



Clinical trial results:

A Randomized, Multicenter, Open-Label, Phase III Trial Comparing Trastuzumab Plus Pertuzumab Plus a Taxane Following Anthracyclines Versus Trastuzumab Emtansine Plus Pertuzumab Following Anthracyclines as Adjuvant Therapy in Patients with Operable HER2-Positive Primary Breast Cancer

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2012-004902-82 |
| Trial protocol | IT GB HU DE CZ ES NO BE SE PL FR |
| Global end of trial date | |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 05 December 2020 |
| First version publication date | 05 December 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BO28407 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01966471 |
| 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 | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 27 November 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 November 2019 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare invasive disease-free survival (IDFS) in the node-positive subpopulation and in the overall protocol-defined population of patients with HER2-positive breast cancer randomized to receive either, a taxane and one year of trastuzumab plus pertuzumab following anthracycline-based chemotherapy or one year of trastuzumab emtansine plus pertuzumab following anthracycline-based chemotherapy.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 31 January 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 10 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------------------------|
| Country: Number of subjects enrolled | Australia: 46 |
| Country: Number of subjects enrolled | Belgium: 22 |
| Country: Number of subjects enrolled | Bosnia and Herzegovina: 13 |
| Country: Number of subjects enrolled | Brazil: 35 |
| Country: Number of subjects enrolled | Canada: 107 |
| Country: Number of subjects enrolled | Chile: 8 |
| Country: Number of subjects enrolled | Colombia: 4 |
| Country: Number of subjects enrolled | Czechia: 35 |
| Country: Number of subjects enrolled | El Salvador: 10 |
| Country: Number of subjects enrolled | France: 81 |
| Country: Number of subjects enrolled | Georgia: 37 |
| Country: Number of subjects enrolled | Germany: 119 |
| Country: Number of subjects enrolled | Guatemala: 10 |
| Country: Number of subjects enrolled | Hong Kong: 16 |
| Country: Number of subjects enrolled | Hungary: 35 |
| Country: Number of subjects enrolled | Israel: 4 |
| Country: Number of subjects enrolled | Italy: 130 |
| Country: Number of subjects enrolled | Japan: 260 |
| Country: Number of subjects enrolled | Korea, Republic of: 90 |
| Country: Number of subjects enrolled | Mexico: 12 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Norway: 10 |
| Country: Number of subjects enrolled | Panama: 12 |
| Country: Number of subjects enrolled | Peru: 6 |
| Country: Number of subjects enrolled | Philippines: 9 |
| Country: Number of subjects enrolled | Poland: 90 |
| Country: Number of subjects enrolled | Romania: 18 |
| Country: Number of subjects enrolled | Russian Federation: 95 |
| Country: Number of subjects enrolled | Singapore: 21 |
| Country: Number of subjects enrolled | Spain: 69 |
| Country: Number of subjects enrolled | Sweden: 21 |
| Country: Number of subjects enrolled | Switzerland: 13 |
| Country: Number of subjects enrolled | Taiwan: 88 |
| Country: Number of subjects enrolled | Thailand: 24 |
| Country: Number of subjects enrolled | Ukraine: 24 |
| Country: Number of subjects enrolled | United Kingdom: 124 |
| Country: Number of subjects enrolled | United States: 148 |
| Worldwide total number of subjects | 1846 |
| EEA total number of subjects | 754 |

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) | 1595 |
| From 65 to 84 years | 251 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1846 subjects were enrolled in the study.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane |

Arm description:

Trastuzumab and pertuzumab were administered concurrently for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) with the taxane (docetaxel or paclitaxel) component of chemotherapy following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | Herceptin |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

An IV infusion (duration 90 minutes) was administered at 8 mg/kg loading dose followed by 6 mg/kg IV q3w for up to 18 cycles (1 cycle = 21 days).

| | |
|--|-----------------|
| Investigational medicinal product name | Pertuzumab |
| Investigational medicinal product code | |
| Other name | Perjeta |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

An infusion (duration 60 minutes) was administered at 840 mg loading dose followed by 420 mg IV q3w for up to 18 cycles (1 cycle = 21 days).

| | |
|--|-----------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

An IV infusion of paclitaxel 80 mg/m² once weekly may be administered concurrently with trastuzumab in combination with pertuzumab for 12 weeks.

| | |
|--|-----------------|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 to 4 cycles (1 cycle = 21 days) of standard of care anthracycline-based chemotherapy using epirubicin may be administered in both treatment arms as per discretion of the investigator and local prescribing information/institutional guidelines.

| | |
|--|-----------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

IV infusion either docetaxel every 3 weeks (q3w) (at 100 milligram per square meter [mg/m²] for 3 cycles (1 cycle = 21 days); at 75 mg/m² for 4 cycles; or start at 75 mg/m² in the first cycle and escalate to 100 mg/m² if no dose limiting toxicity occurs, for a total of 3 cycles at minimum) may be administered concurrently with trastuzumab in combination with pertuzumab.

| | |
|------------------|--|
| Arm title | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab |
|------------------|--|

Arm description:

Trastuzumab emtansine and pertuzumab continued for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab Emtansine |
| Investigational medicinal product code | |
| Other name | Kadcyla |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

An intravenous (IV) infusion (duration 90 minutes) was administered at 3.6 milligram per kilogram (mg/kg) every three weeks (q3w) for up to 18 cycles (1 cycle = 21 days).

| | |
|--|-----------------|
| Investigational medicinal product name | Epirubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 to 4 cycles (1 cycle = 21 days) of standard of care anthracycline-based chemotherapy using epirubicin may be administered in both treatment arms as per discretion of the investigator and local prescribing information/institutional guidelines.

| | |
|--|-----------------|
| Investigational medicinal product name | Pertuzumab |
| Investigational medicinal product code | |
| Other name | Perjeta |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

An infusion (duration 60 minutes) was administered at 840 mg loading dose followed by 420 mg IV q3w for up to 18 cycles (1 cycle = 21 days).

| | |
|--|-----------------|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 to 4 cycles (1 cycle = 21 days) of standard of care anthracycline-based chemotherapy using doxorubicin may be administered in both treatment arms as per discretion of the investigator and local prescribing information/institutional guidelines.

| | |
|--|-----------------|
| Investigational medicinal product name | Epirubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 to 4 cycles (1 cycle = 21 days) of standard of care anthracycline-based chemotherapy using epirubicin may be administered in both treatment arms as per discretion of the investigator and local prescribing information/institutional guidelines.

| | |
|--|-----------------|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 to 4 cycles (1 cycle = 21 days) of standard of care anthracycline-based chemotherapy using epirubicin may be administered in both treatment arms as per discretion of the investigator and local prescribing information/institutional guidelines.

| | |
|--|------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 to 4 cycles (1 cycle = 21 days) of standard of care anthracycline-based chemotherapy using cyclophosphamide (FEC) may be administered in both treatment arms as per discretion of the investigator and local prescribing information/institutional guidelines.

| | |
|--|-----------------|
| Investigational medicinal product name | 5-Fluorouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

3 to 4 cycles (1 cycle = 21 days) of standard of care anthracycline-based chemotherapy using 5-fluorouracil, may be administered in both treatment arms as per discretion of the investigator and local prescribing information/institutional guidelines.

| Number of subjects in period 1 | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab |
|---------------------------------------|--|---|
| Started | 918 | 928 |
| Completed | 815 | 815 |
| Not completed | 103 | 113 |
| Physician decision | 5 | 5 |
| Withdrawal By Subject | 48 | 43 |
| Death | 33 | 44 |
| Multiple Reasons | 3 | 5 |
| Lost to follow-up | 14 | 16 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane |
|-----------------------|---|

Reporting group description:

Trastuzumab and pertuzumab were administered concurrently for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) with the taxane (docetaxel or paclitaxel) component of chemotherapy following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| | |
|-----------------------|--|
| Reporting group title | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab |
|-----------------------|--|

Reporting group description:

Trastuzumab emtansine and pertuzumab continued for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| Reporting group values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | Total |
|---|---|--|-------|
| Number of subjects | 918 | 928 | 1846 |
| Age Categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age <37 weeks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 786 | 809 | 1595 |
| From 65-84 years | 132 | 119 | 251 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 51.6 | 51.9 | - |
| standard deviation | ± 10.8 | ± 10.8 | - |
| Sex: Female, Male Units: Subjects | | | |
| Female | 913 | 926 | 1839 |
| Male | 5 | 2 | 7 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 70 | 68 | 138 |
| Not Hispanic or Latino | 798 | 790 | 1588 |
| Not Stated | 35 | 44 | 79 |
| Unknown | 15 | 26 | 41 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 12 | 12 | 24 |
| Asian | 267 | 275 | 542 |

| | | | |
|---|-----|-----|------|
| Black or African American | 15 | 8 | 23 |
| Native Hawaiian or other Pacific Islander | 1 | 1 | 2 |
| White | 558 | 565 | 1123 |
| Other | 30 | 27 | 57 |
| Multiple | 2 | 2 | 4 |
| Unknown | 33 | 38 | 71 |

Subject analysis sets

| | |
|----------------------------|------------------------------------|
| Subject analysis set title | AC-THP Node Positive Subpopulation |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The lymph node positive population was a subpopulation of the randomized participant population including patients with positive lymph node.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | AC-KP Node Positive Subpopulation |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The lymph node positive population was a subpopulation of the randomized participant population including patients with positive lymph node.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | AC-THP Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety population included all randomized participants who received at least one full or partial dose of any study treatment.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | AC-KP Safety Population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety population included all randomized participants who received at least one full or partial dose of any study treatment.

