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

Summary

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

Results information

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

Trial information

Trial identification

Sponsor protocol code	TOC4129g/WO20698

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 061 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2011
Global end of trial reached?	Yes
Global end of trial date	23 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	681
From 65 to 84 years	126
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

Subjects randomized to this arm received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m^2) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

(mg/m^2) for at least 6 cycles (1 cycle was 21 days). For subjects who tolerated at least one cycle without any significant toxicity, the docetaxel dose was increased to 100 mg/m^2 at the investigator's discretion. On or prior to Cycle 6, docetaxel was only discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician.

Arm title	Placebo + Trastuzumab + Docetaxel

Arm description:

Subjects randomized to this arm received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m^2 IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

Docetaxel was administered as an IV dose of 75 milligrams per square metre of body surface area (mg/m^2) for at least 6 cycles (1 cycle was 21 days). For subjects who tolerated at least one cycle without any significant toxicity, the docetaxel dose was increased to 100 mg/m^2 at the investigator's discretion. On or prior to Cycle 6, docetaxel was only discontinued for PD or unacceptable toxicity. After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician.

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

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

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 2 subjects randomized to the Pertuzumab arm withdrew from the study before receiving any study treatment.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 2 subjects randomized to the Placebo arm withdrew from the study before receiving any study treatment.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 9 subjects randomized to the Placebo arm actually received at least one dose of pertuzumab in error.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: One subject randomized to the Pertuzumab arm actually received placebo in error at every treatment cycle.

Baseline characteristics

Reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Docetaxel

Reporting group description:

Subjects randomized to this arm received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m^2) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

Reporting group title	Placebo + Trastuzumab + Docetaxel

Reporting group description:

Subjects randomized to this arm received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m^2 IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

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

techniques or clinically). Any subjects with non-target lesions only were deemed to have non-measurable disease. The IRF did not evaluate baseline tumor assessments for any subject without a post-baseline tumor assessment.			
Units: Subjects			
Measurable Disease	343	336	679
Non-Measurable Disease	44	43	87
Not Evaluated	15	27	42

End points reporting groups

Reporting group title	Pertuzumab + Trastuzumab + Docetaxel

Reporting group description:

Subjects randomized to this arm received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m^2) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

Reporting group title	Placebo + Trastuzumab + Docetaxel

Reporting group description:

Subjects randomized to this arm received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m^2 IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

Subject analysis set title	Placebo + Trastuzumab + Docetaxel
Subject analysis set type	Safety analysis

Subject analysis set description:

This is the placebo safety population, which includes subjects who received study treatment with placebo at every cycle. Subjects received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m^2 IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

Subject analysis set title	Pertuzumab + Trastuzumab + Docetaxel
Subject analysis set type	Safety analysis

Subject analysis set description:

This is the pertuzumab safety population, which includes subjects who received at least one dose of study treatment with pertuzumab. Subjects received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m^2) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

Subject analysis set title	Crossover From Placebo to Pertuzumab
Subject analysis set type	Safety analysis

Subject analysis set description:

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

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

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

End point description:

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

End point type	Primary

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

Statistical analysis title	PFS by IRF - Stratified

Statistical analysis description:

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

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

Notes:

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

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

Statistical analysis title	PFS by IRF - Unstratified

Statistical analysis description:

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

Comparison groups	Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Log Rank (unstratified)
Parameter estimate	Cox proportional hazard
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.76

Notes:

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

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

Secondary: Overall Survival

End point title	Overall Survival

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	End-of-Study OS Analysis (23-Nov-2018)

Statistical analysis description:

This end-of-study OS analysis is considered exploratory only as the confirmatory OS analysis for statistical interpretation had previously occurred at the second interim OS analysis.

Comparison groups	Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001 [10]
Method	Log Rank (stratified)
Parameter estimate	Cox proportional hazard
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.82

Notes:

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

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

Statistical analysis title	Event-Driven Final OS Analysis (11-Feb-2014)

Statistical analysis description:

This final OS analysis was event-driven and planned to take place after a total of 385 deaths had occurred. It is considered exploratory only as the confirmatory OS analysis for statistical interpretation had previously occurred at the second interim OS analysis.

Comparison groups	Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0002 [12]
Method	Log Rank (stratified)
Parameter estimate	Cox proportional hazard
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.84

Notes:

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

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

Statistical analysis title	Second Interim OS Analysis (14-May-2012)

Statistical analysis description:

For this second interim OS analysis, the pre-defined O'Brien-Fleming stopping boundary for the Lan-DeMets α-spending function was: HR≤0.739, p≤0.0138.

Comparison groups	Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0008 [14]
Method	Log Rank (stratified)
Parameter estimate	Cox proportional hazard
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.84

Notes:

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

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

Statistical analysis title	First Interim OS Analysis (13-May-2011)

Statistical analysis description:

For this first interim OS analysis, the pre-defined O'Brien-Fleming stopping boundary for the Lan-DeMets α-spending function was: HR≤0.603, p≤0.0012.

Comparison groups	Pertuzumab + Trastuzumab + Docetaxel v Placebo + Trastuzumab + Docetaxel
Number of subjects included in analysis	808
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.005 [16]
Method	Log Rank (stratified)
Parameter estimate	Cox proportional hazard
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.88

Notes:

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

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[17] - ITT Population

[18] - ITT Population

Statistical analyses

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

Notes:

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

[20] - Stratified by prior treatment status and region

Secondary: Objective Response Determined by an Independent Review Facility

End point title	Objective Response Determined by an Independent Review Facility

End point description:

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

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

End point type	Secondary

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

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

Notes:

[23] - Difference in the objective response rates between arms is calculated as Pertuzumab arm minus Placebo arm. The 95% CI was calculated using the Hauck-Anderson method.
[24] - Stratified by prior treatment status and region.

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

Notes:

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

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

Notes:

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

Secondary: Time to Symptom Progression

End point title	Time to Symptom Progression

End point description:

Time to symptom progression was defined as the time from randomization to the first symptom progression as evaluated from the Functional Assessment of Cancer Therapy-for participants with Breast Cancer (FACT-B) questionnaire with the Trial Outcomes Index-Physical/Functional/Breast (TOI-PFB) subscale. The FACT-B TOI-PFB subscale contains 24 items from 3 subsections of the FACT-B questionnaire: Physical Well-being, Functional Well-being, and Additional Concerns for breast cancer participants (breast cancer subscale [BCS]). All items in the questionnaire were rated by the patient on a 5-point scale ranging from 0 (“not at all”) to 4 (“very much”). The total score ranged from 0 to 96. A higher score indicates better perceived quality of life. A positive change score from baseline indicates improvement. Symptom progression was defined as a decrease from baseline of 5 points or more.

End point type	Secondary

End point timeframe:

Every 9 weeks from Baseline until investigator-determined progressive disease, up to the primary completion date (up to 3 years, 3 months)

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

Notes:

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

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

Statistical analyses

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

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

Notes:

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

[32] - Stratified by prior treatment status and region

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

At Least One AE - Grade 5	12	8	1	

Notes:

[33] - Safety Population

[34] - Safety Population

[35] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[36] - Safety Population

[37] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[38] - Safety Population

[39] - Safety Population

[40] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

	Adverse Event That Resulted in Interruption or Modification of Any Study Medication

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

Notes:

[41] - Safety Population

[42] - Safety Population

[43] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

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

Notes:

[44] - Safety Population

[45] - Safety Population

[46] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

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

Notes:

[47] - Safety Population

[48] - Safety Population

Statistical analyses

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

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

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

End point description:

Clinical laboratory tests for blood biochemistry parameters were performed at local laboratories; any abnormal values (High or Low) were based on local laboratory normal ranges. Laboratory abnormalities are presented by the highest grade according to NCI-CTCAE v3.0. The 'n' in category titles represent number of subjects per arm with at least one valid laboratory value, in order from left to right column. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: clinically significant (per investigator); accompanied by clinical symptoms; resulted in a change in study treatment; or required a change in concomitant therapy. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks. ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase

End point type	Secondary

End point timeframe:

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

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

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

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

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

Notes:

[49] - Safety Population

[50] - Safety Population

[51] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Clinical laboratory tests for hematology parameters were performed at local laboratories; any abnormal values (High or Low) were based on local laboratory normal ranges. Laboratory abnormalities are presented by the highest grade according to NCI-CTCAE v3.0. The 'n' in category titles represent number of subjects per arm with at least one valid laboratory value, in order from left to right column. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: clinically significant (per investigator); accompanied by clinical symptoms; resulted in a change in study treatment; or required a change in concomitant therapy. Median [range] time on study treatment per arm: Placebo: 49.3 [0.3-514.7] weeks; Pertuzumab: 75.7 [0.6-519.6] weeks; Crossover: 129.9 [0.3-322.3] weeks. INR = International Normalized Ratio; PTT = partial thromboplastin time; WBC = white blood cell

End point type	Secondary

End point timeframe:

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

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

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

Notes:

[52] - Safety Population

[53] - Safety Population

[54] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo + Trastuzumab + Docetaxel

Reporting group description:

This is the placebo safety population, which includes subjects who received study treatment with placebo at every cycle. Subjects received placebo IV q3w and trastuzumab 6 mg/kg IV q3w, plus docetaxel 75 mg/m^2 IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination. For subjects who crossed over to receive open-label pertuzumab, adverse events (AEs) were included in the Placebo group from the day of the first placebo dose through the day just prior to the first pertuzumab dose. Any AEs occurring on the day of the first dose of pertuzumab were included in the Crossover From Placebo to Pertuzumab group.

Reporting group title	Pertuzumab + Trastuzumab + Docetaxel

Reporting group description:

This is the pertuzumab safety population, which includes subjects who received at least one dose of study treatment with pertuzumab. Subjects received pertuzumab 420 milligrams (mg) intravenously (IV) once every 3 weeks (q3w) and trastuzumab 6 milligrams per kilogram (mg/kg) IV q3w, plus docetaxel 75 milligrams per square metre of body surface (mg/m^2) IV q3w (for at least 6 cycles; 1 cycle was 21 days). After Cycle 6, continuation of docetaxel treatment was at the discretion of the subject and treating physician. Subjects remained in the treatment phase of the study until investigator-assessed radiographic or clinical evidence of disease progression, unmanageable toxicity, or study termination and were followed for survival until death, loss to follow-up, withdrawal of consent, or study termination.

Reporting group title	Crossover From Placebo to Pertuzumab

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported