-Study OS Analysis (23-Nov-2018) | 57.1 (50 to 72) | 40.8 (36 to 48) | | |
| Event-Driven Final OS Analysis (11-Feb-2014) | 56.5 (49 to 99999) | 40.8 (36 to 48) | | |
| Second Interim OS Analysis (14-May-2012) | 99999 (42 to 99999) | 37.6 (34 to 99999) | | |
| First Interim OS Analysis (13-May-2011) | 99999 (99999 to 99999) | 99999 (30 to 99999) | | |

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

| Statistical analysis title | End-of-Study OS Analysis (23-Nov-2018) |
|--|--|
| Statistical analysis description: | |
| This end-of-study OS analysis is considered exploratory only as the confirmatory OS analysis for statistical interpretation had previously occurred at the second interim OS analysis. | |
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| P-value | < 0.0001 ^[10] |
| Method | Log Rank (stratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.82 |

Notes:

[9] - Hazard ratio is comparing Pertuzumab arm with Placebo arm.

[10] - Stratified by prior treatment status and region; p-value is exploratory.

| Statistical analysis title | Event-Driven Final OS Analysis (11-Feb-2014) |
|---|--|
| Statistical analysis description: | |
| This final OS analysis was event-driven and planned to take place after a total of 385 deaths had occurred. It is considered exploratory only as the confirmatory OS analysis for statistical interpretation had previously occurred at the second interim OS analysis. | |
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[11] |
| P-value | = 0.0002 ^[12] |
| Method | Log Rank (stratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 0.84 |

Notes:

[11] - Hazard ratio is comparing Pertuzumab arm with Placebo arm.

[12] - Stratified by prior treatment status and region; p-value is exploratory.

| | |
|---|--|
| Statistical analysis title | Second Interim OS Analysis (14-May-2012) |
| Statistical analysis description: For this second interim OS analysis, the pre-defined O'Brien-Fleming stopping boundary for the Lan-DeMets α -spending function was: $HR \leq 0.739$, $p \leq 0.0138$. | |
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | = 0.0008 ^[14] |
| Method | Log Rank (stratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 0.84 |

Notes:

[13] - Hazard ratio (HR) is comparing Pertuzumab arm with Placebo arm.

[14] - Stratified by prior treatment status and region. The threshold for statistical significance was $HR \leq 0.739$, $p \leq 0.0138$.

| | |
|--|--|
| Statistical analysis title | First Interim OS Analysis (13-May-2011) |
| Statistical analysis description: For this first interim OS analysis, the pre-defined O'Brien-Fleming stopping boundary for the Lan-DeMets α -spending function was: $HR \leq 0.603$, $p \leq 0.0012$. | |
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[15] |
| P-value | = 0.005 ^[16] |
| Method | Log Rank (stratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 0.88 |

Notes:

[15] - Hazard ratio (HR) is comparing Pertuzumab arm with Placebo arm.

[16] - Stratified by prior treatment status and region. The threshold for statistical significance was $HR \leq 0.603$, $p \leq 0.0012$.

Secondary: Progression-Free Survival (PFS) Determined by the Investigator

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) Determined by the Investigator |
|-----------------|--|

End point description:

PFS was defined as the time from randomization to first documented radiographical progressive disease (PD), as determined by the investigator using RECIST version 1.0, or death from any cause (within 18 weeks of last tumor assessment), whichever occurred first (Kaplan-Meier method). For target lesions, PD was defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum of the LD recorded since treatment started or the appearance of ≥ 1 new lesion. For non-target lesions, PD was defined as the appearance of ≥ 1 new lesion or unequivocal progression of existing lesions. Subjects without PD or who had not died within 18 weeks of their last investigator-determined, progression-free tumor assessment were censored at the date of the last investigator tumor assessment. Subjects with no post-baseline tumor assessment and who had not died within 18 weeks of baseline were censored at 1 day.

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

End point timeframe:

Tumor assessments every 9 weeks from randomization to investigator-determined PD or death from any cause, whichever occurred first (median [range] time on study in Pertuzumab arm vs. Placebo arm: 201.8 [0.7-520.0] weeks vs. 138.0 [0.4-514.7] weeks)

| End point values | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel | | |
|----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 402 ^[17] | 406 ^[18] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 18.7 (17 to 22) | 12.4 (10 to 14) | | |

Notes:

[17] - ITT Population

[18] - ITT Population

Statistical analyses

| Statistical analysis title | PFS by Investigator - Stratified |
|---|--|
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 808 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| P-value | < 0.0001 ^[20] |
| Method | Log Rank (stratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 0.81 |

Notes:

[19] - Hazard ratio is comparing Pertuzumab arm with Placebo arm.

[20] - Stratified by prior treatment status and region

Secondary: Objective Response Determined by an Independent Review Facility

| | |
|-----------------|---|
| End point title | Objective Response Determined by an Independent Review Facility |
|-----------------|---|

End point description:

An objective response was defined as the percentage of subjects with confirmed best overall response of

complete response (CR) or partial response (PR), as determined by an independent review facility (IRF) using RECIST v1.0 on two consecutive occasions ≥ 4 weeks apart. For target lesions, CR: disappearance of all target lesions; PR: $\geq 30\%$ decrease in the sum of the longest diameter (LD) of target lesions (baseline sum LD as reference); PD: $\geq 20\%$ increase in the sum of the LD of target lesions (smallest sum of the LD recorded as reference) or appearance of ≥ 1 new lesion; SD: neither sufficient shrinkage to qualify for PR nor sufficient increase for PD. For non-target lesions, CR: disappearance of all non-target lesions; Incomplete/SD: persistence of ≥ 1 non-target lesions; PD: unequivocal progression of existing non-target lesions. 95% confidence intervals (CI) were calculated only for clinical responses using the Pearson-Clopper method; '0.099999' and '999999'=95% CIs not calculated.

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

End point timeframe:

Tumor assessments every 9 weeks from Baseline until IRF-determined progressive disease (PD) or death from any cause, up to the primary completion date (up to 3 years, 3 months)

| End point values | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel | | |
|----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 343 ^[21] | 336 ^[22] | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Objective Response (CR + PR) | 80.2 (75.6 to 84.3) | 69.3 (64.1 to 74.2) | | |
| Complete Response (CR) | 5.5 (3.4 to 8.5) | 4.2 (2.3 to 6.9) | | |
| Partial Response (PR) | 74.6 (69.7 to 79.2) | 65.2 (59.8 to 70.3) | | |
| Stable Disease (SD) | 14.6 (11.0 to 18.8) | 20.8 (16.6 to 25.6) | | |
| Progressive Disease (PD) | 3.8 (2.0 to 6.4) | 8.3 (5.6 to 11.8) | | |
| Unable to Assess (UA) | 0.6 (0.1 to 2.1) | 0.6 (0.1 to 2.1) | | |
| Missing (No Assessment) | 0.9 (0.099999 to 999999) | 0.9 (0.099999 to 999999) | | |

Notes:

[21] - ITT Population: only subjects with IRF-determined measurable disease at baseline were included.

[22] - ITT Population: only subjects with IRF-determined measurable disease at baseline were included.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Difference in Objective Response (CR + PR) |
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 679 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[23] |
| P-value | = 0.0011 ^[24] |
| Method | Mantel-Haenszel |
| Parameter estimate | Difference in Objective Response Rates |
| Point estimate | 10.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.2 |
| upper limit | 17.5 |

Notes:

[23] - Difference in the objective response rates between arms is calculated as Pertuzumab arm minus Placebo arm. The 95% CI was calculated using the Hauck-Anderson method.

[24] - Stratified by prior treatment status and region.

| Statistical analysis title | Odds Ratio for Objective Response (CR + PR) |
|---|--|
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 679 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[25] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.26 |
| upper limit | 2.54 |

Notes:

[25] - Odds ratio for objective response is comparing Pertuzumab arm with Placebo arm.

Secondary: Duration of Objective Response Determined by an Independent Review Facility

| | |
|-----------------|---|
| End point title | Duration of Objective Response Determined by an Independent Review Facility |
|-----------------|---|

End point description:

Duration of objective response (estimated using the Kaplan-Meier approach) was defined as the time from the initial confirmed complete response (CR) or partial response (PR), the date of tumor assessment at which the CR/PR was first detected by the independent review facility (IRF) using RECIST version 1.0, until the date of IRF-determined progressive disease (PD) or death from any cause within 18 weeks of the last tumor assessment, whichever occurred first. If the visit when the initial CR or PR was observed spanned multiple dates, the latest date was used. Only subjects in the ITT analysis population with an IRF-determined objective response (CR or PR), observed prior to IRF-assessed PD, death or next line of anti-cancer therapy, were included in the analysis. Subjects who did not progress or die after they had a confirmed response were censored at the date of their last IRF-evaluable tumor measurement.

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

End point timeframe:

From initial IRF-confirmed CR/PR until IRF-determined PD, death from any cause, or next line of anti-cancer therapy (whichever occurred earliest), up to the primary completion date (up to 3 years, 3 months)

| End point values | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel | | |
|----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 275 ^[26] | 233 ^[27] | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 87.6 (71 to 106) | 54.1 (46 to 64) | | |

Notes:

[26] - ITT Population: only subjects with an objective response were included in the analysis

[27] - ITT Population: only subjects with an objective response were included in the analysis

Statistical analyses

| Statistical analysis title | Hazard Ratio |
|---|--|
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[28] |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.66 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.85 |

Notes:

[28] - Hazard ratio is comparing Pertuzumab arm with Placebo arm.

Secondary: Time to Symptom Progression

| | |
|--|-----------------------------|
| End point title | Time to Symptom Progression |
| End point description: | |
| Time to symptom progression was defined as the time from randomization to the first symptom progression as evaluated from the Functional Assessment of Cancer Therapy-for participants with Breast Cancer (FACT-B) questionnaire with the Trial Outcomes Index-Physical/Functional/Breast (TOI-PFB) subscale. The FACT-B TOI-PFB subscale contains 24 items from 3 subsections of the FACT-B questionnaire: Physical Well-being, Functional Well-being, and Additional Concerns for breast cancer participants (breast cancer subscale [BCS]). All items in the questionnaire were rated by the patient on a 5-point scale ranging from 0 ("not at all") to 4 ("very much"). The total score ranged from 0 to 96. A higher score indicates better perceived quality of life. A positive change score from baseline indicates improvement. Symptom progression was defined as a decrease from baseline of 5 points or more. | |
| End point type | Secondary |
| End point timeframe: | |
| Every 9 weeks from Baseline until investigator-determined progressive disease, up to the primary completion date (up to 3 years, 3 months) | |

| End point values | Pertuzumab + Trastuzumab + Docetaxel | Placebo + Trastuzumab + Docetaxel | | |
|----------------------------------|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 402 ^[29] | 404 ^[30] | | |
| Units: Weeks | | | | |
| median (confidence interval 95%) | 18.4 (18 to 27) | 18.3 (18 to 27) | | |

Notes:

[29] - ITT Population: analysis included only female subjects.

[30] - ITT Population: analysis included only female subjects.

Statistical analyses

| Statistical analysis title | Time to Symptom Progression - FACT-B |
|----------------------------|--|
| Comparison groups | Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 806 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[31] |
| P-value | = 0.7161 ^[32] |
| Method | Log Rank (stratified) |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.16 |

Notes:

[31] - Hazard ratio is comparing Pertuzumab arm with Placebo arm.

[32] - Stratified by prior treatment status and region

Secondary: Overall Number of Subjects Who Experienced At Least One Adverse Event, Including Serious and Non-Serious Adverse Events, by Most Severe Intensity (According to NCI-CTCAE v3.0) During the Treatment Period

| | |
|-----------------|---|
| End point title | Overall Number of Subjects Who Experienced At Least One Adverse Event, Including Serious and Non-Serious Adverse Events, by Most Severe Intensity (According to NCI-CTCAE v3.0) During the Treatment Period |
|-----------------|---|

End point description:

An adverse event's (AE) severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (NCI-CTCAE v3.0); if the AE was not specifically listed, the following grades of severity were used: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening or disabling; and Grade 5 = death. Severe and serious are not synonymous. Severity refers to the intensity of an AE, whereas a serious AE must meet criteria set out in the protocol; both were independently assessed for each AE. Only the most severe intensity was counted for multiple occurrences of the same AE in one subject. AEs reported prior to first crossover treatment were included in the Placebo arm, and in the Crossover arm after that date, for subjects who crossed over from placebo to pertuzumab. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks.

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

End point timeframe:

Placebo arm: Baseline to last dose of study treatment +42 days (or crossover date); Pertuzumab arm: Baseline to last dose of study treatment +42 days; Crossover arm: Crossover date to last dose of study treatment +42 days (see Description - time per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|--|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 ^[33] | 408 ^[34] | 50 ^[35] | |
| Units: Subjects | | | | |
| At Least One Serious AE - All Grades | 116 | 160 | 10 | |
| At Least One Non-Serious AE - All Grades | 386 | 400 | 45 | |
| At Least One AE - All Grades | 391 | 408 | 47 | |
| At Least One AE - Grade 1 | 368 | 386 | 44 | |
| At Least One AE - Grade 2 | 350 | 383 | 34 | |
| At Least One AE - Grade 3 | 229 | 264 | 11 | |
| At Least One AE - Grade 4 | 158 | 167 | 1 | |

| | | | | |
|---------------------------|----|---|---|--|
| At Least One AE - Grade 5 | 12 | 8 | 1 | |
|---------------------------|----|---|---|--|

Notes:

[33] - Safety Population

[34] - Safety Population

[35] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Number of Adverse Events by Severity (NCI-CTCAE v3.0 All Grades and Grades 3-5) per 100 Patient-Years of Exposure During the Treatment Period

| | |
|-----------------|---|
| End point title | Overall Number of Adverse Events by Severity (NCI-CTCAE v3.0 All Grades and Grades 3-5) per 100 Patient-Years of Exposure During the Treatment Period |
|-----------------|---|

End point description:

The severity of an adverse event (AE), including serious and non-serious AEs, was assessed according to the NCI-CTCAE version 3.0; if the AE was not specifically listed, the following grades of severity were used: Grade 1 is mild; Grade 2 is moderate; Grade 3 is severe; Grade 4 is life-threatening or disabling; and Grade 5 is death. Multiple occurrences of the same AE in one subject were counted multiple times. Only AEs that started during the overall study treatment period were included. The cutoff date for inclusion of events and for calculation of patient-years was the date of the most recent follow-up of the subject, defined as the last available date during the treatment period, excluding pre-treatment and safety follow-up data. Confidence intervals were calculated assuming the number of events followed a Poisson distribution. Data reported prior to the date of first crossover treatment were included under the Placebo arm for subjects who crossed over from placebo to pertuzumab.

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

End point timeframe:

From Baseline to 42 days after the last dose of study treatment (total patient-years of exposure on study treatment in Placebo arm vs. Pertuzumab arm: 526.81 patient-years vs. 989.88 patient-years)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | | |
|-------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 396 ^[36] | 408 ^[37] | | |
| Units: Events per 100 patient-years | | | | |
| number (confidence interval 90%) | | | | |
| All Grades | 1720.2 (1690.6 to 1750.2) | 1203.0 (1184.9 to 1221.3) | | |
| Grades 3 to 5 | 225.3 (214.7 to 236.4) | 131.7 (125.8 to 137.9) | | |

Notes:

[36] - Safety Population

[37] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiac-Related AEs to Monitor: Percentage of Subjects Who Experienced at Least One Symptomatic Left Ventricular Dysfunction (LVD), Any LVD,

or Serious Adverse Event Suggestive of Congestive Heart Failure by Severity During the Treatment Period

| | |
|-----------------|--|
| End point title | Cardiac-Related AEs to Monitor: Percentage of Subjects Who Experienced at Least One Symptomatic Left Ventricular Dysfunction (LVD), Any LVD, or Serious Adverse Event Suggestive of Congestive Heart Failure by Severity During the Treatment Period |
|-----------------|--|

End point description:

Cardiac-related adverse events (AEs) to monitor during the study included investigator-assessed symptomatic left ventricular dysfunction (LVD), any LVD, or a serious adverse event (SAE) suggestive of congestive heart failure (CHF). All cardiac-related AEs were graded for severity according to NCI-CTCAE v3.0. Asymptomatic (Grades 1-2) and symptomatic (Grades 3-5) left ventricular systolic dysfunction (LVSD) both coded to the MedDRA preferred term LVD. Investigator-assessed events of symptomatic LVD were also graded for severity of symptoms according to Classes I (least severe) to IV (most severe) of the New York Heart Association (NYHA) Classification. SAEs suggestive of CHF were identified as serious events from the Standardized MedDRA Query (SMQ) (Wide) 'Cardiac Failure'. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks.

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

End point timeframe:

Placebo arm: Baseline to last dose of study treatment +42 days (or crossover date); Pertuzumab arm: Baseline to last dose of study treatment +42 days; Crossover arm: Crossover date to last dose of study treatment +42 days (see Description - time per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|--|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 ^[38] | 408 ^[39] | 50 ^[40] | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Symptomatic LVD(Investigator)-All NYHA Classes | 1.8 | 1.5 | 2.0 | |
| Symptomatic LVD(Investigator)-NYHA Classes III/IV | 1.0 | 1.0 | 2.0 | |
| Any LVD - All NCI-CTCAE Grades | 8.6 | 7.8 | 6.0 | |
| Any LVD - NCI-CTCAE Grade ≥3 | 3.3 | 1.5 | 4.0 | |
| SAE Suggestive of CHF - All NCI-CTCAE Grades | 2.0 | 2.0 | 2.0 | |
| SAE Suggestive of CHF - NCI-CTCAE Grade ≥3 | 1.8 | 1.7 | 2.0 | |

Notes:

[38] - Safety Population

[39] - Safety Population

[40] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced at Least One Adverse Event to Monitor (Excluding Cardiac-Related AEs) by Severity During the Treatment Period

| | |
|-----------------|--|
| End point title | Percentage of Subjects Who Experienced at Least One Adverse Event to Monitor (Excluding Cardiac-Related AEs) by Severity During the Treatment Period |
|-----------------|--|

End point description:

The clinical diagnoses listed in this table, excluding cardiac safety (summarized separately), were also selected as adverse events (AEs) to monitor based on clinical and nonclinical data for pertuzumab and the safety profile established for trastuzumab, monoclonal antibodies in general, and potential effects associated with HER receptor inhibition. Search strategies were defined by single or aggregate MedDRA Preferred Terms (PT) through Standardized MedDRA Queries (SMQ), where possible, or based on Roche AE Group Terms (AEGT). Diarrhoea AEs: High-Level Term (HLT) 'Diarrhoea (excl. infective)' and PT 'Diarrhoea infectious'. Leukopenic and Febrile Neutropenic Infections: AEs from 'Infections & Infestations' with start ≤ 14 days after start date of Grade ≥ 3 AEs in SMQ(narrow) 'Leukopenia' or PT 'Febrile neutropenia', respectively. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks.