| Reporting group values | AC-THP Node Positive Subpopulation | AC-KP Node Positive Subpopulation | AC-THP Safety Population |
|---|------------------------------------|-----------------------------------|--------------------------|
| Number of subjects | 826 | 832 | 926 |
| Age Categorical Units: Subjects | | | |
| Preterm newborn infants (gestational age <37 weeks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 708 | 728 | 792 |
| From 65-84 years | 118 | 104 | 134 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 51.2 | 51.7 | 51.6 |
| standard deviation | ± 11.0 | ± 10.8 | ± 10.9 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 821 | 830 | 921 |
| Male | 5 | 2 | 5 |

| | | | |
|---|-----|-----|-----|
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 66 | 60 | 71 |
| Not Hispanic or Latino | 717 | 711 | 801 |
| Not Stated | 30 | 38 | 38 |
| Unknown | 13 | 23 | 16 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 11 | 11 | 12 |
| Asian | 237 | 246 | 270 |
| Black or African American | 15 | 8 | 14 |
| Native Hawaiian or other Pacific Islander | 1 | 1 | 1 |
| White | 502 | 511 | 560 |
| Other | 28 | 20 | 31 |
| Multiple | 2 | 2 | 2 |
| Unknown | 30 | 33 | 36 |

| | | | |
|---|-------------------------|--|--|
| Reporting group values | AC-KP Safety Population | | |
| Number of subjects | 912 | | |
| Age Categorical | | | |
| Units: Subjects | | | |
| Preterm newborn infants (gestational age <37 weeks) | 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) | 797 | | |
| From 65-84 years | 115 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 51.8 | | |
| standard deviation | ± 10.8 | | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 910 | | |
| Male | 2 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 67 | | |
| Not Hispanic or Latino | 779 | | |
| Not Stated | 41 | | |
| Unknown | 25 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 12 | | |
| Asian | 269 | | |
| Black or African American | 8 | | |

| | | | |
|---|-----|--|--|
| Native Hawaiian or other Pacific Islander | 1 | | |
| White | 559 | | |
| Other | 26 | | |
| Multiple | 2 | | |
| Unknown | 35 | | |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane |
|-----------------------|---|

Reporting group description:

Trastuzumab and pertuzumab were administered concurrently for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) with the taxane (docetaxel or paclitaxel) component of chemotherapy following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| | |
|-----------------------|--|
| Reporting group title | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab |
|-----------------------|--|

Reporting group description:

Trastuzumab emtansine and pertuzumab continued for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| | |
|----------------------------|------------------------------------|
| Subject analysis set title | AC-THP Node Positive Subpopulation |
|----------------------------|------------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The lymph node positive population was a subpopulation of the randomized participant population including patients with positive lymph node.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | AC-KP Node Positive Subpopulation |
|----------------------------|-----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

The lymph node positive population was a subpopulation of the randomized participant population including patients with positive lymph node.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | AC-THP Safety Population |
|----------------------------|--------------------------|

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

Subject analysis set description:

The safety population included all randomized participants who received at least one full or partial dose of any study treatment.

| | |
|----------------------------|-------------------------|
| Subject analysis set title | AC-KP Safety Population |
|----------------------------|-------------------------|

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

Subject analysis set description:

The safety population included all randomized participants who received at least one full or partial dose of any study treatment.

Primary: IDFS in the Node-Positive Subpopulation

| | |
|-----------------|---|
| End point title | IDFS in the Node-Positive Subpopulation |
|-----------------|---|

End point description:

IDFS event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer. 3-year IDFS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization.

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

End point timeframe:

From randomization to data cut-off date of 27 November 2019 (approximately up to 70 months)

| End point values | AC-THP Node Positive Subpopulation | AC-KP Node Positive Subpopulation | | |
|----------------------------------|------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 826 | 832 | | |
| Units: Percent Probability | | | | |
| number (confidence interval 95%) | 94.10 (92.46 to 95.73) | 92.75 (90.95 to 94.54) | | |

Statistical analyses

| Statistical analysis title | IDFS in the Node-Positive Subpopulation |
|---|--|
| Comparison groups | AC-THP Node Positive Subpopulation v AC-KP Node Positive Subpopulation |
| Number of subjects included in analysis | 1658 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.827 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.32 |

Primary: Invasive Disease-Free Survival (IDFS) in the Overall Population

| | |
|------------------------|--|
| End point title | Invasive Disease-Free Survival (IDFS) in the Overall Population |
| End point description: | IDFS event was defined as the first occurrence of one of the following events: Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion); ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast); distant recurrence (i.e., evidence of breast cancer in any anatomic site - other than the two above mentioned sites); death attributable to any cause; contralateral invasive breast cancer. 3-year IDFS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization. |
| End point type | Primary |
| End point timeframe: | From randomization to data cut-off date of 27 November 2019 (approximately up to 70 months) |

| | | | | |
|----------------------------------|---|--|--|--|
| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 918 | 928 | | |
| Units: Percent Probability | | | | |
| number (confidence interval 95%) | 94.22 (92.68 to 95.76) | 93.05 (91.38 to 94.72) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | IDFS |
| Comparison groups | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane v Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab |
| Number of subjects included in analysis | 1846 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8692 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.32 |

Secondary: IDFS Plus Second Primary Non-Breast Cancer

| | |
|--|--|
| End point title | IDFS Plus Second Primary Non-Breast Cancer |
| End point description: | |
| IDFS including second primary non-breast cancer was defined the same way as IDFS for the primary endpoint but including second primary non breast invasive cancer as an event (with the exception of non-melanoma skin cancers and carcinoma in situ (CIS) of any site). 3-year IDFS including second primary non-breast cancer event-free rates per treatment arm in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to approximately 10 years | |

| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | | |
| Units: Percent Probability | | | | |
| number (confidence interval 95%) | (to) | (to) | | |

Notes:

[1] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[2] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS)

| | |
|--|-----------------------------|
| End point title | Disease-Free Survival (DFS) |
| End point description: | |
| DFS was defined as time between randomization and first occurrence of IDFS, second primary non-breast cancer and contralateral or ipsilateral ductal carcinoma in situ (DCIS). 3-year DFS event-free rates per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline up to approximately 10 years | |

| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[3] | 0 ^[4] | | |
| Units: Percent Probability | | | | |
| number (confidence interval 95%) | (to) | (to) | | |

Notes:

[3] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[4] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Recurrence-Free Interval (DRFI)

| | |
|---|---|
| End point title | Distant Recurrence-Free Interval (DRFI) |
| End point description: | |
| DRFI was defined as time between randomization and first occurrence of distant breast cancer recurrence. 3 years DRFI event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 3 years after randomization. | |
| End point type | Secondary |

End point timeframe:

Baseline up to approximately 10 years

| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | | |
| Units: Percent Probability | | | | |
| number (confidence interval 95%) | (to) | (to) | | |

Notes:

[5] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[6] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from randomization to death due to any cause. 5 years OS event-free rate per randomized treatment arms in the ITT population were estimated using the Kaplan-Meier method and estimated the probability of a patient being event-free after 5 years after randomization.

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

End point timeframe:

Baseline up to approximately 10 years

| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[7] | 0 ^[8] | | |
| Units: Percent Probability | | | | |
| number (confidence interval 95%) | (to) | (to) | | |

Notes:

[7] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[8] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

| | |
|-----------------|--|
| End point title | Percentage of Participants With Adverse Events |
|-----------------|--|

End point description:

An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. AEs were reported based on the national cancer institute common terminology criteria for AEs, Version 4.0 (NCI-CTCAE, v4.0). Reported are the number of subjects with AEs, Grade 3-5 AEs, and Serious Adverse Events (SAEs).

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

End point timeframe:

From randomization to data cut-off date of 27 November 2019 (approximately up to 70 months)

| End point values | AC-THP Safety Population | AC-KP Safety Population | | |
|-----------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 926 | 912 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | 98.5 | 99.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Decrease in Left Ventricular Ejection Fraction (LVEF) From Baseline Over Time

| | |
|-----------------|---|
| End point title | Percentage of Participants With Decrease in Left Ventricular Ejection Fraction (LVEF) From Baseline Over Time |
|-----------------|---|

End point description:

LVEF was assessed using either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans.

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

End point timeframe:

Baseline up to approximately 10 years

| End point values | AC-THP Safety Population | AC-KP Safety Population | | |
|-----------------------------------|--------------------------|-------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 0 ^[9] | 0 ^[10] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[9] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[10] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

Secondary: European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Score

| | |
|-----------------|--|
| End point title | European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) Score |
|-----------------|--|

End point description:

The EORTC QLQ-C30 included global health status, functional scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain) and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Most questions used a 4-point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale [1 'very poor' to 7 'Excellent']). Scores were averaged and transformed to 0 - 100 scale, whereby higher scores indicate greater functioning, greater quality of life, or a greater degree of symptoms, with changes of 7 - 15 points considered to be a clinically meaningful deterioration to participants. A positive value means an increase, while a negative value means a decrease, in score at the indicated time-point relative to the score at baseline (Cycle 1, Day 1). The value '999999' indicates that the mean and standard deviation were not evaluable.

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

End point timeframe:

Baseline, Cycles 1, 2, 3, 4, 5, 9, 14, End of Treatment, Follow-up Month 6, Follow-up Month 12, Follow-up Month 18

| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 869 | 891 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: Appetite Loss | 8.2 (± 17.6) | 7.6 (± 16.8) | | |
| Change at Cycle 1: Appetite Loss | 12.2 (± 27.9) | 10.8 (± 26.6) | | |
| Change at Cycle 2: Appetite Loss | 15.2 (± 27.7) | 13.1 (± 26.7) | | |
| Change at Cycle 3: Appetite Loss | 14.3 (± 28.2) | 10.3 (± 25.7) | | |
| Change at Cycle 4: Appetite Loss | 16.2 (± 29.8) | 9.4 (± 25.5) | | |
| Change at Cycle 5: Appetite Loss | 12.0 (± 28.4) | 9.0 (± 26.2) | | |
| Change at Cycle 9: Appetite Loss | 5.7 (± 23.9) | 8.2 (± 25.7) | | |
| Change at Cycle 14: Appetite Loss | 2.2 (± 23.1) | 6.4 (± 25.4) | | |
| Change at EoT: Appetite Loss | 0.5 (± 22.3) | 5.6 (± 25.1) | | |
| Change at FU Month 6: Appetite Loss | -1.3 (± 20.7) | -2.4 (± 20.3) | | |
| Change at FU Month 12: Appetite Loss | -2.2 (± 20.8) | -2.3 (± 20.5) | | |
| Change at FU Month 18: Appetite Loss | 99999999 (± 9999999) | -16.7 (± 23.6) | | |
| Baseline: Constipation | 9.6 (± 19.4) | 9.0 (± 19.6) | | |
| Change at Cycle 1: Constipation | 8.4 (± 22.5) | 8.0 (± 26.1) | | |
| Change at Cycle 2: Constipation | 1.1 (± 25.0) | 0.9 (± 23.1) | | |
| Change at Cycle 3: Constipation | 2.0 (± 24.6) | 0.2 (± 22.2) | | |
| Change at Cycle 4: Constipation | 2.5 (± 24.3) | -0.6 (± 23.2) | | |
| Change at Cycle 5: Constipation | 0.5 (± 22.4) | -0.4 (± 22.1) | | |
| Change at Cycle 9: Constipation | -0.7 (± 21.7) | 3.3 (± 24.7) | | |
| Change at Cycle 14: Constipation | 0.6 (± 21.1) | 4.2 (± 24.6) | | |

| | | | | |
|--|----------------------|----------------|--|--|
| Change at EoT: Constipation | 0.2 (± 21.8) | 4.7 (± 25.1) | | |
| Change at FU Month 6: Constipation | 3.4 (± 23.2) | 1.5 (± 24.1) | | |
| Change at FU Month 12: Constipation | 2.8 (± 22.8) | 2.0 (± 23.3) | | |
| Change at FU Month 18: Constipation | 99999999 (± 9999999) | 0.0 (± 0.0) | | |
| Baseline: Diarrhea | 5.2 (± 13.2) | 4.7 (± 12.9) | | |
| Change at Cycle 1: Diarrhea | 4.7 (± 20.3) | 4.2 (± 18.4) | | |
| Change at Cycle 2: Diarrhea | 32.5 (± 32.8) | 16.0 (± 26.9) | | |
| Change at Cycle 3: Diarrhea | 28.4 (± 30.5) | 11.3 (± 23.5) | | |
| Change at Cycle 4: Diarrhea | 26.5 (± 30.0) | 10.3 (± 23.6) | | |
| Change at Cycle 5: Diarrhea | 23.9 (± 30.4) | 8.8 (± 22.8) | | |
| Change at Cycle 9: Diarrhea | 12.6 (± 24.6) | 4.7 (± 21.7) | | |
| Change at Cycle 14: Diarrhea | 12.5 (± 26.4) | 5.1 (± 20.3) | | |
| Change at EoT: Diarrhea | 10.3 (± 25.2) | 3.0 (± 19.4) | | |
| Change at FU Month 6: Diarrhea | -0.3 (± 16.4) | -1.1 (± 16.3) | | |
| Change at FU Month 12: Diarrhea | -0.3 (± 17.8) | 0.0 (± 17.1) | | |
| Change at FU Month 18: Diarrhea | 99999999 (± 9999999) | -16.7 (± 23.6) | | |
| Baseline: Dyspnea | 5.8 (± 14.0) | 6.2 (± 14.3) | | |
| Change at Cycle 1: Dyspnea | 10.4 (± 21.4) | 9.2 (± 21.8) | | |
| Change at Cycle 2: Dyspnea | 11.6 (± 22.0) | 7.4 (± 20.6) | | |
| Change at Cycle 3: Dyspnea | 13.4 (± 23.2) | 6.5 (± 20.5) | | |
| Change at Cycle 4: Dyspnea | 14.3 (± 23.7) | 5.9 (± 20.8) | | |
| Change at Cycle 5: Dyspnea | 13.7 (± 22.4) | 5.6 (± 19.8) | | |
| Change at Cycle 9: Dyspnea | 7.8 (± 19.3) | 7.5 (± 21.4) | | |
| Change at Cycle 14: Dyspnea | 6.8 (± 20.8) | 8.1 (± 21.6) | | |
| Change at EoT: Dyspnea | 7.6 (± 21.1) | 8.8 (± 22.3) | | |
| Change at FU Month 6: Dyspnea | 7.0 (± 20.8) | 5.3 (± 19.7) | | |
| Change at FU Month 12: Dyspnea | 6.2 (± 20.9) | 5.8 (± 20.5) | | |
| Change at FU Month 18: Dyspnea | 99999999 (± 9999999) | -16.7 (± 23.6) | | |
| Baseline: Fatigue | 21.5 (± 18.6) | 20.6 (± 18.6) | | |
| Change at Cycle 1: Fatigue | 13.2 (± 21.5) | 14.4 (± 22.1) | | |
| Change at Cycle 2: Fatigue | 15.4 (± 22.7) | 11.2 (± 21.7) | | |
| Change at Cycle 3: Fatigue | 15.3 (± 23.1) | 8.7 (± 20.9) | | |
| Change at Cycle 4: Fatigue | 16.0 (± 23.4) | 8.2 (± 20.7) | | |
| Change at Cycle 5: Fatigue | 14.9 (± 22.8) | 8.4 (± 21.1) | | |
| Change at Cycle 9: Fatigue | 8.4 (± 22.0) | 9.8 (± 20.8) | | |
| Change at Cycle 14: Fatigue | 6.7 (± 22.0) | 10.6 (± 22.4) | | |
| Change at EoT: Fatigue | 5.5 (± 22.9) | 9.3 (± 21.9) | | |
| Change at FU Month 6: Fatigue | 2.8 (± 21.9) | 3.1 (± 21.9) | | |
| Change at FU Month 12: Fatigue | 1.9 (± 22.1) | 1.8 (± 20.8) | | |
| Change at FU Month 18: Fatigue | 99999999 (± 9999999) | -5.6 (± 39.3) | | |
| Baseline: Financial Difficulties | 20.1 (± 28.3) | 19.9 (± 28.5) | | |
| Change at Cycle 1: Financial Difficulties | 2.2 (± 25.2) | 0.3 (± 24.8) | | |
| Change at Cycle 2: Financial Difficulties | 2.0 (± 25.7) | -0.6 (± 25.3) | | |
| Change at Cycle 3: Financial Difficulties | 3.9 (± 24.7) | -0.4 (± 25.0) | | |
| Change at Cycle 4: Financial Difficulties | 3.7 (± 24.9) | -0.2 (± 25.4) | | |
| Change at Cycle 5: Financial Difficulties | 3.4 (± 25.3) | 0.7 (± 26.2) | | |
| Change at Cycle 9: Financial Difficulties | 0.9 (± 25.6) | -0.5 (± 26.6) | | |
| Change at Cycle 14: Financial Difficulties | -1.4 (± 25.1) | -1.0 (± 27.2) | | |

| | | | | |
|---|----------------------|----------------|--|--|
| Change at EoT: Financial Difficulties | -1.1 (± 27.3) | -1.7 (± 25.7) | | |
| Change at FU Month 6: Financial Difficulties | -3.8 (± 27.4) | -5.2 (± 28.7) | | |
| Change at FU Month 12: Financial Difficulties | -5.1 (± 28.6) | -6.8 (± 28.3) | | |
| Change at FU Month 18: Financial Difficulties | 99999999 (± 9999999) | 0.0 (± 0.0) | | |
| Baseline: Insomnia | 23.9 (± 26.1) | 24.9 (± 27.6) | | |
| Change at Cycle 1: Insomnia | 3.6 (± 30.2) | 1.8 (± 28.8) | | |
| Change at Cycle 2: Insomnia | 6.0 (± 30.5) | 0.4 (± 30.0) | | |
| Change at Cycle 3: Insomnia | 6.2 (± 30.2) | -0.1 (± 30.3) | | |
| Change at Cycle 4: Insomnia | 8.6 (± 31.3) | 1.1 (± 30.4) | | |
| Change at Cycle 5: Insomnia | 5.2 (± 31.1) | 1.1 (± 29.9) | | |
| Change at Cycle 9: Insomnia | 4.3 (± 30.5) | 1.1 (± 29.9) | | |
| Change at Cycle 14: Insomnia | 2.7 (± 30.6) | 2.7 (± 30.2) | | |
| Change at EoT: Insomnia | 2.5 (± 30.8) | 0.9 (± 30.2) | | |
| Change at FU Month 6: Insomnia | 0.9 (± 29.5) | -2.3 (± 29.6) | | |
| Change at FU Month 12: Insomnia | 0.0 (± 30.2) | -2.9 (± 30.4) | | |
| Change at FU Month 18: Insomnia | 99999999 (± 9999999) | -16.7 (± 23.6) | | |
| Baseline: Nausea/Vomiting | 2.6 (± 9.4) | 2.3 (± 7.1) | | |
| Change at Cycle 1: Nausea/Vomiting | 10.4 (± 19.5) | 10.5 (± 17.8) | | |
| Change at Cycle 2: Nausea/Vomiting | 6.0 (± 16.5) | 7.5 (± 16.1) | | |
| Change at Cycle 3: Nausea/Vomiting | 5.0 (± 16.2) | 5.2 (± 13.9) | | |
| Change at Cycle 4: Nausea/Vomiting | 4.7 (± 16.0) | 3.7 (± 12.8) | | |
| Change at Cycle 5: Nausea/Vomiting | 4.0 (± 15.6) | 3.2 (± 13.1) | | |
| Change at Cycle 9: Nausea/Vomiting | 1.1 (± 13.8) | 2.8 (± 11.5) | | |
| Change at Cycle 14: Nausea/Vomiting | 1.1 (± 12.3) | 3.0 (± 12.1) | | |
| Change at EoT: Nausea/Vomiting | 0.9 (± 13.2) | 1.7 (± 12.0) | | |
| Change at FU Month 6: Nausea/Vomiting | 0.2 (± 11.6) | 0.1 (± 10.1) | | |
| Change at FU Month 12: Nausea/Vomiting | 0.5 (± 12.4) | 0.6 (± 10.3) | | |
| Change at FU Month 18: Nausea/Vomiting | 99999999 (± 9999999) | -8.3 (± 11.8) | | |
| Baseline: Pain | 17.4 (± 20.1) | 16.4 (± 20.0) | | |
| Change at Cycle 1: Pain | 1.8 (± 22.8) | 1.1 (± 22.5) | | |
| Change at Cycle 2: Pain | 5.0 (± 24.5) | 2.8 (± 23.1) | | |
| Change at Cycle 3: Pain | 3.5 (± 23.7) | 2.5 (± 22.6) | | |
| Change at Cycle 4: Pain | 5.4 (± 23.2) | 3.1 (± 23.5) | | |
| Change at Cycle 5: Pain | 5.2 (± 23.7) | 3.8 (± 23.5) | | |
| Change at Cycle 9: Pain | 3.4 (± 22.6) | 3.9 (± 23.3) | | |
| Change at Cycle 14: Pain | 2.0 (± 23.4) | 5.7 (± 24.1) | | |
| Change at EoT: Pain | 1.9 (± 23.3) | 5.1 (± 24.5) | | |
| Change at FU Month 6: Pain | 0.8 (± 23.0) | 1.4 (± 22.6) | | |
| Change at FU Month 12: Pain | 0.0 (± 23.3) | 0.5 (± 21.5) | | |
| Change at FU Month 18: Pain | 99999999 (± 9999999) | -25.0 (± 35.4) | | |
| Baseline: Cognitive Functioning | 88.6 (± 16.9) | 88.7 (± 16.3) | | |
| Change at Cycle 1: Cognitive Functioning | -9.7 (± 20.8) | -6.9 (± 19.3) | | |
| Change at Cycle 2: Cognitive Functioning | -9.4 (± 20.0) | -6.8 (± 19.3) | | |
| Change at Cycle 3: Cognitive Functioning | -10.1 (± 20.8) | -6.4 (± 19.4) | | |

| | | | | |
|--|----------------------|---------------|--|--|
| Change at Cycle 4: Cognitive Functioning | -11.8 (± 21.6) | -6.9 (± 19.6) | | |
| Change at Cycle 5: Cognitive Functioning | -10.8 (± 21.6) | -7.3 (± 20.3) | | |
| Change at Cycle 9: Cognitive Functioning | -8.3 (± 20.2) | -7.6 (± 20.1) | | |
| Change at Cycle 14: Cognitive Functioning | -8.1 (± 20.3) | -8.1 (± 20.6) | | |
| Change at EoT: Cognitive Functioning | -8.7 (± 22.3) | -8.4 (± 20.9) | | |
| Change at FU Month 6: Cognitive Functioning | -8.0 (± 20.4) | -6.1 (± 19.7) | | |
| Change at FU Month 12: Cognitive Functioning | -7.1 (± 22.5) | -6.0 (± 20.7) | | |
| Change at FU Month 18: Cognitive Functioning | 99999999 (± 9999999) | 16.7 (± 23.6) | | |
| Baseline: Emotional Functioning | 76.0 (± 19.7) | 75.7 (± 20.9) | | |
| Change at Cycle 1: Emotional Functioning | -1.1 (± 20.3) | 0.0 (± 19.2) | | |
| Change at Cycle 2: Emotional Functioning | -1.0 (± 20.8) | 1.6 (± 19.7) | | |
| Change at Cycle 3: Emotional Functioning | -0.9 (± 21.2) | 2.2 (± 19.6) | | |
| Change at Cycle 4: Emotional Functioning | -2.5 (± 22.3) | 2.8 (± 20.0) | | |
| Change at Cycle 5: Emotional Functioning | -1.2 (± 22.2) | 2.6 (± 21.1) | | |
| Change at Cycle 9: Emotional Functioning | 3.1 (± 20.9) | 2.9 (± 21.21) | | |
| Change at Cycle 14: Emotional Functioning | 4.1 (± 21.0) | 2.5 (± 21.3) | | |
| Change at EoT: Emotional Functioning | 3.0 (± 22.4) | 3.1 (± 21.3) | | |
| Change at FU Month 6: Emotional Functioning | 4.7 (± 21.2) | 6.1 (± 21.8) | | |
| Change at FU Month 12: Emotional Functioning | 5.8 (± 22.1) | 6.5 (± 21.9) | | |
| Change at FU Month 18: Emotional Functioning | 99999999 (± 9999999) | 12.5 (± 17.7) | | |
| Baseline: Physical Functioning | 88.4 (± 13.5) | 89.1 (± 12.3) | | |
| Change at Cycle 1: Physical Functioning | -6.0 (± 14.5) | -5.9 (± 13.4) | | |
| Change at Cycle 2: Physical Functioning | -7.8 (± 15.8) | -4.8 (± 12.8) | | |
| Change at Cycle 3: Physical Functioning | -7.1 (± 15.4) | -4.1 (± 13.0) | | |
| Change at Cycle 4: Physical Functioning | -8.4 (± 16.2) | -3.5 (± 13.1) | | |
| Change at Cycle 5: Physical Functioning | -8.3 (± 16.1) | -3.5 (± 13.3) | | |
| Change at Cycle 9: Physical Functioning | -4.0 (± 15.0) | -3.8 (± 14.2) | | |
| Change at Cycle 14: Physical Functioning | -2.7 (± 14.2) | -4.2 (± 14.2) | | |
| Change at EoT: Physical Functioning | -2.2 (± 14.7) | -4.9 (± 15.0) | | |
| Change at FU Month 6: Physical Functioning | -0.6 (± 14.4) | -1.6 (± 13.6) | | |
| Change at FU Month 12: Physical Functioning | -0.1 (± 15.4) | -0.8 (± 13.2) | | |
| Change at FU Month 18: Physical Functioning | 99999999 (± 9999999) | 13.3 (± 18.9) | | |
| Baseline: Role Functioning | 83.1 (± 21.7) | 83.4 (± 21.3) | | |
| Change at Cycle 1: Role Functioning | -5.1 (± 24.5) | -5.7 (± 24.9) | | |
| Change at Cycle 2: Role Functioning | -9.7 (± 26.6) | -5.5 (± 24.0) | | |
| Change at Cycle 3: Role Functioning | -8.9 (± 26.7) | -2.7 (± 23.2) | | |
| Change at Cycle 4: Role Functioning | -10.7 (± 27.5) | -3.2 (± 23.7) | | |
| Change at Cycle 5: Role Functioning | -9.4 (± 27.3) | -3.5 (± 23.9) | | |

| | | | | |
|---|----------------------|---------------|--|--|
| Change at Cycle 9: Role Functioning | -3.3 (± 25.4) | -3.2 (± 24.1) | | |
| Change at Cycle 14: Role Functioning | -0.5 (± 25.0) | -4.3 (± 25.3) | | |
| Change at EoT: Role Functioning | -0.2 (± 26.3) | -3.5 (± 24.9) | | |
| Change at FU Month 6: Role Functioning | 2.2 (± 24.7) | 2.4 (± 24.1) | | |
| Change at FU Month 12: Role Functioning | 2.6 (± 25.9) | 3.7 (± 23.8) | | |
| Change at FU Month 18: Role Functioning | 99999999 (± 9999999) | 8.3 (± 11.8) | | |
| Baseline: Social Functioning | 83.0 (± 22.9) | 83.2 (± 21.6) | | |
| Change at Cycle 1: Social Functioning | -8.0 (± 24.3) | -5.3 (± 22.8) | | |
| Change at Cycle 2: Social Functioning | -10.1 (± 26.1) | -4.1 (± 23.6) | | |
| Change at Cycle 3: Social Functioning | -9.5 (± 25.6) | -3.3 (± 24.4) | | |
| Change at Cycle 4: Social Functioning | -10.3 (± 26.3) | -3.2 (± 24.2) | | |
| Change at Cycle 5: Social Functioning | -8.7 (± 26.5) | -2.6 (± 23.7) | | |
| Change at Cycle 9: Social Functioning | -1.7 (± 25.1) | -3.4 (± 24.9) | | |
| Change at Cycle 14: Social Functioning | -0.1 (± 25.3) | -2.4 (± 24.9) | | |
| Change at EoT: Social Functioning | 0.3 (± 26.1) | -1.6 (± 24.1) | | |
| Change at FU Month 6: Social Functioning | 3.3 (± 24.8) | 4.0 (± 24.7) | | |
| Change at FU Month 12: Social Functioning | 4.6 (± 25.2) | 6.4 (± 22.7) | | |
| Change at FU Month 18: Social Functioning | 99999999 (± 9999999) | 33.3 (± 47.1) | | |
| Baseline: Global Health Status | 74.3 (± 18.7) | 73.9 (± 18.7) | | |
| Change at Cycle 1: Global Health Status | -7.5 (± 20.1) | -7.2 (± 20.4) | | |
| Change at Cycle 2: Global Health Status | -12.4 (± 22.6) | -7.1 (± 20.2) | | |
| Change at Cycle 3: Global Health Status | -11.7 (± 20.6) | -5.2 (± 19.1) | | |
| Change at Cycle 4: Global Health Status | -12.7 (± 21.3) | -5.5 (± 19.6) | | |
| Change at Cycle 5: Global Health Status | -12.1 (± 21.7) | -5.8 (± 19.7) | | |
| Change at Cycle 9: Global Health Status | -5.9 (± 20.1) | -6.4 (± 20.6) | | |
| Change at Cycle 14: Global Health Status | -3.9 (± 21.1) | -6.3 (± 20.8) | | |
| Change at EoT: Global Health Status | -3.5 (± 21.3) | -4.9 (± 20.7) | | |
| Change at FU Month 6: Global Health Status | -0.6 (± 21.3) | 0.3 (± 21.4) | | |
| Change at FU Month 12: Global Health Status | -0.2 (± 21.9) | 1.2 (± 20.8) | | |
| Change at FU Month 18: Global Health Status | 99999999 (± 9999999) | 16.7 (± 23.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: EORTC Quality of Life Questionnaire-Breast Cancer 23 (QLQ-BR23) Score

| | |
|-----------------|---|
| End point title | EORTC Quality of Life Questionnaire-Breast Cancer 23 (QLQ-BR23) Score |
|-----------------|---|

End point description:

EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30. There are four functional scales (body image, sexual enjoyment, sexual functioning, future perspective [FP]) and four symptom scales (systemic side effects [SE], upset by hair loss, arm symptoms, breast symptoms). Questions used 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores averaged and transformed to 0-100 scale. High score for functional scale indicated high/better level of functioning/healthy functioning. Higher scores for symptom scales represent higher levels of

symptoms/problems. For functional scales, positive change from baseline indicated improvement in quality of life (QOL) while negative change from baseline indicated a deterioration. For symptom scales, positive change from baseline indicated deterioration and negative change indicated improvement. The value '999999' indicates that the values were not evaluable.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Cycles 1, 2, 3, 4, 5, 9, 14, End of Treatment, Follow-up Month 6, Follow-up Month 12, Follow-up Month 18 | |

| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
|--|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 869 | 891 | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: Arm Symptoms | 19.9 (± 18.7) | 19.5 (± 18.4) | | |
| Change at Cycle 1: Arm Symptoms | -1.3 (± 19.2) | -3.1 (± 18.7) | | |
| Change at Cycle 2: Arm Symptoms | -2.8 (± 18.8) | -3.0 (± 18.7) | | |
| Change at Cycle 3: Arm Symptoms | -3.5 (± 18.7) | -3.5 (± 18.1) | | |
| Change at Cycle 4: Arm Symptoms | -2.0 (± 19.8) | -2.9 (± 19.2) | | |
| Change at Cycle 5: Arm Symptoms | -0.5 (± 20.8) | -2.6 (± 19.8) | | |
| Change at Cycle 9: Arm Symptoms | -0.2 (± 20.4) | -1.1 (± 19.6) | | |
| Change at Cycle 14: Arm Symptoms | 0.3 (± 21.3) | 1.3 (± 21.8) | | |
| Change at EoT: Arm Symptoms | 0.1 (± 21.6) | 0.4 (± 21.7) | | |
| Change at FU Month 6: Arm Symptoms | -0.1 (± 22.1) | -1.3 (± 20.0) | | |
| Change at FU Month 12: Arm Symptoms | -0.8 (± 22.4) | -2.8 (± 20.5) | | |
| Change at FU Month 18: Arm Symptoms | 99999999 (± 9999999) | 99999999 (± 9999999) | | |
| Baseline: Breast Symptoms | 17.5 (± 17.4) | 16.8 (± 16.3) | | |
| Change at Cycle 1: Breast Symptoms | -2.3 (± 16.3) | -2.5 (± 16.2) | | |
| Change at Cycle 2: Breast Symptoms | -3.3 (± 17.1) | -2.9 (± 16.7) | | |
| Change at Cycle 3: Breast Symptoms | -4.0 (± 17.5) | -3.1 (± 16.5) | | |
| Change at Cycle 4: Breast Symptoms | -3.9 (± 17.7) | -3.3 (± 17.4) | | |
| Change at Cycle 5: Breast Symptoms | -3.1 (± 18.6) | -2.6 (± 18.2) | | |
| Change at Cycle 9: Breast Symptoms | 1.7 (± 19.7) | 0.3 (± 17.5) | | |
| Change at Cycle 14: Breast Symptoms | -0.2 (± 18.8) | 0.5 (± 19.1) | | |
| Change at EoT: Breast Symptoms | -1.0 (± 19.3) | 0.3 (± 18.8) | | |
| Change at FU Month 6: Breast Symptoms | -2.5 (± 19.1) | -1.5 (± 18.4) | | |
| Change at FU Month 12: Breast Symptoms | -4.2 (± 18.9) | -3.7 (± 18.0) | | |
| Change at FU Month 18: Breast Symptoms | 99999999 (± 9999999) | 99999999 (± 9999999) | | |
| Baseline: Systemic Therapy Side Effects (SE) | 8.5 (± 9.9) | 8.7 (± 9.9) | | |
| Change at Cycle 1: Systemic Therapy SE | 24.9 (± 17.3) | 23.3 (± 17.6) | | |
| Change at Cycle 2: Systemic Therapy SE | 24.1 (± 18.1) | 18.3 (± 16.6) | | |
| Change at Cycle 3: Systemic Therapy SE | 23.4 (± 17.8) | 15.1 (± 15.5) | | |

| | | | | |
|--|----------------------|----------------------|--|--|
| Change at Cycle 4: Systemic Therapy SE | 23.1 (± 18.1) | 13.2 (± 15.4) | | |
| Change at Cycle 5: Systemic Therapy SE | 20.0 (± 17.6) | 11.8 (± 14.7) | | |
| Change at Cycle 9: Systemic Therapy SE | 9.5 (± 13.1) | 10.4 (± 14.0) | | |
| Change at Cycle 14: Systemic Therapy SE | 7.5 (± 12.9) | 9.8 (± 13.9) | | |
| Change at EoT: Systemic Therapy SE | 7.2 (± 13.4) | 8.5 (± 13.9) | | |
| Change at FU Month 6: Systemic Therapy SE | 5.8 (± 12.3) | 4.2 (± 12.5) | | |
| Change at FU Month 12: Systemic Therapy SE | 5.4 (± 12.9) | 4.2 (± 13.0) | | |
| Change at FU Month 18: Systemic Therapy SE | 99999999 (± 9999999) | 99999999 (± 9999999) | | |
| Baseline: Upset by Hair Loss Item | 13.2 (± 23.7) | 14.2 (± 22.9) | | |
| Change at Cycle 1: Upset by Hair Loss Item | 35.1 (± 37.3) | 25.2 (± 35.1) | | |
| Change at Cycle 2: Upset by Hair Loss Item | 28.7 (± 36.0) | 21.8 (± 36.6) | | |
| Change at Cycle 3: Upset by Hair Loss Item | 28.8 (± 36.3) | 21.4 (± 38.4) | | |
| Change at Cycle 4: Upset by Hair Loss Item | 28.4 (± 37.1) | 19.7 (± 34.2) | | |
| Change at Cycle 5: Upset by Hair Loss Item | 26.4 (± 36.8) | 10.0 (± 36.3) | | |
| Change at Cycle 9: Upset by Hair Loss Item | 11.8 (± 33.6) | 6.0 (± 36.8) | | |
| Change at Cycle 14: Upset by Hair Loss Item | 9.3 (± 32.5) | 2.5 (± 26.0) | | |
| Change at EoT: Upset by Hair Loss Item | 17.3 (± 33.9) | 0.0 (± 28.1) | | |
| Change at FU Month 6: Upset by Hair Loss Item | 6.2 (± 26.8) | -3.5 (± 21.0) | | |
| Change at FU Month 12: Upset by Hair Loss Item | 2.4 (± 28.7) | -2.8 (± 29.7) | | |
| Change at FU Month 18: Upset by Hair Loss Item | 99999999 (± 9999999) | 99999999 (± 9999999) | | |
| Baseline: Body Image | 78.5 (± 23.2) | 78.9 (± 24.2) | | |
| Change at Cycle 1: Body Image | -13.7 (± 23.5) | -13.3 (± 23.1) | | |
| Change at Cycle 2: Body Image | -12.7 (± 23.9) | -10.1 (± 23.9) | | |
| Change at Cycle 3: Body Image | -11.5 (± 24.8) | -6.6 (± 22.6) | | |
| Change at Cycle 4: Body Image | -11.4 (± 24.8) | -5.9 (± 23.2) | | |
| Change at Cycle 5: Body Image | -10.5 (± 24.6) | -5.0 (± 22.6) | | |
| Change at Cycle 9: Body Image | -5.9 (± 22.8) | -4.2 (± 21.7) | | |
| Change at Cycle 14: Body Image | -4.5 (± 23.6) | -2.4 (± 23.2) | | |
| Change at EoT: Body Image | -3.3 (± 23.1) | -2.9 (± 22.8) | | |
| Change at FU Month 6: Body Image | -1.3 (± 23.4) | 0.3 (± 23.3) | | |
| Change at FU Month 12: Body Image | 0.0 (± 24.2) | 0.7 (± 23.5) | | |
| Change at FU Month 18: Body Image | 99999999 (± 9999999) | 99999999 (± 9999999) | | |
| Baseline: Future Perspectives (FP) | 49.3 (± 31.4) | 49.8 (± 30.9) | | |
| Change at Cycle 1: FP | -1.3 (± 30.3) | -0.3 (± 31.1) | | |
| Change at Cycle 2: FP | 1.4 (± 31.7) | 3.7 (± 30.4) | | |
| Change at Cycle 3: FP | 3.2 (± 32.0) | 6.5 (± 30.1) | | |
| Change at Cycle 4: FP | 4.2 (± 31.7) | 7.8 (± 30.5) | | |
| Change at Cycle 5: FP | 5.9 (± 32.4) | 9.7 (± 30.7) | | |
| Change at Cycle 9: FP | 8.2 (± 32.2) | 8.4 (± 31.3) | | |
| Change at Cycle 14: FP | 9.5 (± 32.0) | 7.9 (± 33.4) | | |

| | | | | |
|---|----------------------|----------------------|--|--|
| Change at EoT: FP | 8.5 (± 32.6) | 7.6 (± 32.3) | | |
| Change at FU Month 6: FP | 10.5 (± 31.3) | 12.6 (± 32.6) | | |
| Change at FU Month 12: FP | 15.0 (± 34.0) | 13.1 (± 33.2) | | |
| Change at FU Month 18: FP | 99999999 (± 9999999) | 99999999 (± 9999999) | | |
| Baseline: Sexual Enjoyment | 43.4 (± 32.1) | 46.7 (± 34.8) | | |
| Change at Cycle 1: Sexual Enjoyment | -5.9 (± 26.8) | -8.2 (± 27.0) | | |
| Change at Cycle 2: Sexual Enjoyment | -9.5 (± 30.2) | -10.7 (± 29.2) | | |
| Change at Cycle 3: Sexual Enjoyment | -11.4 (± 26.8) | -8.9 (± 31.6) | | |
| Change at Cycle 4: Sexual Enjoyment | -11.9 (± 30.6) | -9.2 (± 28.3) | | |
| Change at Cycle 5: Sexual Enjoyment | -14.2 (± 28.1) | -8.8 (± 30.4) | | |
| Change at Cycle 9: Sexual Enjoyment | -9.4 (± 29.5) | -7.4 (± 30.9) | | |
| Change at Cycle 14: Sexual Enjoyment | -3.9 (± 28.6) | -9.7 (± 31.4) | | |
| Change at EoT: Sexual Enjoyment | -6.5 (± 29.2) | -9.7 (± 29.4) | | |
| Change at FU Month 6: Sexual Enjoyment | -4.6 (± 28.8) | -3.0 (± 30.5) | | |
| Change at FU Month 12: Sexual Enjoyment | -5.7 (± 30.9) | -2.3 (± 31.0) | | |
| Change at FU Month 18: Sexual Enjoyment | 99999999 (± 9999999) | 99999999 (± 9999999) | | |
| Baseline: Sexual Function | 16.7 (± 22.3) | 18.3 (± 22.9) | | |
| Change at Cycle 1: Sexual Function | -2.3 (± 18.9) | -3.5 (± 18.4) | | |
| Change at Cycle 2: Sexual Function | -4.8 (± 19.9) | -4.4 (± 18.4) | | |
| Change at Cycle 3: Sexual Function | -5.6 (± 19.6) | -3.3 (± 19.0) | | |
| Change at Cycle 4: Sexual Function | -6.8 (± 19.7) | -3.4 (± 17.9) | | |
| Change at Cycle 5: Sexual Function | -5.9 (± 19.5) | -3.0 (± 19.5) | | |
| Change at Cycle 9: Sexual Function | -3.4 (± 19.3) | -1.8 (± 20.8) | | |
| Change at Cycle 14: Sexual Function | -1.8 (± 20.0) | -2.8 (± 20.6) | | |
| Change at EoT: Sexual Function | -1.5 (± 20.9) | -1.7 (± 19.7) | | |
| Change at FU Month 6: Sexual Function | 1.6 (± 22.6) | 0.6 (± 20.4) | | |
| Change at FU Month 12: Sexual Function | 0.9 (± 21.7) | 0.9 (± 20.9) | | |
| Change at FU Month 18: Sexual Function | 99999999 (± 9999999) | 99999999 (± 9999999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinically Meaningful Deterioration in the Global Health Status/ Quality of Life and Functional (Physical, Role, and Cognitive) Subscales of the QLQ-C30 From First HER2-Targeted Treatment

| | |
|-----------------|---|
| End point title | Time to Clinically Meaningful Deterioration in the Global Health Status/ Quality of Life and Functional (Physical, Role, and Cognitive) Subscales of the QLQ-C30 From First HER2-Targeted Treatment |
|-----------------|---|

End point description:

The time to clinically meaningful deterioration in the global health status/HRQoL subscale (question 29 and 30 of the QLQ-C30) was used to assess the time from first HER2-targeted treatment to worsening in HRQoL. Clinically meaningful deterioration is defined as a decrease in score of 10 points in Physical functioning and HRQoL; decrease of 7 points in Cognitive functioning, decrease of 14 points in Role functioning. The value '999999' indicates that the median and upper 95% CI were not evaluable.

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

End point timeframe:

From randomization up to 18 months after end of study treatment

| End point values | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 864 | 884 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| GHS/QoL Score | 2.73 (2.10 to 2.83) | 13.57 (9.20 to 21.91) | | |
| Physical Function | 25.53 (13.34 to 9999999) | 99999999 (27.43 to 99999999) | | |
| Role Function | 2.23 (2.10 to 2.79) | 9.92 (9.00 to 14.36) | | |
| Cognitive Function | 5.49 (2.79 to 5.82) | 9.46 (8.57 to 12.91) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization to data cut-off date of 27 November 2019 (approximately up to 70 months)

Adverse event reporting additional description:

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane |
|-----------------------|---|

Reporting group description:

Trastuzumab and pertuzumab were administered concurrently for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) with the taxane (docetaxel or paclitaxel) component of chemotherapy following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| | |
|-----------------------|--|
| Reporting group title | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab |
|-----------------------|--|

Reporting group description:

Trastuzumab emtansine and pertuzumab continued for up to a total duration of 1 year (up to 18 cycles [1 Cycle = 21 days]) following anthracycline [5 fluorouracil, epirubicin, and cyclophosphamide (FEC) or epirubicin and cyclophosphamide (EC) or doxorubicin and cyclophosphamide (AC)] based chemotherapy.

| Serious adverse events | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 216 / 926 (23.33%) | 195 / 912 (21.38%) | |
| number of deaths (all causes) | 34 | 44 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| ACUTE PROMYELOCYTIC LEUKAEMIA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLON NEOPLASM | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| FIBROMA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMANGIOMA OF SKIN | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UTERINE LEIOMYOMA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UTERINE LEIOMYOSARCOMA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EMBOLISM | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMATOMA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOTENSION | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUBCLAVIAN VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VENOUS THROMBOSIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VENOUS THROMBOSIS LIMB | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| CATHETER SITE PAIN | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CATHETER SITE VESICLES | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST DISCOMFORT | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST PAIN | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FATIGUE | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENERAL PHYSICAL HEALTH DETERIORATION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| IMPAIRED HEALING | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFUSION SITE EXTRAVASATION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MALAISE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MEDICAL DEVICE PAIN | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYREXIA | | | |
| subjects affected / exposed | 13 / 926 (1.40%) | 19 / 912 (2.08%) | |
| occurrences causally related to treatment / all | 8 / 14 | 15 / 22 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| ANAPHYLACTIC REACTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DRUG HYPERSENSITIVITY | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERSENSITIVITY | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| BREAST NECROSIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENDOMETRIAL HYPERPLASIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FIBROCYSTIC BREAST DISEASE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METRORRHAGIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UTERINE CYST | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VAGINAL HAEMORRHAGE | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| BRONCHOSPASM | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSпноEA | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| EPISTAXIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYDROTHORAX | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| INTERSTITIAL LUNG DISEASE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLEURAL EFFUSION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONITIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 926 (0.22%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMOTHORAX | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 5 / 926 (0.54%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUS PAIN | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| ANXIETY | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEPRESSION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| SUICIDE ATTEMPT | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |

| | | | |
|---|-----------------|-----------------|--|
| DEVICE BREAKAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD CREATINE INCREASED | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BLOOD PRESSURE DECREASED | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ELECTROCARDIOGRAM REPOLARISATION ABNORMALITY | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| N-TERMINAL PROHORMONE BRAIN NATRIURETIC PEPTIDE INCREASED | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 3 / 926 (0.32%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PLATELET COUNT DECREASED | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 4 / 912 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| ANKLE FRACTURE | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FALL | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEMORAL NECK FRACTURE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAND FRACTURE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HIP FRACTURE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HUMERUS FRACTURE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLAMMATION OF WOUND | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 9 / 912 (0.99%) | |
| occurrences causally related to treatment / all | 1 / 2 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| JOINT DISLOCATION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LIGAMENT SPRAIN | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OVERDOSE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POSTOPERATIVE WOUND COMPLICATION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RADIATION PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RADIATION SKIN INJURY | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ROAD TRAFFIC ACCIDENT | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEROMA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPINAL COMPRESSION FRACTURE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THERMAL BURN | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VASCULAR ACCESS COMPLICATION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WRIST FRACTURE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| ARRHYTHMIA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 5 / 926 (0.54%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 5 / 5 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIAC FAILURE CONGESTIVE | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 926 (0.32%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CARDIOMYOPATHY | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONGESTIVE CARDIOMYOPATHY | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEFT VENTRICULAR DYSFUNCTION | | | |
| subjects affected / exposed | 3 / 926 (0.32%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MYOCARDIAL ISCHAEMIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUS TACHYCARDIA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| CEREBRAL ISCHAEMIA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEMENTIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HEADACHE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOAESTHESIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTRACRANIAL ANEURYSM | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LACUNAR INFARCTION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METABOLIC ENCEPHALOPATHY | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MIGRAINE WITH AURA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEIZURE | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SYNCOPE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TENSION HEADACHE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 51 / 926 (5.51%) | 31 / 912 (3.40%) | |
| occurrences causally related to treatment / all | 54 / 55 | 32 / 32 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 16 / 926 (1.73%) | 10 / 912 (1.10%) | |
| occurrences causally related to treatment / all | 18 / 18 | 11 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|------------------|-----------------|--|
| HYPOACUSIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| CATARACT | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 4 / 926 (0.43%) | 4 / 912 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 4 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COLITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CONSTIPATION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 20 / 926 (2.16%) | 8 / 912 (0.88%) | |
| occurrences causally related to treatment / all | 19 / 22 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIVERTICULUM | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DUODENAL PERFORATION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| DUODENAL ULCER | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DUODENAL ULCER HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DYSPHAGIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTERITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTEROCOLITIS | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRIC ULCER HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTRITIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GINGIVAL BLEEDING | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMATEMESIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HAEMORRHOIDS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MOUTH HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NAUSEA | | | |
| subjects affected / exposed | 6 / 926 (0.65%) | 9 / 912 (0.99%) | |
| occurrences causally related to treatment / all | 4 / 6 | 7 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OESOPHAGITIS | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PANCREATITIS ACUTE | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PEPTIC ULCER HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SMALL INTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SMALL INTESTINAL OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| STOMATITIS | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER GASTROINTESTINAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VARICES OESOPHAGEAL | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VOMITING | | | |
| subjects affected / exposed | 10 / 926 (1.08%) | 7 / 912 (0.77%) | |
| occurrences causally related to treatment / all | 8 / 10 | 4 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| BILE DUCT OBSTRUCTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHOLELITHIASIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NODULAR REGENERATIVE HYPERPLASIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PORTAL HYPERTENSION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RASH | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPIDER NAEVUS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| RENAL COLIC | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RENAL FAILURE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BACK PAIN | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GROIN PAIN | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INTERVERTEBRAL DISC PROTRUSION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| OSTEOARTHRITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| OSTEONECROSIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SPONDYLOLISTHESIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| ANAL ABSCESS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| APPENDICITIS | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARTHRITIS BACTERIAL | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ARTHRITIS INFECTIVE | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BREAST CELLULITIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 926 (0.11%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| BRONCHITIS | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CATHETER SITE INFECTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CELLULITIS | | | |
| subjects affected / exposed | 3 / 926 (0.32%) | 4 / 912 (0.44%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CHEST WALL ABSCESS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| CLOSTRIDIUM DIFFICILE INFECTION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEVICE RELATED SEPSIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DIVERTICULITIS | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTERITIS INFECTIOUS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ENTEROCOLITIS INFECTIOUS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| ERYSIPELAS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROENTERITIS VIRAL | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GASTROINTESTINAL BACTERIAL INFECTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| GENITAL HERPES | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HERPES ZOSTER | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INCISION SITE ABSCESS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFECTED SEROMA | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| INFLUENZA | | | |
| subjects affected / exposed | 4 / 926 (0.43%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LARYNGITIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| MASTITIS | | | |
| subjects affected / exposed | 8 / 926 (0.86%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| NEUTROPENIC SEPSIS | | | |
| subjects affected / exposed | 7 / 926 (0.76%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 7 / 8 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PAROTITIS | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PHARYNGITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PNEUMONIA | | | |
| subjects affected / exposed | 12 / 926 (1.30%) | 12 / 912 (1.32%) | |
| occurrences causally related to treatment / all | 5 / 12 | 5 / 12 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| POST PROCEDURAL INFECTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| POSTOPERATIVE WOUND INFECTION | | | |
| subjects affected / exposed | 2 / 926 (0.22%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PULMONARY SEPSIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| PYELONEPHRITIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 926 (0.32%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| RESPIRATORY TRACT INFECTION VIRAL | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 3 / 912 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SINUSITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SKIN INFECTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| SUBCUTANEOUS ABSCESS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| TONSILLITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 3 / 926 (0.32%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| URINARY TRACT INFECTION | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 926 (0.65%) | 8 / 912 (0.88%) | |
| occurrences causally related to treatment / all | 4 / 6 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VASCULAR DEVICE INFECTION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VESTIBULAR NEURONITIS | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIRAL INFECTION | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIRAL PHARYNGITIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| WOUND INFECTION | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 1 / 926 (0.11%) | 0 / 912 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| DEHYDRATION | | | |
| subjects affected / exposed | 7 / 926 (0.76%) | 2 / 912 (0.22%) | |
| occurrences causally related to treatment / all | 5 / 8 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERCREATININAEMIA | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| METABOLIC ACIDOSIS | | | |
| subjects affected / exposed | 0 / 926 (0.00%) | 1 / 912 (0.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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

| Non-serious adverse events | Anthracycline Followed by Trastuzumab, Pertuzumab, and Taxane | Anthracycline Followed by Trastuzumab Emtansine and Pertuzumab | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 902 / 926 (97.41%) | 902 / 912 (98.90%) | |
| Vascular disorders | | | |
| HOT FLUSH | | | |
| subjects affected / exposed | 167 / 926 (18.03%) | 100 / 912 (10.96%) | |
| occurrences (all) | 190 | 110 | |
| HYPERTENSION | | | |
| subjects affected / exposed | 36 / 926 (3.89%) | 63 / 912 (6.91%) | |
| occurrences (all) | 51 | 83 | |
| LYMPHOEDEMA | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 68 / 926 (7.34%) 70 | 30 / 912 (3.29%) 31 | |
| General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all) | 121 / 926 (13.07%) 222 | 131 / 912 (14.36%) 254 | |
| CHILLS subjects affected / exposed occurrences (all) | 40 / 926 (4.32%) 45 | 67 / 912 (7.35%) 79 | |
| FATIGUE subjects affected / exposed occurrences (all) | 439 / 926 (47.41%) 672 | 419 / 912 (45.94%) 659 | |
| INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all) | 26 / 926 (2.81%) 33 | 62 / 912 (6.80%) 72 | |
| MALAISE subjects affected / exposed occurrences (all) | 46 / 926 (4.97%) 63 | 60 / 912 (6.58%) 90 | |
| MUCOSAL INFLAMMATION subjects affected / exposed occurrences (all) | 156 / 926 (16.85%) 213 | 111 / 912 (12.17%) 134 | |
| OEDEMA PERIPHERAL subjects affected / exposed occurrences (all) | 156 / 926 (16.85%) 173 | 74 / 912 (8.11%) 91 | |
| PYREXIA subjects affected / exposed occurrences (all) | 175 / 926 (18.90%) 242 | 227 / 912 (24.89%) 354 | |
| Reproductive system and breast disorders BREAST PAIN subjects affected / exposed occurrences (all) | 45 / 926 (4.86%) 57 | 55 / 912 (6.03%) 65 | |
| Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) | 148 / 926 (15.98%) 189 | 157 / 912 (17.21%) 190 | |

| | | | |
|---|---------------------------|---------------------------|--|
| DYSпноEA subjects affected / exposed occurrences (all) | 73 / 926 (7.88%) 87 | 79 / 912 (8.66%) 91 | |
| EPISTAXIS subjects affected / exposed occurrences (all) | 182 / 926 (19.65%) 226 | 333 / 912 (36.51%) 487 | |
| OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all) | 111 / 926 (11.99%) 132 | 100 / 912 (10.96%) 123 | |
| RHINORRHOEA subjects affected / exposed occurrences (all) | 77 / 926 (8.32%) 87 | 82 / 912 (8.99%) 96 | |
| Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) | 58 / 926 (6.26%) 63 | 42 / 912 (4.61%) 48 | |
| DEPRESSION subjects affected / exposed occurrences (all) | 52 / 926 (5.62%) 54 | 53 / 912 (5.81%) 55 | |
| INSOMNIA subjects affected / exposed occurrences (all) | 170 / 926 (18.36%) 203 | 155 / 912 (17.00%) 190 | |
| Investigations ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all) | 108 / 926 (11.66%) 134 | 300 / 912 (32.89%) 417 | |
| ASPARTATE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all) | 98 / 926 (10.58%) 113 | 317 / 912 (34.76%) 431 | |
| BLOOD ALKALINE PHOSPHATASE INCREASED subjects affected / exposed occurrences (all) | 20 / 926 (2.16%) 24 | 85 / 912 (9.32%) 100 | |
| BLOOD BILIRUBIN INCREASED subjects affected / exposed occurrences (all) | 4 / 926 (0.43%) 6 | 80 / 912 (8.77%) 127 | |

| | | | |
|---|---------------------------|---------------------------|--|
| EJECTION FRACTION DECREASED subjects affected / exposed occurrences (all) | 61 / 926 (6.59%) 72 | 28 / 912 (3.07%) 34 | |
| NEUTROPHIL COUNT DECREASED subjects affected / exposed occurrences (all) | 83 / 926 (8.96%) 148 | 75 / 912 (8.22%) 135 | |
| PLATELET COUNT DECREASED subjects affected / exposed occurrences (all) | 15 / 926 (1.62%) 21 | 143 / 912 (15.68%) 203 | |
| WEIGHT DECREASED subjects affected / exposed occurrences (all) | 57 / 926 (6.16%) 61 | 79 / 912 (8.66%) 82 | |
| Injury, poisoning and procedural complications | | | |
| INFUSION RELATED REACTION subjects affected / exposed occurrences (all) | 115 / 926 (12.42%) 132 | 126 / 912 (13.82%) 157 | |
| RADIATION SKIN INJURY subjects affected / exposed occurrences (all) | 207 / 926 (22.35%) 210 | 205 / 912 (22.48%) 213 | |
| Nervous system disorders | | | |
| DIZZINESS subjects affected / exposed occurrences (all) | 117 / 926 (12.63%) 140 | 105 / 912 (11.51%) 138 | |
| DYSGEUSIA subjects affected / exposed occurrences (all) | 176 / 926 (19.01%) 200 | 159 / 912 (17.43%) 174 | |
| HEADACHE subjects affected / exposed occurrences (all) | 234 / 926 (25.27%) 328 | 261 / 912 (28.62%) 419 | |
| NEUROPATHY PERIPHERAL subjects affected / exposed occurrences (all) | 163 / 926 (17.60%) 203 | 140 / 912 (15.35%) 164 | |
| PARAESTHESIA subjects affected / exposed occurrences (all) | 85 / 926 (9.18%) 102 | 101 / 912 (11.07%) 129 | |
| PERIPHERAL SENSORY NEUROPATHY | | | |

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|--------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 214 / 926 (23.11%) | 194 / 912 (21.27%) | |
| occurrences (all) | 236 | 210 | |
| TASTE DISORDER | | | |
| subjects affected / exposed | 60 / 926 (6.48%) | 63 / 912 (6.91%) | |
| occurrences (all) | 72 | 72 | |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 184 / 926 (19.87%) | 174 / 912 (19.08%) | |
| occurrences (all) | 249 | 243 | |
| LEUKOPENIA | | | |
| subjects affected / exposed | 73 / 926 (7.88%) | 51 / 912 (5.59%) | |
| occurrences (all) | 134 | 96 | |
| NEUTROPENIA | | | |
| subjects affected / exposed | 232 / 926 (25.05%) | 220 / 912 (24.12%) | |
| occurrences (all) | 411 | 403 | |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 25 / 926 (2.70%) | 162 / 912 (17.76%) | |
| occurrences (all) | 29 | 298 | |
| Eye disorders | | | |
| DRY EYE | | | |
| subjects affected / exposed | 62 / 926 (6.70%) | 75 / 912 (8.22%) | |
| occurrences (all) | 69 | 87 | |
| LACRIMATION INCREASED | | | |
| subjects affected / exposed | 112 / 926 (12.10%) | 73 / 912 (8.00%) | |
| occurrences (all) | 120 | 75 | |
| VISION BLURRED | | | |
| subjects affected / exposed | 42 / 926 (4.54%) | 46 / 912 (5.04%) | |
| occurrences (all) | 44 | 49 | |
| Gastrointestinal disorders | | | |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 83 / 926 (8.96%) | 86 / 912 (9.43%) | |
| occurrences (all) | 103 | 110 | |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 82 / 926 (8.86%) | 87 / 912 (9.54%) | |
| occurrences (all) | 89 | 109 | |
| CONSTIPATION | | | |

| | | | |
|--|--------------------|--------------------|--|
| subjects affected / exposed | 287 / 926 (30.99%) | 299 / 912 (32.79%) | |
| occurrences (all) | 369 | 413 | |
| DIARRHOEA | | | |
| subjects affected / exposed | 605 / 926 (65.33%) | 405 / 912 (44.41%) | |
| occurrences (all) | 1158 | 759 | |
| DRY MOUTH | | | |
| subjects affected / exposed | 63 / 926 (6.80%) | 105 / 912 (11.51%) | |
| occurrences (all) | 68 | 116 | |
| DYSPEPSIA | | | |
| subjects affected / exposed | 123 / 926 (13.28%) | 106 / 912 (11.62%) | |
| occurrences (all) | 146 | 123 | |
| GASTROOESOPHAGEAL REFLUX DISEASE | | | |
| subjects affected / exposed | 58 / 926 (6.26%) | 39 / 912 (4.28%) | |
| occurrences (all) | 64 | 41 | |
| GINGIVAL BLEEDING | | | |
| subjects affected / exposed | 6 / 926 (0.65%) | 57 / 912 (6.25%) | |
| occurrences (all) | 6 | 64 | |
| HAEMORRHOIDS | | | |
| subjects affected / exposed | 58 / 926 (6.26%) | 46 / 912 (5.04%) | |
| occurrences (all) | 71 | 50 | |
| NAUSEA | | | |
| subjects affected / exposed | 596 / 926 (64.36%) | 605 / 912 (66.34%) | |
| occurrences (all) | 1034 | 1246 | |
| STOMATITIS | | | |
| subjects affected / exposed | 276 / 926 (29.81%) | 228 / 912 (25.00%) | |
| occurrences (all) | 441 | 338 | |
| VOMITING | | | |
| subjects affected / exposed | 243 / 926 (26.24%) | 289 / 912 (31.69%) | |
| occurrences (all) | 358 | 502 | |
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 630 / 926 (68.03%) | 600 / 912 (65.79%) | |
| occurrences (all) | 652 | 618 | |
| DERMATITIS ACNEIFORM | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 52 / 926 (5.62%) | 53 / 912 (5.81%) | |
| occurrences (all) | 59 | 60 | |
| DRY SKIN | | | |
| subjects affected / exposed | 132 / 926 (14.25%) | 100 / 912 (10.96%) | |
| occurrences (all) | 143 | 112 | |
| ERYTHEMA | | | |
| subjects affected / exposed | 86 / 926 (9.29%) | 75 / 912 (8.22%) | |
| occurrences (all) | 100 | 82 | |
| NAIL DISCOLOURATION | | | |
| subjects affected / exposed | 103 / 926 (11.12%) | 76 / 912 (8.33%) | |
| occurrences (all) | 103 | 78 | |
| NAIL DISORDER | | | |
| subjects affected / exposed | 72 / 926 (7.78%) | 43 / 912 (4.71%) | |
| occurrences (all) | 76 | 43 | |
| PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME | | | |
| subjects affected / exposed | 66 / 926 (7.13%) | 25 / 912 (2.74%) | |
| occurrences (all) | 74 | 31 | |
| PRURITUS | | | |
| subjects affected / exposed | 169 / 926 (18.25%) | 126 / 912 (13.82%) | |
| occurrences (all) | 222 | 151 | |
| RASH | | | |
| subjects affected / exposed | 250 / 926 (27.00%) | 214 / 912 (23.46%) | |
| occurrences (all) | 354 | 290 | |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 47 / 926 (5.08%) | 42 / 912 (4.61%) | |
| occurrences (all) | 56 | 59 | |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 261 / 926 (28.19%) | 237 / 912 (25.99%) | |
| occurrences (all) | 342 | 291 | |
| BACK PAIN | | | |
| subjects affected / exposed | 119 / 926 (12.85%) | 92 / 912 (10.09%) | |
| occurrences (all) | 136 | 109 | |
| BONE PAIN | | | |

| | | | |
|------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 70 / 926 (7.56%) | 56 / 912 (6.14%) | |
| occurrences (all) | 94 | 69 | |
| MUSCLE SPASMS | | | |
| subjects affected / exposed | 86 / 926 (9.29%) | 97 / 912 (10.64%) | |
| occurrences (all) | 92 | 129 | |
| MUSCULOSKELETAL PAIN | | | |
| subjects affected / exposed | 67 / 926 (7.24%) | 57 / 912 (6.25%) | |
| occurrences (all) | 86 | 70 | |
| MYALGIA | | | |
| subjects affected / exposed | 215 / 926 (23.22%) | 153 / 912 (16.78%) | |
| occurrences (all) | 257 | 197 | |
| PAIN IN EXTREMITY | | | |
| subjects affected / exposed | 119 / 926 (12.85%) | 114 / 912 (12.50%) | |
| occurrences (all) | 153 | 136 | |
| Infections and infestations | | | |
| CONJUNCTIVITIS | | | |
| subjects affected / exposed | 49 / 926 (5.29%) | 42 / 912 (4.61%) | |
| occurrences (all) | 51 | 44 | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 175 / 926 (18.90%) | 169 / 912 (18.53%) | |
| occurrences (all) | 269 | 255 | |
| PARONYCHIA | | | |
| subjects affected / exposed | 53 / 926 (5.72%) | 50 / 912 (5.48%) | |
| occurrences (all) | 59 | 54 | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 139 / 926 (15.01%) | 126 / 912 (13.82%) | |
| occurrences (all) | 197 | 177 | |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 73 / 926 (7.88%) | 63 / 912 (6.91%) | |
| occurrences (all) | 99 | 82 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 241 / 926 (26.03%) | 244 / 912 (26.75%) | |
| occurrences (all) | 348 | 371 | |
| HYPOKALAEMIA | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 41 / 926 (4.43%) | 67 / 912 (7.35%) | |
| occurrences (all) | 50 | 102 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 16 June 2014 | Safety data reports related to concurrent radiotherapy and/or hormonal therapy will be monitored by the iDMC at least once every 3 months; HCV RNA testing was added to the exclusion criteria; Criteria for dose recalculation due to weight change was updated; Pulmonary Toxicity was updated to remove language regarding advanced malignancy; Hepatotoxicity was updated to provide clarity on Hy's law and to match the latest Trastuzumab Emtansine Investigator's Brochure; Anthracycline Treatment Phase and Trastuzumab plus Pertuzumab plus Taxane Treatment Arm-1 sections were updated to provide the guidance to refer to local prescribing information for contraindications, requirements on contraception duration, and concomitant medications; Dose Modifications and Delays were updated; Additional information added regarding sample size calculation for the invasive disease-free survival (IDFS) primary endpoint. |
| 30 July 2015 | Sample size was reduced while maintaining statistical validity of the study in addressing its primary endpoint; the Rationale for Adjuvant Regimens and Duration of Therapy was updated to reflect the impact of new data. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported