



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			

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