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

End point timeframe:

Placebo arm: Baseline to last dose of study treatment +42 days (or crossover date); Pertuzumab arm: Baseline to last dose of study treatment +42 days; Crossover arm: Crossover date to last dose of study treatment +42 days (see Description - time per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|---|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 | 408 | 50 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Diarrhoea (HLT+PT) - All Grades | 48.2 | 68.6 | 50.0 | |
| Diarrhoea (HLT+PT) - Grade ≥ 3 | 5.1 | 9.8 | 2.0 | |
| Rash (AEGT) - All Grades | 39.1 | 52.2 | 36.0 | |
| Rash (AEGT) - Grade ≥ 3 | 1.5 | 3.7 | 0.0 | |
| Leukopenia (SMQ-narrow) - All Grades | 58.3 | 63.0 | 2.0 | |
| Leukopenia (SMQ-narrow) - Grade ≥ 3 | 53.3 | 58.3 | 0.0 | |
| Leukopenic Infection (PTs) - All Grades | 9.6 | 13.0 | 0.0 | |
| Leukopenic Infection (PTs) - Grade ≥ 3 | 2.3 | 4.4 | 0.0 | |
| Febrile Neutropenic Infection (PTs) - All Grades | 0.8 | 3.4 | 0.0 | |
| Febrile Neutropenic Infection (PTs) - Grade ≥ 3 | 0.3 | 1.5 | 0.0 | |
| Anaphylaxis and Hypersensitivity (AEGT)-All Grades | 9.3 | 11.8 | 2.0 | |
| Anaphylaxis and Hypersensitivity (AEGT)-Grade ≥ 3 | 2.5 | 2.2 | 0.0 | |
| Interstitial Lung Disease (SMQ-narrow) - All Grades | 1.5 | 2.5 | 2.0 | |
| Interstitial Lung Disease (SMQ-narrow) - Grade ≥ 3 | 0.5 | 0.7 | 0.0 | |
| QT Prolongation (SMQ-wide) - All Grades | 1.3 | 3.9 | 0.0 | |
| QT Prolongation (SMQ-wide) - Grade ≥ 3 | 0.3 | 1.7 | 0.0 | |
| Mucositis (AEGT) - All Grades | 38.9 | 51.0 | 24.0 | |
| Mucositis (AEGT) - Grade ≥ 3 | 2.0 | 3.4 | 0.0 | |
| Drug-Related Hepatic Disorder(SMQ-wide)-All Grades | 10.9 | 11.5 | 0.0 | |
| Drug-Related Hepatic Disorder (SMQ wide)-Grade ≥ 3 | 1.3 | 2.0 | 0.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Percentage of Subjects Who Experienced at Least One Adverse Event Leading to Discontinuation of Any or All Study Medication

| | |
|-----------------|---|
| End point title | Overall Percentage of Subjects Who Experienced at Least One Adverse Event Leading to Discontinuation of Any or All Study Medication |
|-----------------|---|

End point description:

Subjects could continue study treatment with pertuzumab/placebo plus trastuzumab when docetaxel was discontinued due to an adverse event (AE). Discontinuation of pertuzumab/placebo or trastuzumab due to an AE led to discontinuation of all study medication. The percentage of subjects who discontinued any study medication due to an AE includes those who discontinued all study medication and those who discontinued docetaxel only and then continued on targeted therapy (note that some of these subjects may have subsequently discontinued all treatment due to a separate AE). Multiple occurrences of the same AE in one subject was counted only once. AEs reported prior to first crossover treatment were included in the Placebo arm, and after that date in the Crossover arm, for subjects who crossed over from placebo to pertuzumab. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks.

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

End point timeframe:

Placebo arm: Baseline to last dose of study treatment +42 days (or crossover date); Pertuzumab arm: Baseline to last dose of study treatment +42 days; Crossover arm: Crossover date to last dose of study treatment +42 days (see Description - time per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|---|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 | 408 | 50 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| AE Leading to Discontinuation-Any Study Medication | 28.8 | 32.1 | 10.0 | |
| AE Leading to Discontinuation-All Study Medication | 6.1 | 9.6 | 8.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Percentage of Subjects Who Experienced at Least One Adverse Event That Resulted in Interruption or Modification of Any Study Medication

| | |
|-----------------|---|
| End point title | Overall Percentage of Subjects Who Experienced at Least One |
|-----------------|---|

End point description:

Pertuzumab, trastuzumab, and docetaxel administration could have been delayed to assess or treat adverse events. Docetaxel dose reduction was allowed for myelosuppression, hepatic dysfunction, and other toxicities. No dose reduction was allowed for pertuzumab or trastuzumab. Multiple occurrences of the same adverse event in one subject was counted only once. Adverse events reported prior to first crossover treatment were included in the Placebo arm, and after that date in the Crossover arm, for subjects who crossed over from placebo to pertuzumab. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks

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

End point timeframe:

Placebo arm: Baseline to last dose of study treatment +42 days (or crossover date); Pertuzumab arm: Baseline to last dose of study treatment +42 days; Crossover arm: Crossover date to last dose of study treatment +42 days (see Description - time per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|-------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 | 408 | 50 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | 54.8 | 65.0 | 32.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced at Least One Adverse Event During the Post-Treatment Follow-Up Period

| | |
|-----------------|--|
| End point title | Percentage of Subjects Who Experienced at Least One Adverse Event During the Post-Treatment Follow-Up Period |
|-----------------|--|

End point description:

The post-treatment period was defined as the period following the treatment discontinuation visit. Only the following new adverse events (AEs) should have been reported during the post-treatment follow-up period: 1. Cardiac events (regardless of causality or seriousness) that started up to 1 year after the last dose, except for symptomatic left ventricular systolic dysfunction (regardless of causality) that started up to 3 years after the last dose; and 2. Treatment-related serious AEs, regardless of start date. AEs are listed by Medical Dictionary for Regulatory Activities, Version 21.1 (MedDRA v21.1) System Organ Class (SOC) and Preferred Term (PT); PTs fall under the SOC that is listed immediately above it in the table. Multiple occurrences of the same AE in one subject was counted only once. AEs reported prior to first crossover treatment were included in the Placebo arm, and after that date in the Crossover arm, for subjects who crossed over from placebo to pertuzumab.

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

End point timeframe:

From Day 43 after discontinuation of all study medication up to end of the post-treatment follow-up period (up to 3 years)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|--|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 ^[41] | 408 ^[42] | 50 ^[43] | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Total with at Least One AE During Post-Treatment | 4.5 | 4.2 | 6.0 | |
| Cardiac Disorders (SOC) | 2.0 | 2.2 | 2.0 | |
| Left Ventricular Dysfunction (PT) | 1.5 | 1.2 | 2.0 | |
| Cardiac Failure (PT) | 0.0 | 0.5 | 0.0 | |
| Bundle Branch Block Left (PT) | 0.0 | 0.2 | 0.0 | |
| Cardiopulmonary Failure (PT) | 0.3 | 0.0 | 0.0 | |
| Myocardial Ischaemia (PT) | 0.3 | 0.0 | 0.0 | |
| Pericardial Effusion (PT) | 0.0 | 0.2 | 0.0 | |
| Prinzmetal Angina (PT) | 0.3 | 0.0 | 0.0 | |
| General Disorders & Admin. Site Conditions (SOC) | 0.8 | 0.5 | 0.0 | |
| Oedema Peripheral (PT) | 0.5 | 0.2 | 0.0 | |
| Asthenia (PT) | 0.3 | 0.0 | 0.0 | |
| Influenza Like Illness (PT) | 0.0 | 0.2 | 0.0 | |
| Infections & Infestations (SOC) | 0.3 | 0.2 | 4.0 | |
| Influenza (PT) | 0.0 | 0.0 | 2.0 | |
| Viral Infection (PT) | 0.0 | 0.0 | 2.0 | |
| Abscess Limb (PT) | 0.0 | 0.2 | 0.0 | |
| Nasopharyngitis (PT) | 0.3 | 0.0 | 0.0 | |
| Subcutaneous Abscess (PT) | 0.0 | 0.2 | 0.0 | |
| Musculoskeletal & Connective Tissue Disorders(SOC) | 0.3 | 0.0 | 2.0 | |
| Back Pain (PT) | 0.0 | 0.0 | 2.0 | |
| Pain in Extremity (PT) | 0.3 | 0.0 | 0.0 | |
| Nervous System Disorders (SOC) | 0.5 | 0.5 | 0.0 | |
| Neuropathy Peripheral (PT) | 0.3 | 0.2 | 0.0 | |
| Cognitive Disorder (PT) | 0.3 | 0.0 | 0.0 | |
| Dizziness (PT) | 0.0 | 0.2 | 0.0 | |
| Headache (PT) | 0.0 | 0.2 | 0.0 | |
| Respiratory, Thoracic & Mediastinal Disorders(SOC) | 0.5 | 0.2 | 0.0 | |
| Cough (PT) | 0.3 | 0.0 | 0.0 | |
| Dyspnoea (PT) | 0.3 | 0.0 | 0.0 | |
| Rhinitis Allergic (PT) | 0.0 | 0.2 | 0.0 | |
| Skin & Subcutaneous Tissue Disorders (SOC) | 0.3 | 0.5 | 0.0 | |
| Erythema (PT) | 0.0 | 0.2 | 0.0 | |
| Nail Disorder (PT) | 0.3 | 0.0 | 0.0 | |
| Rash Macular (PT) | 0.0 | 0.2 | 0.0 | |
| Blood & Lymphatic System Disorders (SOC) | 0.3 | 0.2 | 0.0 | |
| Febrile Neutropenia (PT) | 0.3 | 0.0 | 0.0 | |
| Leukopenia (PT) | 0.0 | 0.2 | 0.0 | |
| Gastrointestinal Disorders (SOC) | 0.0 | 0.5 | 0.0 | |
| Diarrhoea (PT) | 0.0 | 0.2 | 0.0 | |
| Stomatitis (PT) | 0.0 | 0.2 | 0.0 | |

| | | | | |
|--|-----|-----|-----|--|
| Endocrine Disorders (SOC) | 0.3 | 0.0 | 0.0 | |
| Thyroid Mass (PT) | 0.3 | 0.0 | 0.0 | |
| Eye Disorders (SOC) | 0.3 | 0.0 | 0.0 | |
| Retinal Detachment (PT) | 0.3 | 0.0 | 0.0 | |
| Immune System Disorders (SOC) | 0.0 | 0.2 | 0.0 | |
| Iodine Allergy (PT) | 0.0 | 0.2 | 0.0 | |
| Investigations (SOC) | 0.3 | 0.0 | 0.0 | |
| Aspartate Aminotransferase Increased (PT) | 0.3 | 0.0 | 0.0 | |
| Renal & Urinary Disorders (SOC) | 0.0 | 0.2 | 0.0 | |
| Dysuria (PT) | 0.0 | 0.2 | 0.0 | |
| Reproductive System & Breast Disorders (SOC) | 0.0 | 0.2 | 0.0 | |
| Breast Induration (PT) | 0.0 | 0.2 | 0.0 | |
| Vascular Disorders (SOC) | 0.0 | 0.2 | 0.0 | |
| Venous Thrombosis (PT) | 0.0 | 0.2 | 0.0 | |

Notes:

[41] - Safety Population

[42] - Safety Population

[43] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by Categories for the Maximum Absolute Decrease From Baseline in LVEF Value During the Treatment Period

| | |
|-----------------|--|
| End point title | Percentage of Subjects by Categories for the Maximum Absolute Decrease From Baseline in LVEF Value During the Treatment Period |
|-----------------|--|

End point description:

All subjects were required to have an left ventricular ejection fraction (LVEF) $\geq 50\%$ at baseline, as measured by echocardiogram (preferred) or multiple-gated acquisition (MUGA) scan. The same method of LVEF assessment and the same institution/facility used at baseline was used throughout the study, to the extent possible. The baseline value was defined as the last valid value recorded during the pre-treatment period before or on study Day 1. The maximum absolute decrease in LVEF value was defined as the lowest post-baseline value up to the end of the overall study treatment period. Data reported prior to first crossover treatment were included in the Placebo arm, and after that date in the Crossover arm, for subjects who crossed over from placebo to pertuzumab. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks.

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

End point timeframe:

Every 9 weeks from the date of randomization until Treatment Discontinuation Visit (see Description for time on study treatment per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|-------------------------------|-----------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 378 ^[44] | 394 ^[45] | 49 ^[46] | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |

| | | | | |
|--|------|------|------|--|
| LVEF Increase/No Change/Decrease From BL <10% Points | 66.7 | 63.2 | 61.2 | |
| LVEF <50% and Decrease From BL ≥10% to <15% Points | 2.4 | 1.8 | 0 | |
| LVEF <50% and Decrease From BL ≥15% Points | 5.0 | 5.3 | 6.1 | |
| LVEF ≥50% and Decrease From BL ≥10% Points | 25.1 | 29.2 | 30.6 | |
| No Baseline (BL) LVEF Value | 0.8 | 0.5 | 2.0 | |

Notes:

[44] - Safety Population

[45] - Safety Population

[46] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Baseline LVEF Value and Change From Baseline at Maximum Absolute Decrease in LVEF Value During the Treatment Period

| | |
|-----------------|---|
| End point title | Baseline LVEF Value and Change From Baseline at Maximum Absolute Decrease in LVEF Value During the Treatment Period |
|-----------------|---|

End point description:

All subjects were required to have a left ventricular ejection fraction (LVEF) ≥50% at baseline, as measured by echocardiogram (preferred) or multiple-gated acquisition (MUGA) scan. The same method of LVEF assessment and the same institution/facility used at baseline was used throughout the study, to the extent possible. The baseline value was defined as the last valid value recorded during the pre-treatment period before or on study Day 1. The maximum absolute decrease in LVEF value was defined as the lowest post-baseline value up to the end of the overall study treatment period. Only data reported prior to the date of first crossover treatment were included for subjects who crossed over from placebo to open-label pertuzumab. Subjects with evaluable LVEF assessments at baseline (BL) or at BL and post-BL (for change in LVEF from BL at maximum decrease value) were included in the analyses.

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

End point timeframe:

Every 9 weeks from the date of randomization until Treatment Discontinuation Visit (median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | | |
|---|-----------------------------------|--------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 396 ^[47] | 408 ^[48] | | |
| Units: Percentage points of LVEF | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (BL) LVEF Value (n=393,406) | 65.6 (± 6.51) | 64.8 (± 6.71) | | |
| Change from BL: LVEF Maximum Decrease (n=375,392) | -7.3 (± 7.15) | -7.5 (± 7.75) | | |

Notes:

[47] - Safety Population

[48] - Safety Population

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Wilcoxon Test of Maximum Decrease in LVEF From BL |
| Comparison groups | Placebo + Trastuzumab + Docetaxel v Pertuzumab + Trastuzumab + Docetaxel |
| Number of subjects included in analysis | 804 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.7174 |
| Method | Wilcoxon Rank-Sum Test |

Secondary: Percentage of Subjects with Laboratory Abnormalities in Blood Biochemistry Tests by Highest Grade According to NCI-CTCAE v3.0 During the Treatment Period

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Laboratory Abnormalities in Blood Biochemistry Tests by Highest Grade According to NCI-CTCAE v3.0 During the Treatment Period |
|-----------------|---|

End point description:

Clinical laboratory tests for blood biochemistry parameters 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 grade according to NCI-CTCAE v3.0. The 'n' in category titles represent number of subjects per arm with at least one valid laboratory value, in order from left to right column. 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 change in concomitant therapy. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks. ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

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

End point timeframe:

On Day 1 of every treatment cycle (1 cycle is 21 days) until Treatment Discontinuation Visit (see Description for time on study treatment per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|--|-----------------------------------|--------------------------------------|--------------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 ^[49] | 408 ^[50] | 50 ^[51] | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Albumin (g/L) - Low, Any Grade (Gr.)(n=385,396,49) | 42.3 | 49.5 | 30.6 | |
| Albumin (g/L) - Low, Gr. 1 (n=385,396,49) | 29.4 | 33.3 | 20.4 | |
| Albumin (g/L) - Low, Gr. 2 (n=385,396,49) | 11.9 | 14.6 | 8.2 | |
| Albumin (g/L) - Low, Gr. 3 (n=385,396,49) | 1.0 | 1.5 | 2.0 | |
| Albumin (g/L) - Low, Gr. 4 (n=385,396,49) | 0.0 | 0.0 | 0.0 | |
| ALP (U/L) - High, Any Gr. (n=388,400,49) | 47.4 | 52.5 | 34.7 | |
| ALP (U/L) - High, Gr. 1 (n=388,400,49) | 40.7 | 44.3 | 34.7 | |
| ALP (U/L) - High, Gr. 2 (n=388,400,49) | 4.9 | 6.0 | 0.0 | |
| ALP (U/L) - High, Gr. 3 (n=388,400,49) | 1.8 | 2.3 | 0.0 | |

| | | | | |
|--|------|------|------|--|
| ALP (U/L) - High, Gr. 4 (n=388,400,49) | 0.0 | 0.0 | 0.0 | |
| Calcium (mmol/L) - Low, Any Gr. (n=387,399,49) | 40.3 | 50.9 | 28.6 | |
| Calcium (mmol/L) - Low, Gr. 1 (n=387,399,49) | 27.6 | 34.8 | 22.4 | |
| Calcium (mmol/L) - Low, Gr. 2 (n=387,399,49) | 11.6 | 12.3 | 0.0 | |
| Calcium (mmol/L) - Low, Gr. 3 (n=387,399,49) | 0.8 | 1.8 | 2.0 | |
| Calcium (mmol/L) - Low, Gr. 4 (n=387,399,49) | 0.3 | 2.0 | 4.1 | |
| Calcium (mmol/L) - High, Any Gr. (n=387,399,49) | 14.0 | 19.8 | 24.5 | |
| Calcium (mmol/L) - High, Gr. 1 (n=387,399,49) | 12.9 | 16.3 | 14.3 | |
| Calcium (mmol/L) - High, Gr. 2 (n=387,399,49) | 0.0 | 0.5 | 2.0 | |
| Calcium (mmol/L) - High, Gr. 3 (n=387,399,49) | 0.8 | 0.5 | 0.0 | |
| Calcium (mmol/L) - High, Gr. 4 (n=387,399,49) | 0.3 | 2.5 | 8.2 | |
| Creatinine (umol/L) - High, Any Gr. (n=390,402,49) | 81.3 | 86.1 | 77.6 | |
| Creatinine (umol/L) - High, Gr. 1 (n=390,402,49) | 69.5 | 69.4 | 55.1 | |
| Creatinine (umol/L) - High, Gr. 2 (n=390,402,49) | 11.3 | 13.4 | 18.4 | |
| Creatinine (umol/L) - High, Gr. 3 (n=390,402,49) | 0.5 | 1.5 | 0.0 | |
| Creatinine (umol/L) - High, Gr. 4 (n=390,402,49) | 0.0 | 1.7 | 4.1 | |
| Glucose (mmol/L) - Low, Any Gr. (n=387,400,49) | 10.9 | 18.8 | 12.2 | |
| Glucose (mmol/L) - Low, Gr. 1 (n=387,400,49) | 8.3 | 15.3 | 8.2 | |
| Glucose (mmol/L) - Low, Gr. 2 (n=387,400,49) | 2.3 | 2.3 | 0.0 | |
| Glucose (mmol/L) - Low, Gr. 3 (n=387,400,49) | 0.3 | 0.5 | 0.0 | |
| Glucose (mmol/L) - Low, Gr. 4 (n=387,400,49) | 0.0 | 0.8 | 4.1 | |
| Glucose (mmol/L) - High, Any Gr. (n=387,400,49) | 70.0 | 74.8 | 69.4 | |
| Glucose (mmol/L) - High, Gr. 1 (n=387,400,49) | 43.4 | 48.0 | 53.1 | |
| Glucose (mmol/L) - High, Gr. 2 (n=387,400,49) | 21.4 | 19.5 | 16.3 | |
| Glucose (mmol/L) - High, Gr. 3 (n=387,400,49) | 5.2 | 6.5 | 0.0 | |
| Glucose (mmol/L) - High, Gr. 4 (n=387,400,49) | 0.0 | 0.8 | 0.0 | |
| GGT (U/L) - High, Any Gr. (n=375,394,48) | 55.7 | 57.1 | 29.2 | |
| GGT (U/L) - High, Gr. 1 (n=375,394,48) | 35.5 | 36.5 | 18.8 | |
| GGT (U/L) - High, Gr. 2 (n=375,394,48) | 10.9 | 13.2 | 8.3 | |
| GGT (U/L) - High, Gr. 3 (n=375,394,48) | 8.0 | 6.9 | 2.1 | |
| GGT (U/L) - High, Gr. 4 (n=375,394,48) | 1.3 | 0.5 | 0.0 | |
| Magnesium (mmol/L) - Low, Any Gr. (n=371,398,49) | 21.3 | 29.4 | 16.3 | |
| Magnesium (mmol/L) - Low, Gr. 1 (n=371,398,49) | 19.1 | 24.6 | 12.2 | |

| | | | | |
|--|------|------|------|--|
| Magnesium (mmol/L) - Low, Gr. 2 (n=371,398,49) | 1.9 | 3.3 | 0.0 | |
| Magnesium (mmol/L) - Low, Gr. 3 (n=371,398,49) | 0.3 | 0.8 | 0.0 | |
| Magnesium (mmol/L) - Low, Gr. 4 (n=371,398,49) | 0.0 | 0.8 | 4.1 | |
| Magnesium (mmol/L) - High, Any Gr. (n=371,398,49) | 20.5 | 26.4 | 32.7 | |
| Magnesium (mmol/L) - High, Gr. 1 (n=371,398,49) | 15.6 | 20.1 | 22.4 | |
| Magnesium (mmol/L) - High, Gr. 2 (n=371,398,49) | 0.0 | 0.0 | 0.0 | |
| Magnesium (mmol/L) - High, Gr. 3 (n=371,398,49) | 4.9 | 5.5 | 8.2 | |
| Magnesium (mmol/L) - High, Gr. 4 (n=371,398,49) | 0.0 | 0.8 | 2.0 | |
| Potassium (mmol/L) - Low, Any Gr. (n=389,401,49) | 20.6 | 35.9 | 22.4 | |
| Potassium (mmol/L) - Low, Gr. 1 (n=389,401,49) | 0.0 | 0.0 | 0.0 | |
| Potassium (mmol/L) - Low, Gr. 2 (n=389,401,49) | 17.5 | 29.4 | 16.3 | |
| Potassium (mmol/L) - Low, Gr. 3 (n=389,401,49) | 2.6 | 4.5 | 4.1 | |
| Potassium (mmol/L) - Low, Gr. 4 (n=389,401,49) | 0.5 | 2.0 | 2.0 | |
| Potassium (mmol/L) - High, Any Gr. (n=389,401,49) | 17.2 | 19.5 | 26.5 | |
| Potassium (mmol/L) - High, Gr. 1 (n=389,401,49) | 12.6 | 13.7 | 22.4 | |
| Potassium (mmol/L) - High, Gr. 2 (n=389,401,49) | 3.9 | 4.2 | 4.1 | |
| Potassium (mmol/L) - High, Gr. 3 (n=389,401,49) | 0.8 | 1.5 | 0.0 | |
| Potassium (mmol/L) - High, Gr. 4 (n=389,401,49) | 0.0 | 0.0 | 0.0 | |
| SGOT (U/L) - High, Any Gr. (n=389,400,49) | 47.3 | 48.3 | 34.7 | |
| SGOT (U/L) - High, Gr. 1 (n=389,400,49) | 43.4 | 42.5 | 30.6 | |
| SGOT (U/L) - High, Gr. 2 (n=389,400,49) | 2.8 | 3.0 | 4.1 | |
| SGOT (U/L) - High, Gr. 3 (n=389,400,49) | 1.0 | 2.5 | 0.0 | |
| SGOT (U/L) - High, Gr. 4 (n=389,400,49) | 0.0 | 0.3 | 0.0 | |
| SGPT (U/L) - High, Any Gr. (n=390,400,49) | 50.0 | 52.3 | 38.8 | |
| SGPT (U/L) - High, Gr. 1 (n=390,400,49) | 44.1 | 43.8 | 34.7 | |
| SGPT (U/L) - High, Gr. 2 (n=390,400,49) | 4.6 | 4.8 | 4.1 | |
| SGPT (U/L) - High, Gr. 3 (n=390,400,49) | 1.3 | 3.5 | 0.0 | |
| SGPT (U/L) - High, Gr. 4 (n=390,400,49) | 0.0 | 0.3 | 0.0 | |
| Sodium (mmol/L) - Low, Any Gr. (n=389,402,49) | 28.0 | 33.6 | 51.0 | |
| Sodium (mmol/L) - Low, Gr. 1 (n=389,402,49) | 22.4 | 30.1 | 44.9 | |
| Sodium (mmol/L) - Low, Gr. 2 (n=389,402,49) | 0.0 | 0.0 | 0.0 | |

| | | | | |
|---|------|------|------|--|
| Sodium (mmol/L) - Low, Gr. 3 (n=389,402,49) | 5.4 | 3.0 | 2.0 | |
| Sodium (mmol/L) - Low, Gr. 4 (n=389,402,49) | 0.3 | 0.5 | 4.1 | |
| Sodium (mmol/L) - High, Any Gr. (n=389,402,49) | 19.5 | 25.6 | 18.4 | |
| Sodium (mmol/L) - High, Gr. 1 (n=389,402,49) | 18.3 | 22.6 | 14.3 | |
| Sodium (mmol/L) - High, Gr. 2 (n=389,402,49) | 1.0 | 2.2 | 4.1 | |
| Sodium (mmol/L) - High, Gr. 3 (n=389,402,49) | 0.3 | 0.5 | 0.0 | |
| Sodium (mmol/L) - High, Gr. 4 (n=389,402,49) | 0.0 | 0.2 | 0.0 | |
| Tot. Bilirubin (umol/L)-High,Any Gr.(n=390,401,49) | 9.0 | 14.2 | 14.3 | |
| Tot. Bilirubin (umol/L)-High, Gr. 1 (n=390,401,49) | 6.7 | 11.0 | 12.2 | |
| Tot. Bilirubin (umol/L)-High, Gr. 2 (n=390,401,49) | 1.8 | 2.2 | 0.0 | |
| Tot. Bilirubin (umol/L)-High, Gr. 3 (n=390,401,49) | 0.5 | 0.5 | 0.0 | |
| Tot. Bilirubin (umol/L)-High, Gr. 4 (n=390,401,49) | 0.0 | 0.5 | 2.0 | |
| Uric Acid (umol/L) - High, Any Gr. (n=370,397,49) | 31.9 | 28.5 | 30.6 | |
| Uric Acid (umol/L) - High, Gr. 1 (n=370,397,49) | 0.0 | 0.0 | 0.0 | |
| Uric Acid (umol/L) - High, Gr. 2 (n=370,397,49) | 0.0 | 0.0 | 0.0 | |
| Uric Acid (umol/L) - High, Gr. 3 (n=370,397,49) | 31.4 | 24.7 | 20.4 | |
| Uric Acid (umol/L) - High, Gr. 4 (n=370,397,49) | 0.5 | 3.8 | 10.2 | |

Notes:

[49] - Safety Population

[50] - Safety Population

[51] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Laboratory Abnormalities in Hematology Tests by Highest Grade According to NCI-CTCAE v3.0 During the Treatment Period

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Laboratory Abnormalities in Hematology Tests by Highest Grade According to NCI-CTCAE v3.0 During the Treatment Period |
|-----------------|---|

End point description:

Clinical laboratory tests for hematology parameters 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 grade according to NCI-CTCAE v3.0. The 'n' in category titles represent number of subjects per arm with at least one valid laboratory value, in order from left to right column. 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 change in concomitant therapy. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks. INR = International Normalized Ratio; PTT = partial thromboplastin time; WBC = white blood cell

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

End point timeframe:

On Day 1 (and Day 8 for some measures) of every treatment cycle (1 cycle is 21 days) until Treatment Discontinuation Visit (see Description for time on study treatment per arm)

| End point values | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab | |
|---|---|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 396 ^[52] | 408 ^[53] | 50 ^[54] | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Hemoglobin (g/L) -Low,Any Grade(Gr.)(n=392,404,49) | 89.3 | 92.1 | 40.8 | |
| Hemoglobin (g/L) - Low, Gr. 1 (n=392,404,49) | 51.5 | 46.0 | 18.4 | |
| Hemoglobin (g/L) - Low, Gr. 2 (n=392,404,49) | 32.4 | 39.9 | 12.2 | |
| Hemoglobin (g/L) - Low, Gr. 3 (n=392,404,49) | 5.4 | 6.2 | 10.2 | |
| Hemoglobin (g/L) - Low, Gr. 4 (n=392,404,49) | 0.0 | 0.0 | 0.0 | |
| Hemoglobin (g/L) - High, Any Gr. (n=392,404,49) | 2.6 | 5.7 | 8.2 | |
| Hemoglobin (g/L) - High, Gr. 1 (n=392,404,49) | 2.3 | 5.0 | 4.1 | |
| Hemoglobin (g/L) - High, Gr. 2 (n=392,404,49) | 0.3 | 0.5 | 0.0 | |
| Hemoglobin (g/L) - High, Gr. 3 (n=392,404,49) | 0.0 | 0.2 | 4.1 | |
| Hemoglobin (g/L) - High, Gr. 4 (n=392,404,49) | 0.0 | 0.0 | 0.0 | |
| Lymphocytes (10 ⁹ /L) - Low, Any Gr. (n=391,404,49) | 66.2 | 68.3 | 16.3 | |
| Lymphocytes (10 ⁹ /L) - Low, Gr. 1 (n=391,404,49) | 9.2 | 9.7 | 0.0 | |
| Lymphocytes (10 ⁹ /L) - Low, Gr. 2 (n=391,404,49) | 32.7 | 33.7 | 8.2 | |
| Lymphocytes (10 ⁹ /L) - Low, Gr. 3 (n=391,404,49) | 16.4 | 17.1 | 6.1 | |
| Lymphocytes (10 ⁹ /L) - Low, Gr. 4 (n=391,404,49) | 7.9 | 7.9 | 2.0 | |
| Lymphocytes (10 ⁹ /L)- High, Any Gr. (n=391,404,49) | 14.8 | 17.8 | 18.4 | |
| Lymphocytes (10 ⁹ /L)- High, Gr. 1 (n=391,404,49) | 0.0 | 0.0 | 0.0 | |
| Lymphocytes (10 ⁹ /L)- High, Gr. 2 (n=391,404,49) | 12.5 | 14.1 | 12.2 | |
| Lymphocytes (10 ⁹ /L)- High, Gr. 3 (n=391,404,49) | 2.3 | 3.7 | 6.1 | |
| Lymphocytes (10 ⁹ /L)- High, Gr. 4 (n=391,404,49) | 0.0 | 0.0 | 0.0 | |
| Neutrophils (10 ⁹ /L)- Low, Any Gr. (n=391,404,49) | 89.3 | 91.8 | 4.1 | |
| Neutrophils (10 ⁹ /L)- Low, Gr. 1 (n=391,404,49) | 1.8 | 1.0 | 0.0 | |
| Neutrophils (10 ⁹ /L)- Low, Gr. 2 (n=391,404,49) | 6.4 | 8.4 | 0.0 | |

| | | | | |
|---|------|------|------|--|
| Neutrophils (10 ⁹ /L)- Low, Gr. 3 (n=391,404,49) | 20.7 | 24.5 | 0.0 | |
| Neutrophils (10 ⁹ /L)- Low, Gr. 4 (n=391,404,49) | 60.4 | 57.9 | 4.1 | |
| PTT (sec) - High, Any Gr. (n=28,35,3) | 21.4 | 25.7 | 33.3 | |
| PTT (sec) - High, Gr. 1 (n=28,35,3) | 17.9 | 5.7 | 33.3 | |
| PTT (sec) - High, Gr. 2 (n=28,35,3) | 0.0 | 11.4 | 0.0 | |
| PTT (sec) - High, Gr. 3 (n=28,35,3) | 3.6 | 8.6 | 0.0 | |
| PTT (sec) - High, Gr. 4 (n=28,35,3) | 0.0 | 0.0 | 0.0 | |
| Platelets (10 ⁹ /L) - Low, Any Gr. (n=392,404,49) | 20.9 | 22.8 | 26.5 | |
| Platelets (10 ⁹ /L) - Low, Gr. 1 (n=392,404,49) | 19.1 | 19.3 | 22.4 | |
| Platelets (10 ⁹ /L) - Low, Gr. 2 (n=392,404,49) | 1.3 | 1.2 | 0.0 | |
| Platelets (10 ⁹ /L) - Low, Gr. 3 (n=392,404,49) | 0.5 | 0.7 | 0.0 | |
| Platelets (10 ⁹ /L) - Low, Gr. 4 (n=392,404,49) | 0.0 | 1.5 | 4.1 | |
| Prothrombin Time (INR)-High,Any Gr. (n=198,216,14) | 68.2 | 72.7 | 78.6 | |
| Prothrombin Time (INR)- High, Gr. 1 (n=198,216,14) | 64.1 | 63.0 | 64.3 | |
| Prothrombin Time (INR)- High, Gr. 2 (n=198,216,14) | 1.5 | 2.8 | 0.0 | |
| Prothrombin Time (INR)- High, Gr. 3 (n=198,216,14) | 2.5 | 6.9 | 14.3 | |
| Prothrombin Time (INR)- High, Gr. 4 (n=198,216,14) | 0.0 | 0.0 | 0.0 | |
| WBC (10 ⁹ /L) - Low, Any Gr. (n=392,404,49) | 93.4 | 95.8 | 10.2 | |
| WBC (10 ⁹ /L) - Low, Gr. 1 (n=392,404,49) | 9.2 | 8.4 | 2.0 | |
| WBC (10 ⁹ /L) - Low, Gr. 2 (n=392,404,49) | 23.5 | 22.8 | 6.1 | |
| WBC (10 ⁹ /L) - Low, Gr. 3 (n=392,404,49) | 47.4 | 51.0 | 0.0 | |
| WBC (10 ⁹ /L) - Low, Gr. 4 (n=392,404,49) | 13.3 | 13.6 | 2.1 | |
| WBC (10 ⁹ /L) - High, Any Gr. (n=392,404,49) | 0.0 | 0.7 | 2.0 | |
| WBC (10 ⁹ /L) - High, Gr. 1 (n=392,404,49) | 0.0 | 0.0 | 0.0 | |
| WBC (10 ⁹ /L) - High, Gr. 2 (n=392,404,49) | 0.0 | 0.0 | 0.0 | |
| WBC (10 ⁹ /L) - High, Gr. 3 (n=392,404,49) | 0.0 | 0.7 | 2.0 | |
| WBC (10 ⁹ /L) - High, Gr. 4 (n=392,404,49) | 0.0 | 0.0 | 0.0 | |

Notes:

[52] - Safety Population

[53] - Safety Population

[54] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first treatment dose (12-Feb-2008) through end of study (23-Nov-2018) for a total safety analysis timeframe of 10 years, 9.5 months.

Adverse event reporting additional description:

Of enrolled subjects (Pertuzumab [Ptz]: N=402, Placebo [Pla]: N=406), 2 in each arm received no treatment (total of 4), 9 in Pla arm received at least 1 dose of Ptz, and 1 in Ptz arm received Pla at every cycle; resulting in a Safety Population of Ptz: N=408 (402-2+9-1), Pla: N=396 (406-2-9+1), and 50 subjects in Pla arm crossed over to Ptz.

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

Dictionary used

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

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|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Placebo + Trastuzumab + Docetaxel |
|-----------------------|-----------------------------------|

Reporting group description:

This is the placebo safety population, which includes subjects who received study treatment with placebo at every cycle. Subjects received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m² IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination. For subjects who crossed over to receive open-label pertuzumab, adverse events (AEs) were included in the Placebo group from the day of the first placebo dose through the day just prior to the first pertuzumab dose. Any AEs occurring on the day of the first dose of pertuzumab were included in the Crossover From Placebo to Pertuzumab group.

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

Reporting group description:

This is the pertuzumab safety population, which includes subjects who received at least one dose of study treatment with pertuzumab. Subjects received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m²) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Crossover From Placebo to Pertuzumab |
|-----------------------|--------------------------------------|

Reporting group description:

Fifty of 406 subjects (12.3%) randomized to the placebo treatment group whose disease had not progressed crossed over to an open-label pertuzumab treatment group between July 2012 and November 2018. Subjects received pertuzumab administered as an IV loading dose of 840 mg at cycle 1 then 420 mg IV every q3w. Trastuzumab and docetaxel doses continued in accordance with the pre-crossover placebo treatment regimens and according to dosing specifications indicated in the study protocol. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination. Any adverse events occurring on the day of the first crossover dose of open-label pertuzumab were included in this analysis group.

| Serious adverse events | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 116 / 396 (29.29%) | 160 / 408 (39.22%) | 10 / 50 (20.00%) |
| number of deaths (all causes) | 261 | 238 | 14 |
| number of deaths resulting from adverse events | 12 | 8 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Endometrial cancer | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glioblastoma multiforme | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ocular neoplasm | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pituitary tumour benign | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 3 / 408 (0.74%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis limb | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Abortion induced | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 396 (0.76%) | 6 / 408 (1.47%) | 2 / 50 (4.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 6 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 396 (0.51%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Drowning | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 3 / 396 (0.76%) | 3 / 408 (0.74%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 3 / 408 (0.74%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Breast haemorrhage | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metrorrhagia | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 396 (1.01%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 1 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 6 / 408 (1.47%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | | |
|-----------------------------|---|-----------------|-----------------|----------------|
| Asthma | subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | | |
| Suicide attempt | | | | |
| | subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | | |
| Blood electrolytes abnormal | | | | |
| | subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Blood glucose increased | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 3 / 408 (0.74%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Compression fracture | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Contusion | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post procedural discomfort | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Scapula fracture | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Tendon injury | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thermal burn | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 7 / 396 (1.77%) | 6 / 408 (1.47%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 7 / 7 | 6 / 6 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 396 (0.76%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 396 (0.76%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Monoparesis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensorimotor neuropathy | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |

| | | | |
|---|------------------|-------------------|----------------|
| subjects affected / exposed | 20 / 396 (5.05%) | 46 / 408 (11.27%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 22 / 23 | 48 / 48 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 3 / 3 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 19 / 396 (4.80%) | 18 / 408 (4.41%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 20 / 20 | 23 / 23 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 3 / 396 (0.76%) | 3 / 408 (0.74%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 3 / 4 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Granulocytopenia | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 396 (1.26%) | 13 / 408 (3.19%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 3 / 5 | 12 / 16 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|----------------|
| Vomiting | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Volvulus | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug eruption | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 0 / 408 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|------------------|----------------|
| Myalgia | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 11 / 396 (2.78%) | 7 / 408 (1.72%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 2 / 11 | 2 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 10 / 408 (2.45%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 4 / 12 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic infection | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 4 / 408 (0.98%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 396 (0.51%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 3 / 396 (0.76%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 4 / 408 (0.98%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 3 / 396 (0.76%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 3 / 408 (0.74%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 2 / 396 (0.51%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute sinusitis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast abscess | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cellulitis | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coccidioidomycosis | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| H1N1 influenza | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis chronic | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash pustular | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis syndrome | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis gangrenous | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 396 (0.00%) | 0 / 408 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymph node tuberculosis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 0 / 408 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 2 / 408 (0.49%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute hepatitis B | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 0 / 408 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 0 / 408 (0.00%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin abscess | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 396 (0.51%) | 1 / 408 (0.25%) | 1 / 50 (2.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 396 (0.25%) | 0 / 408 (0.00%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fluid retention | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 396 (0.00%) | 1 / 408 (0.25%) | 0 / 50 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Placebo + Trastuzumab + Docetaxel | Pertuzumab + Trastuzumab + Docetaxel | Crossover From Placebo to Pertuzumab |
|---|---|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 386 / 396 (97.47%) | 400 / 408 (98.04%) | 45 / 50 (90.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 31 / 396 (7.83%) | 53 / 408 (12.99%) | 4 / 50 (8.00%) |
| occurrences (all) | 93 | 83 | 4 |

| | | | |
|--|--------------------|--------------------|-----------------|
| Hot flush | | | |
| subjects affected / exposed | 21 / 396 (5.30%) | 23 / 408 (5.64%) | 0 / 50 (0.00%) |
| occurrences (all) | 39 | 26 | 0 |
| Lymphoedema | | | |
| subjects affected / exposed | 16 / 396 (4.04%) | 24 / 408 (5.88%) | 0 / 50 (0.00%) |
| occurrences (all) | 18 | 25 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 148 / 396 (37.37%) | 156 / 408 (38.24%) | 5 / 50 (10.00%) |
| occurrences (all) | 291 | 320 | 16 |
| Asthenia | | | |
| subjects affected / exposed | 122 / 396 (30.81%) | 114 / 408 (27.94%) | 3 / 50 (6.00%) |
| occurrences (all) | 268 | 265 | 3 |
| Oedema peripheral | | | |
| subjects affected / exposed | 111 / 396 (28.03%) | 102 / 408 (25.00%) | 1 / 50 (2.00%) |
| occurrences (all) | 163 | 141 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 78 / 396 (19.70%) | 111 / 408 (27.21%) | 1 / 50 (2.00%) |
| occurrences (all) | 111 | 185 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 72 / 396 (18.18%) | 81 / 408 (19.85%) | 3 / 50 (6.00%) |
| occurrences (all) | 94 | 138 | 6 |
| Oedema | | | |
| subjects affected / exposed | 49 / 396 (12.37%) | 49 / 408 (12.01%) | 1 / 50 (2.00%) |
| occurrences (all) | 76 | 84 | 2 |
| Chills | | | |
| subjects affected / exposed | 15 / 396 (3.79%) | 34 / 408 (8.33%) | 1 / 50 (2.00%) |
| occurrences (all) | 18 | 36 | 7 |
| Chest pain | | | |
| subjects affected / exposed | 21 / 396 (5.30%) | 15 / 408 (3.68%) | 0 / 50 (0.00%) |
| occurrences (all) | 24 | 17 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 10 / 396 (2.53%) | 23 / 408 (5.64%) | 2 / 50 (4.00%) |
| occurrences (all) | 12 | 41 | 2 |
| Pain | | | |

| | | | |
|--|--------------------------|---------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 22 / 396 (5.56%) 26 | 26 / 408 (6.37%) 31 | 0 / 50 (0.00%) 0 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 21 / 396 (5.30%) 29 | 28 / 408 (6.86%) 33 | 1 / 50 (2.00%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 79 / 396 (19.95%) 118 | 101 / 408 (24.75%) 146 | 6 / 50 (12.00%) 10 |
| Dyspnoea subjects affected / exposed occurrences (all) | 62 / 396 (15.66%) 87 | 67 / 408 (16.42%) 99 | 1 / 50 (2.00%) 2 |
| Epistaxis subjects affected / exposed occurrences (all) | 35 / 396 (8.84%) 47 | 41 / 408 (10.05%) 56 | 2 / 50 (4.00%) 4 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 27 / 396 (6.82%) 32 | 32 / 408 (7.84%) 55 | 1 / 50 (2.00%) 1 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 23 / 396 (5.81%) 29 | 33 / 408 (8.09%) 43 | 3 / 50 (6.00%) 4 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 55 / 396 (13.89%) 72 | 67 / 408 (16.42%) 95 | 2 / 50 (4.00%) 3 |
| Depression subjects affected / exposed occurrences (all) | 20 / 396 (5.05%) 22 | 26 / 408 (6.37%) 33 | 2 / 50 (4.00%) 2 |
| Anxiety subjects affected / exposed occurrences (all) | 20 / 396 (5.05%) 28 | 20 / 408 (4.90%) 25 | 1 / 50 (2.00%) 1 |
| Investigations Weight decreased subjects affected / exposed occurrences (all) | 19 / 396 (4.80%) 22 | 37 / 408 (9.07%) 51 | 3 / 50 (6.00%) 3 |

| | | | |
|---|---------------------------|---------------------------|-----------------------|
| Weight increased subjects affected / exposed occurrences (all) | 22 / 396 (5.56%) 35 | 17 / 408 (4.17%) 21 | 0 / 50 (0.00%) 0 |
| Cardiac disorders Left ventricular dysfunction subjects affected / exposed occurrences (all) | 27 / 396 (6.82%) 33 | 27 / 408 (6.62%) 43 | 3 / 50 (6.00%) 9 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 76 / 396 (19.19%) 128 | 106 / 408 (25.98%) 187 | 7 / 50 (14.00%) 9 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 79 / 396 (19.95%) 114 | 95 / 408 (23.28%) 138 | 1 / 50 (2.00%) 1 |
| Dysgeusia subjects affected / exposed occurrences (all) | 62 / 396 (15.66%) 116 | 75 / 408 (18.38%) 95 | 1 / 50 (2.00%) 30 |
| Dizziness subjects affected / exposed occurrences (all) | 53 / 396 (13.38%) 73 | 67 / 408 (16.42%) 133 | 4 / 50 (8.00%) 4 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 59 / 396 (14.90%) 82 | 52 / 408 (12.75%) 93 | 2 / 50 (4.00%) 2 |
| Paraesthesia subjects affected / exposed occurrences (all) | 41 / 396 (10.35%) 60 | 43 / 408 (10.54%) 52 | 0 / 50 (0.00%) 0 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 11 / 396 (2.78%) 15 | 21 / 408 (5.15%) 28 | 1 / 50 (2.00%) 1 |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 191 / 396 (48.23%) 797 | 209 / 408 (51.23%) 849 | 1 / 50 (2.00%) 1 |
| Anaemia subjects affected / exposed occurrences (all) | 77 / 396 (19.44%) 143 | 100 / 408 (24.51%) 151 | 6 / 50 (12.00%) 15 |
| Leukopenia | | | |

| | | | |
|---|---------------------------|---------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 82 / 396 (20.71%) 344 | 75 / 408 (18.38%) 288 | 0 / 50 (0.00%) 0 |
| Eye disorders | | | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 55 / 396 (13.89%) 63 | 60 / 408 (14.71%) 74 | 0 / 50 (0.00%) 0 |
| Dry eye subjects affected / exposed occurrences (all) | 8 / 396 (2.02%) 8 | 24 / 408 (5.88%) 27 | 2 / 50 (4.00%) 2 |
| Cataract subjects affected / exposed occurrences (all) | 1 / 396 (0.25%) 1 | 7 / 408 (1.72%) 8 | 3 / 50 (6.00%) 3 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 191 / 396 (48.23%) 428 | 277 / 408 (67.89%) 989 | 25 / 50 (50.00%) 155 |
| Nausea subjects affected / exposed occurrences (all) | 168 / 396 (42.42%) 359 | 184 / 408 (45.10%) 394 | 4 / 50 (8.00%) 7 |
| Vomiting subjects affected / exposed occurrences (all) | 96 / 396 (24.24%) 150 | 110 / 408 (26.96%) 184 | 5 / 50 (10.00%) 7 |
| Constipation subjects affected / exposed occurrences (all) | 100 / 396 (25.25%) 179 | 69 / 408 (16.91%) 135 | 4 / 50 (8.00%) 6 |
| Stomatitis subjects affected / exposed occurrences (all) | 63 / 396 (15.91%) 138 | 82 / 408 (20.10%) 167 | 6 / 50 (12.00%) 13 |
| Abdominal pain subjects affected / exposed occurrences (all) | 50 / 396 (12.63%) 66 | 64 / 408 (15.69%) 86 | 2 / 50 (4.00%) 2 |
| Dyspepsia subjects affected / exposed occurrences (all) | 48 / 396 (12.12%) 73 | 55 / 408 (13.48%) 80 | 3 / 50 (6.00%) 8 |
| Abdominal pain upper | | | |

| | | | |
|--|---------------------------|---------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 43 / 396 (10.86%) 54 | 44 / 408 (10.78%) 69 | 2 / 50 (4.00%) 2 |
| Gastritis subjects affected / exposed occurrences (all) | 7 / 396 (1.77%) 8 | 16 / 408 (3.92%) 20 | 3 / 50 (6.00%) 3 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 240 / 396 (60.61%) 256 | 248 / 408 (60.78%) 264 | 4 / 50 (8.00%) 5 |
| Rash subjects affected / exposed occurrences (all) | 96 / 396 (24.24%) 185 | 156 / 408 (38.24%) 288 | 11 / 50 (22.00%) 19 |
| Nail disorder subjects affected / exposed occurrences (all) | 92 / 396 (23.23%) 105 | 96 / 408 (23.53%) 106 | 2 / 50 (4.00%) 2 |
| Pruritus subjects affected / exposed occurrences (all) | 40 / 396 (10.10%) 67 | 75 / 408 (18.38%) 117 | 6 / 50 (12.00%) 6 |
| Dry skin subjects affected / exposed occurrences (all) | 25 / 396 (6.31%) 26 | 47 / 408 (11.52%) 53 | 4 / 50 (8.00%) 6 |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 22 / 396 (5.56%) 25 | 28 / 408 (6.86%) 38 | 1 / 50 (2.00%) 1 |
| Erythema subjects affected / exposed occurrences (all) | 20 / 396 (5.05%) 27 | 23 / 408 (5.64%) 28 | 1 / 50 (2.00%) 1 |
| Eczema subjects affected / exposed occurrences (all) | 5 / 396 (1.26%) 6 | 5 / 408 (1.23%) 5 | 3 / 50 (6.00%) 3 |
| Renal and urinary disorders | | | |
| Dysuria subjects affected / exposed occurrences (all) | 11 / 396 (2.78%) 12 | 23 / 408 (5.64%) 27 | 0 / 50 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------------|-------------------|-------------------|------------------|
| Myalgia | | | |
| subjects affected / exposed | 98 / 396 (24.75%) | 97 / 408 (23.77%) | 5 / 50 (10.00%) |
| occurrences (all) | 209 | 202 | 30 |
| Arthralgia | | | |
| subjects affected / exposed | 71 / 396 (17.93%) | 83 / 408 (20.34%) | 5 / 50 (10.00%) |
| occurrences (all) | 130 | 133 | 5 |
| Pain in extremity | | | |
| subjects affected / exposed | 52 / 396 (13.13%) | 76 / 408 (18.63%) | 5 / 50 (10.00%) |
| occurrences (all) | 79 | 116 | 6 |
| Back pain | | | |
| subjects affected / exposed | 48 / 396 (12.12%) | 66 / 408 (16.18%) | 6 / 50 (12.00%) |
| occurrences (all) | 58 | 98 | 17 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 38 / 396 (9.60%) | 40 / 408 (9.80%) | 2 / 50 (4.00%) |
| occurrences (all) | 57 | 51 | 2 |
| Bone pain | | | |
| subjects affected / exposed | 31 / 396 (7.83%) | 37 / 408 (9.07%) | 1 / 50 (2.00%) |
| occurrences (all) | 56 | 48 | 1 |
| Muscle spasms | | | |
| subjects affected / exposed | 20 / 396 (5.05%) | 50 / 408 (12.25%) | 3 / 50 (6.00%) |
| occurrences (all) | 24 | 94 | 5 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 17 / 396 (4.29%) | 22 / 408 (5.39%) | 1 / 50 (2.00%) |
| occurrences (all) | 22 | 27 | 1 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 57 / 396 (14.39%) | 90 / 408 (22.06%) | 13 / 50 (26.00%) |
| occurrences (all) | 99 | 174 | 32 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 60 / 396 (15.15%) | 76 / 408 (18.63%) | 13 / 50 (26.00%) |
| occurrences (all) | 108 | 161 | 58 |
| Urinary tract infection | | | |
| subjects affected / exposed | 29 / 396 (7.32%) | 39 / 408 (9.56%) | 4 / 50 (8.00%) |
| occurrences (all) | 39 | 65 | 6 |
| Influenza | | | |

| | | | |
|--|---------------------------|---------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 22 / 396 (5.56%) 33 | 30 / 408 (7.35%) 43 | 6 / 50 (12.00%) 10 |
| Paronychia subjects affected / exposed occurrences (all) | 16 / 396 (4.04%) 23 | 32 / 408 (7.84%) 45 | 6 / 50 (12.00%) 8 |
| Rhinitis subjects affected / exposed occurrences (all) | 22 / 396 (5.56%) 35 | 22 / 408 (5.39%) 50 | 4 / 50 (8.00%) 13 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 19 / 396 (4.80%) 22 | 31 / 408 (7.60%) 45 | 2 / 50 (4.00%) 2 |
| Pharyngitis subjects affected / exposed occurrences (all) | 9 / 396 (2.27%) 10 | 22 / 408 (5.39%) 28 | 3 / 50 (6.00%) 6 |
| Bronchitis subjects affected / exposed occurrences (all) | 15 / 396 (3.79%) 19 | 16 / 408 (3.92%) 29 | 4 / 50 (8.00%) 5 |
| Cellulitis subjects affected / exposed occurrences (all) | 12 / 396 (3.03%) 14 | 16 / 408 (3.92%) 20 | 3 / 50 (6.00%) 6 |
| Cystitis subjects affected / exposed occurrences (all) | 6 / 396 (1.52%) 7 | 16 / 408 (3.92%) 25 | 5 / 50 (10.00%) 6 |
| Pneumonia subjects affected / exposed occurrences (all) | 8 / 396 (2.02%) 8 | 12 / 408 (2.94%) 20 | 4 / 50 (8.00%) 4 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 106 / 396 (26.77%) 176 | 120 / 408 (29.41%) 229 | 2 / 50 (4.00%) 3 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 21 / 396 (5.30%) 28 | 37 / 408 (9.07%) 60 | 3 / 50 (6.00%) 3 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 11 / 396 (2.78%) 24 | 17 / 408 (4.17%) 19 | 3 / 50 (6.00%) 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 12 December 2007 | Protocol Amendment Version B key elements: - Modified inclusion criterion 4 to include the collection of historic left ventricular ejection fraction (LVEF) values - Added LVEF assessments during follow-up to allow long-term follow-up of cardiac function - Aligned the reporting and grading of symptomatic left ventricular dysfunction (LVSD) with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 3.0 - Increased surveillance of anti-pertuzumab antibodies - Updated statistical analysis plan in relation to objective response, and statistical considerations and the analytical plan were further clarified - Added a hematology test on Day 8 of each treatment cycle during chemotherapy - Described with more accuracy the tumor assessment scans required at baseline |
| 23 June 2009 | Protocol Amendment Version C key elements: - Updated definition of postmenopausal women and the contraceptive requirements for women of childbearing potential, male participants with partners of childbearing potential, and pregnant partners to align with Medicines and Health Care Products Regulatory Agency (MHRA) recommendations, in accordance with the International Conference on Harmonization (ICH) M3 guideline - Added pregnancy testing requirements after discontinuation of study treatment - Clarified eligibility for enrollment into the study for participants with bone-only metastases - Clarified prior hormonal therapy in the metastatic breast cancer (MBC) setting and exclusion criterion 6 was amended to allow enrollment of participants with a history of squamous cell carcinoma - Clarified non-eligibility for participants in other interventional and non-interventional studies - Added clarification to exclusion criterion 14 regarding acceptable transaminases and alkaline phosphatase levels for inclusion into the study - Updated the schedule of assessments, deleting unnecessary assessments and correcting time points at which an assessment was required - Clarified use of positron emission tomography/computed tomography (PET/CT) scans when bone scans could not be performed due to isotope shortages - Clarified the administration and discontinuation of docetaxel - Clarified the follow-up period for LVEF assessments following discontinuation of study treatment |
| 26 August 2011 | Protocol Amendment Version D key elements: - Continuation of tumor assessments until investigator-determined PD (instead of IRF-determined PD) or until 15 April 2012 (with the exception of sites in Japan) - Continuation of sites in Japan to perform tumor assessments until IRF-determined disease progression and send tumor assessment data to the IRF until notified by the Study Management Team - Maintained the study blinding procedures to reduce the chances of bias or crossover occurring after disease progression - Updated timelines for the quality-of-life assessment (FACT-B questionnaire), sampling for antibodies to pertuzumab, and Eastern Cooperative Oncology Group (ECOG) performance status assessments - Eliminated sampling for shed HER2 extracellular domain (ECD) and HER ligands |
| 04 May 2012 | Protocol Amendment Version E key elements: - Inserted information relating to the second interim OS analysis as requested by regulatory authorities - Added an open-label pertuzumab crossover treatment group offered to participants in the placebo treatment group who had not experienced disease progression and were still receiving study treatment. The addition of the open-label pertuzumab crossover treatment group was subject to the results of the second interim OS analysis and was allowed because a statistical significance was achieved at the second interim OS analysis. - Added a change in serious adverse event (SAE) reporting that all SAEs should be reported to the Sponsor within 24 hours of the investigator becoming aware of the event to comply with European regulations |

| | |
|--------------|--|
| 10 July 2014 | Protocol Amendment Version F key elements: -Removed study-related assessments and procedures that will not be used for any future analyses for those subjects who continue to receive study drug treatment or who are participating in the survival follow up phase of the study; -To continue to monitor the safety of subjects still receiving study treatment; -Increased the duration of required contraceptive use and the prohibition of breastfeeding to 7 months after receipt of the final dose of all study drugs, to be consistent with the revised pharmacokinetic (PK) findings for trastuzumab; -Collect long term safety data regarding pertuzumab and trastuzumab use; -Enable further analyses of safety and survival |
|--------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported