Clinical trial results:
A randomized, two-arm, open-label, multicenter Phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first line patients with HER2-positive and hormone receptor-positive advanced (metastatic or locally advanced) breast cancer

Summary

EudraCT number	2011-002132-10
Trial protocol	FR ES GB IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	27 May 2017
First version publication date	27 May 2017

Trial information

Trial identification

Sponsor protocol code	MO27775

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01491737
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124,, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	17 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare PFS of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor (AI) versus trastuzumab plus an AI.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 February 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 40
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	India: 26
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	258
EEA total number of subjects	135

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)	172
From 65 to 84 years	81
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 258 subjects were enrolled in the study from 17 February 2012. Results are presented here up to data cut-off date (17 March 2016).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Pertuzumab+Trastuzumab+AI)

Arm description:

Subjects received pertuzumab at a loading dose of 840 mg followed by 420 mg along with trastuzumab at a loading dose of 8 mg/kg of body weight followed by 6 mg/kg of body weight on Day 1 or Day 2 of each 3-weekly cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death, or the predefined end of study whichever occurs first. Participant received aromatase inhibitor (AI), orally as per product labeling (anastrozole: 1 mg once daily or letrozole: 2.5 mg once daily). Subjects receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly), administered in line with the respective product labeling.

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

Dosage and administration details:

Pertuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 or Day 2 of each subsequent 3 weekly cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 8 mg/kg, followed by 6 mg/kg on Day 1 or Day 2 of each subsequent 3 weekly cycle.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Anastrozole was administered 1 mg once daily.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole was administered 2.5 mg once daily.

Investigational medicinal product name	Taxane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Taxane was administered (docetaxel every 3 weeks or paclitaxel weekly) in line with the respective product labeling.

Arm title	Arm B (Trastuzumab+AI)

Arm description:

Subjects received trastuzumab at a loading dose of 8 mg/kg of body weight followed by 6 mg/kg of body weight on Day 1 or Day 2 of each 3-weekly cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death, or the predefined end of study whichever occurs first. Participant received aromatase inhibitor (AI), orally as per product labeling (anastrozole: 1 mg once daily or letrozole: 2.5 mg once daily). Subjects receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly), administered in line with the respective product labeling.

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 8 mg/kg, followed by 6 mg/kg on Day 1 or Day 2 of each subsequent 3 weekly cycle.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Anastrozole was administered 1 mg once daily.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole was administered 2.5 mg once daily.

Investigational medicinal product name	Taxane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Taxane was administered (docetaxel every 3 weeks or paclitaxel weekly) in line with the respective product labeling.

Number of subjects in period 1	Arm A (Pertuzumab+Trastuzumab+AI)	Arm B (Trastuzumab+AI)
Started	129	129
Completed	80	79
Not completed	49	50
Consent withdrawn by subject	13	13
Death	33	28
Reason not specified	2	3
Lost to follow-up	1	6

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Pertuzumab+Trastuzumab+AI)

Reporting group description:

Subjects received pertuzumab at a loading dose of 840 mg followed by 420 mg along with trastuzumab at a loading dose of 8 mg/kg of body weight followed by 6 mg/kg of body weight on Day 1 or Day 2 of each 3-weekly cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death, or the predefined end of study whichever occurs first. Participant received aromatase inhibitor (AI), orally as per product labeling (anastrozole: 1 mg once daily or letrozole: 2.5 mg once daily). Subjects receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly), administered in line with the respective product labeling.

Reporting group title	Arm B (Trastuzumab+AI)

Reporting group description:

Subjects received trastuzumab at a loading dose of 8 mg/kg of body weight followed by 6 mg/kg of body weight on Day 1 or Day 2 of each 3-weekly cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death, or the predefined end of study whichever occurs first. Participant received aromatase inhibitor (AI), orally as per product labeling (anastrozole: 1 mg once daily or letrozole: 2.5 mg once daily). Subjects receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly), administered in line with the respective product labeling.

Reporting group values	Arm A (Pertuzumab+Trastuzumab+AI)	Arm B (Trastuzumab+AI)	Total
Number of subjects	129	129	258
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	60.9	62.3	
standard deviation	± 10.85	± 11.54	-
Gender, Male/Female Units: Subjects			
Female	129	129	258
Male	0	0	0

End points

End points reporting groups

Reporting group title	Arm A (Pertuzumab+Trastuzumab+AI)

Reporting group description:

Subjects received pertuzumab at a loading dose of 840 mg followed by 420 mg along with trastuzumab at a loading dose of 8 mg/kg of body weight followed by 6 mg/kg of body weight on Day 1 or Day 2 of each 3-weekly cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death, or the predefined end of study whichever occurs first. Participant received aromatase inhibitor (AI), orally as per product labeling (anastrozole: 1 mg once daily or letrozole: 2.5 mg once daily). Subjects receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly), administered in line with the respective product labeling.

Reporting group title	Arm B (Trastuzumab+AI)

Reporting group description:

Subjects received trastuzumab at a loading dose of 8 mg/kg of body weight followed by 6 mg/kg of body weight on Day 1 or Day 2 of each 3-weekly cycle until disease progression, unacceptable toxicity, withdrawal of consent, or death, or the predefined end of study whichever occurs first. Participant received aromatase inhibitor (AI), orally as per product labeling (anastrozole: 1 mg once daily or letrozole: 2.5 mg once daily). Subjects receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly), administered in line with the respective product labeling.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS is defined as the time from randomization until the first radiographically documented progression of disease or death from any cause, whichever occurred first (either during study treatment or during follow-up). Progression of disease was evaluated according to the response evaluation criteria in solid tumors (RECIST) (version 1.1). Progressive disease is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of one or more new lesions is also considered progression). Participants with no PFS events were censored at the time of the last evaluable tumor assessment. Intent-to-treat (ITT) population included all randomized subjects.

End point type	Primary

End point timeframe:

Baseline to progressive disease or death (approximately, up to 49 months)

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: months				
median (confidence interval 95%)	18.89 (14.09 to 27.66)	15.8 (11.04 to 18.56)		

Statistical analyses

Statistical analysis title	PFS

Statistical analysis description:

Stratified log-rank test based upon Kaplan-Meier including induction chemotherapy and prior adjuvant therapy stratification factors from interactive response system (IXRS). Hazard ratio from stratified Cox proportional hazards model including stratification factors from interactive response system (IXRS).

Comparison groups	Arm A (Pertuzumab+Trastuzumab+AI) v Arm B (Trastuzumab+AI)
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.89

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from the date of randomisation to the date of death, regardless of the cause of death. Subjects who were alive at the time of the analysis were censored at the date of the last follow-up assessment. Subjects without follow-up assessment were censored at the day of last study medication (pertuzumab, trastuzumab, AI or induction chemotherapy), and subjects with no post-baseline information were censored at the date of randomisation. ITT population included all randomised subjects. Here, 99999 indicates median, lower and upper limit of confidence limit (CI) for Arm A as it was not reached. 99999 indicates median and upper limit of CI for Arm B as it was not reached.

End point type	Secondary

End point timeframe:

From the date of randomisation until first documented death (approximately, up to 49 months)

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: months				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (41.4 to 99999)		

Statistical analyses

Statistical analysis title	Overall Survival

Statistical analysis description:

Stratified log-rank test based upon Kaplan-Meier including induction chemotherapy and prior adjuvant therapy stratification factors from IXRS.Hazard ratio from stratified Cox proportional hazards model including stratification factors from IXRS.

Comparison groups	Arm A (Pertuzumab+Trastuzumab+AI) v Arm B (Trastuzumab+AI)
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.585
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.91

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the period from the date of initial confirmed partial response (PR) or complete response (CR) until the date of progressive disease or death from any cause. According to RECIST version 1.1, CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Subjects with no documented progression after CR or PR were censored at the last date at which they were known to have had the CR or PR, respectively. ITT population included all randomised subjects. Here, 99999 indicates upper limit of CI as it was not reached.

End point type	Secondary

End point timeframe:

Baseline up to 49 months, approximately

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[1]	59[2]		
Units: Percentage				
median (confidence interval 95%)	27.1 (14.13 to 99999)	15.11 (12.09 to 20.96)		

Notes:

[1] - Number of subjects analyzed: subjects who were responders and had measurable disease at baseline.

[2] - Number of subjects analyzed: subjects who were responders and had measurable disease at baseline.

Statistical analyses

Statistical analysis title	DOR

Statistical analysis description:

Median and log-rank test from unstratified analysis based upon Kaplan-Meier approach. 95% CI for medians are determined using the log-log transformation. Hazard ratio from stratified Cox proportional hazards model including stratification factors from IXRS.

Comparison groups	Arm A (Pertuzumab+Trastuzumab+AI) v Arm B (Trastuzumab+AI)
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0181
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.91

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR was defined as the time from the date of randomisation to the date of first CR or PR. According to RECIST version 1.1, CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. A censored time to response was calculated at the date of the last adequate tumor assessment as there was no date of confirmed response (CR or PR). If no tumor assessment is performed for the participant (or all post-baseline assessments are not evaluable or PD) the censoring day would be set to day 1 (date of randomisation).

End point type	Secondary

End point timeframe:

Baseline up to 49 months, approximately

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[3]	106[4]		
Units: Months				
median (confidence interval 95%)	2.53 (2.1 to 4.37)	3.91 (2.1 to 4.17)		

Notes:

[3] - Here, number of subjects analyzed are the responders who had measurable disease at baseline.

[4] - Here, number of subjects analyzed are the responders who had measurable disease at baseline.

Statistical analyses

Statistical analysis title	TTR

Statistical analysis description:

Median and log-rank test from unstratified analysis based upon Kaplan-Meier approach. 95% CI for medians are determined using the log-log transformation. Hazard ratio from stratified Cox proportional hazards model including stratification factors from IXRS.

Comparison groups	Arm A (Pertuzumab+Trastuzumab+AI) v Arm B (Trastuzumab+AI)
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5597
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.57

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR was defined as subjects with best (confirmed) overall response (BOR) of either CR or PR. ORR was assessed by the investigator according to RECIST version 1.1 and is based on BOR, which is defined as best response recorded from start of study treatment until disease progression/recurrence or death. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference baseline sum diameters; SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Subjects needed to have two consecutive assessments of PR or CR to be a responder. Only subjects with measurable disease at baseline were included in the analysis of BOR and who did not have any evaluable post-baseline assessments were classified as not evaluable.

End point type	Secondary

End point timeframe:

Baseline up to 49 months, approximately

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[5]	106[6]		
Units: percentage of subjects				
number (confidence interval 95%)	63.3 (53.5 to 72.3)	55.7 (45.7 to 65.3)		

Notes:

[5] - Here, number of subjects analyzed are the subjects who had measurable disease at baseline.

[6] - Here, number of subjects analyzed are the subjects who had measurable disease at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response (CBR)

End point title	Clinical Benefit Response (CBR)

End point description:

CBR is percentage of subjects with best (confirmed) PR or CR or SD for at least 6 months. According to RECIST version 1.1, CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters; stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. ITT population included all randomised subjects.

End point type	Secondary

End point timeframe:

Baseline up to 49 months, approximately

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[7]	106[8]		
Units: percentage of subjects				
number (confidence interval 95%)	68.8 (59.2 to 77.3)	67 (57.2 to 75.8)		

Notes:

[7] - Here, number of subjects analyzed are the subjects who had measurable disease at baseline.

[8] - Here, number of subjects analyzed are the subjects who had measurable disease at baseline.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health-Related Quality of Life as Determined by European Quality of Life 5-Dimension (EQ-5D) Visual Analog Scale (VAS) Scores

End point title	Change From Baseline in Health-Related Quality of Life as Determined by European Quality of Life 5-Dimension (EQ-5D) Visual Analog Scale (VAS) Scores

End point description:

EQ-5D VAS: subjectt rated questionnaire to assess health-related quality of life (QoL) in terms of a single index value. The VAS component rates current health state on a scale from 0 mm (worst imaginable health state) to 100 mm (best imaginable health state); higher scores indicate a better health state. ITT population included all randomised subjects. Here, 'n' number of subjects who were evaluated at specified time point. Here, 99999 indicates standard deviation as it was not estimable because only 1 subject was evaluated for Cycle 57. 99999 indicates mean and standard deviation as no subject was evaluated at Cycle 60.

End point type	Secondary

End point timeframe:

Baseline, every 3 cycles (21-day cycle), and every 3 months after treatment discontinuation (up to 49 months, approximately)

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: EQ-5D VAS				
arithmetic mean (standard deviation)				
Cycle 3 (n= 87, 87)	3.3 (± 14.9)	1.9 (± 15.67)		
Cycle 6 (n= 82, 75)	3.5 (± 18.91)	0.5 (± 13.63)		
Cycle 9 (n= 68, 66)	5.3 (± 18.8)	2.1 (± 15.2)		
Cycle 12 (n= 58, 52)	10.7 (± 17.91)	4 (± 15.34)		
Cycle 15 (n= 54, 50)	9.1 (± 17.25)	1.4 (± 22.16)		
Cycle 18 (n= 47, 43)	7.5 (± 12.85)	3.5 (± 15.76)		
Cycle 21 (n= 44, 39)	5.8 (± 13.68)	3.5 (± 19.7)		
Cycle 24 (n= 39, 38)	6.2 (± 14.3)	3.2 (± 16.66)		
Cycle 27 (n= 35, 33)	7.5 (± 14.01)	2.6 (± 21.08)		
Cycle 30 (n= 32, 28)	8.4 (± 14.46)	3.3 (± 14.86)		
Cycle 33 (n= 30, 23)	4.8 (± 14.94)	3.6 (± 15.56)		
Cycle 36 (n= 25, 20)	5 (± 13.46)	5.3 (± 15.26)		
Cycle 39 (n= 21, 14)	6 (± 15.46)	10.4 (± 15.89)		
Cycle 42 (n= 16, 11)	3.4 (± 17.67)	11.4 (± 19.38)		
Cycle 45 (n= 13, 8)	8.5 (± 12.48)	9.3 (± 21.3)		
Cycle 48 (n= 9, 4)	3.3 (± 8.66)	-1.8 (± 2.36)		
Cycle 51 (n= 6, 4)	3.3 (± 11.69)	7 (± 12.36)		
Cycle 54 (n= 3, 2)	16.7 (± 17.56)	17.5 (± 17.68)		
Cycle 57 (n= 2, 0)	5 (± 7.07)	99999 (± 99999)		
Cycle 60 (n= 1, 0)	-5 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With any Adverse Event (AE)

End point title	Percentage of Subjects With any Adverse Event (AE)

End point description:

An AE was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study and laboratory or clinical tests that resulted in a change in treatment or discontinuation from study drug were reported as adverse events. Safety population included all subjects who had received at least 1 dose of any study medication assigned to treatment arms as treated.

End point type	Secondary

End point timeframe:

Up to 49 months approximately

End point values	Arm A (Pertuzumab+ Trastuzumab+ AI)	Arm B (Trastuzumab+ AI)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	124		
Units: percentage of subjects				
number (not applicable)	96.1	98.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to cut-off date 17 March 2016 (approximate 49 months)

Adverse event reporting additional description:

Safety population included all subjects who had received at least 1 dose of any study medication assigned to treatment arms as treated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Arm A (Pertuzumab+Trastuzumab+AI)

Reporting group description:

Pertuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 or Day 2 of each subsequent 3 weekly cycle. Trastuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 8 mg/kg, followed by 6 mg/kg on Day 1 or Day 2 of each subsequent 3 weekly cycle. An AI (oral) was to be administered in line with product labeling (anastrozole: 1 mg once daily; letrozole: 2.5 mg once daily). Patients receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly),administered in line with the respective product labeling.

Reporting group title	Arm B (Trastuzumab+AI)

Reporting group description:

Trastuzumab was administered as an intravenous infusion on Day 1 or Day 2 of the first treatment cycle as a loading dose of 8 mg/kg, followed by 6 mg/kg on Day 1 or Day 2 of each subsequent 3 weekly cycle. An AI (oral) was to be administered in line with product labeling (anastrozole: 1 mg once daily; letrozole: 2.5 mg once daily). Patients receiving induction chemotherapy up to the first 18-24 weeks of the treatment period were to receive a taxane (docetaxel every 3 weeks or paclitaxel weekly),administered in line with the respective product labeling.

Serious adverse events	Arm A (Pertuzumab+Trastuzumab+AI)	Arm B (Trastuzumab+AI)	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 127 (33.07%)	24 / 124 (19.35%)	
number of deaths (all causes)	33	28	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoid cystic carcinoma of salivary gland			

subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Colostomy closure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media allergy			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	3 / 127 (2.36%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	2 / 127 (1.57%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 127 (1.57%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	3 / 127 (2.36%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycaemic coma			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 127 (3.15%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal haemorrhage			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			

subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 127 (0.79%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 127 (2.36%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	1 / 127 (0.79%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 127 (3.94%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	1 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 127 (0.79%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 127 (0.00%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A (Pertuzumab+Trastuzumab+AI)	Arm B (Trastuzumab+AI)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 127 (93.70%)	115 / 124 (92.74%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 127 (6.30%)	9 / 124 (7.26%)	
occurrences (all)	12	17	
Hypertension			
subjects affected / exposed	19 / 127 (14.96%)	23 / 124 (18.55%)	
occurrences (all)	42	63	
Lymphoedema			
subjects affected / exposed	7 / 127 (5.51%)	4 / 124 (3.23%)	
occurrences (all)	9	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 127 (30.71%)	31 / 124 (25.00%)	
occurrences (all)	69	74	
Chest pain			
subjects affected / exposed	9 / 127 (7.09%)	7 / 124 (5.65%)	
occurrences (all)	11	9	
Chills			
subjects affected / exposed	8 / 127 (6.30%)	7 / 124 (5.65%)	
occurrences (all)	8	7	
Fatigue			
subjects affected / exposed	21 / 127 (16.54%)	24 / 124 (19.35%)	
occurrences (all)	32	41	
Influenza like illness			

subjects affected / exposed	9 / 127 (7.09%)	6 / 124 (4.84%)	
occurrences (all)	15	7	
Mucosal inflammation			
subjects affected / exposed	14 / 127 (11.02%)	11 / 124 (8.87%)	
occurrences (all)	20	13	
Oedema peripheral			
subjects affected / exposed	31 / 127 (24.41%)	22 / 124 (17.74%)	
occurrences (all)	46	32	
Pyrexia			
subjects affected / exposed	15 / 127 (11.81%)	11 / 124 (8.87%)	
occurrences (all)	20	11	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 127 (17.32%)	17 / 124 (13.71%)	
occurrences (all)	27	23	
Dyspnoea			
subjects affected / exposed	18 / 127 (14.17%)	12 / 124 (9.68%)	
occurrences (all)	19	15	
Epistaxis			
subjects affected / exposed	14 / 127 (11.02%)	12 / 124 (9.68%)	
occurrences (all)	18	15	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 127 (9.45%)	5 / 124 (4.03%)	
occurrences (all)	12	5	
Depression			
subjects affected / exposed	9 / 127 (7.09%)	6 / 124 (4.84%)	
occurrences (all)	9	7	
Insomnia			
subjects affected / exposed	13 / 127 (10.24%)	17 / 124 (13.71%)	
occurrences (all)	14	21	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	12 / 127 (9.45%)	6 / 124 (4.84%)	
occurrences (all)	16	7	
Weight decreased			

subjects affected / exposed	13 / 127 (10.24%)	10 / 124 (8.06%)	
occurrences (all)	15	11	
Weight increased			
subjects affected / exposed	9 / 127 (7.09%)	5 / 124 (4.03%)	
occurrences (all)	11	10	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 127 (14.96%)	11 / 124 (8.87%)	
occurrences (all)	26	11	
Dysguesia			
subjects affected / exposed	9 / 127 (7.09%)	8 / 124 (6.45%)	
occurrences (all)	12	10	
Headache			
subjects affected / exposed	22 / 127 (17.32%)	14 / 124 (11.29%)	
occurrences (all)	28	24	
Neuropathy peripheral			
subjects affected / exposed	17 / 127 (13.39%)	17 / 124 (13.71%)	
occurrences (all)	22	19	
Paraesthesia			
subjects affected / exposed	13 / 127 (10.24%)	11 / 124 (8.87%)	
occurrences (all)	18	13	
Peripheral sensory neropathy			
subjects affected / exposed	9 / 127 (7.09%)	9 / 124 (7.26%)	
occurrences (all)	11	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 127 (20.47%)	18 / 124 (14.52%)	
occurrences (all)	44	30	
Neutropenia			
subjects affected / exposed	11 / 127 (8.66%)	12 / 124 (9.68%)	
occurrences (all)	14	22	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	8 / 127 (6.30%)	7 / 124 (5.65%)	
occurrences (all)	8	8	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	10 / 127 (7.87%)	12 / 124 (9.68%)	
occurrences (all)	11	14	
Abdominal pain upper			
subjects affected / exposed	8 / 127 (6.30%)	6 / 124 (4.84%)	
occurrences (all)	11	6	
Constipation			
subjects affected / exposed	16 / 127 (12.60%)	19 / 124 (15.32%)	
occurrences (all)	24	25	
Diarrhoea			
subjects affected / exposed	70 / 127 (55.12%)	44 / 124 (35.48%)	
occurrences (all)	200	84	
Dyspepsia			
subjects affected / exposed	8 / 127 (6.30%)	8 / 124 (6.45%)	
occurrences (all)	9	9	
Nausea			
subjects affected / exposed	41 / 127 (32.28%)	32 / 124 (25.81%)	
occurrences (all)	59	53	
Stomatitis			
subjects affected / exposed	17 / 127 (13.39%)	11 / 124 (8.87%)	
occurrences (all)	23	21	
Vomiting			
subjects affected / exposed	29 / 127 (22.83%)	21 / 124 (16.94%)	
occurrences (all)	39	31	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	36 / 127 (28.35%)	40 / 124 (32.26%)	
occurrences (all)	38	49	
Dry skin			
subjects affected / exposed	7 / 127 (5.51%)	6 / 124 (4.84%)	
occurrences (all)	9	7	
Nail disorder			
subjects affected / exposed	9 / 127 (7.09%)	4 / 124 (3.23%)	
occurrences (all)	13	6	
Pruritus			

subjects affected / exposed	18 / 127 (14.17%)	12 / 124 (9.68%)	
occurrences (all)	32	15	
Rash			
subjects affected / exposed	22 / 127 (17.32%)	11 / 124 (8.87%)	
occurrences (all)	32	17	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	9 / 127 (7.09%)	1 / 124 (0.81%)	
occurrences (all)	13	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	37 / 127 (29.13%)	29 / 124 (23.39%)	
occurrences (all)	49	42	
Back pain			
subjects affected / exposed	20 / 127 (15.75%)	20 / 124 (16.13%)	
occurrences (all)	21	26	
Bone pain			
subjects affected / exposed	16 / 127 (12.60%)	9 / 124 (7.26%)	
occurrences (all)	25	11	
Muscle spasms			
subjects affected / exposed	12 / 127 (9.45%)	5 / 124 (4.03%)	
occurrences (all)	13	6	
Musculoskeletal chest pain			
subjects affected / exposed	9 / 127 (7.09%)	4 / 124 (3.23%)	
occurrences (all)	9	5	
Musculoskeletal pain			
subjects affected / exposed	8 / 127 (6.30%)	6 / 124 (4.84%)	
occurrences (all)	8	8	
Myalgia			
subjects affected / exposed	11 / 127 (8.66%)	9 / 124 (7.26%)	
occurrences (all)	12	9	
Pain in extremity			
subjects affected / exposed	21 / 127 (16.54%)	15 / 124 (12.10%)	
occurrences (all)	30	22	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	11 / 127 (8.66%)	6 / 124 (4.84%)	
occurrences (all)	20	7	
Upper respiratory tract infection NOS			
subjects affected / exposed	12 / 127 (9.45%)	13 / 124 (10.48%)	
occurrences (all)	20	17	
Urinary tract infection			
subjects affected / exposed	16 / 127 (12.60%)	14 / 124 (11.29%)	
occurrences (all)	20	17	
Influenza			
subjects affected / exposed	4 / 127 (3.15%)	7 / 124 (5.65%)	
occurrences (all)	4	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	20 / 127 (15.75%)	10 / 124 (8.06%)	
occurrences (all)	21	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 August 2012	1.The decision to include induction chemotherapy had to be made prior to randomization 2. The chemotherapy induction period was amended from "18 weeks" to "18 to 24 weeks" to allow for the application of different treatment schedules 3. Exclusion criteria were amended to exclude participants with CNS metastases only if they were not medically well controlled after receiving local therapy, to reduce the period since major surgery to randomization to 14 days, since receipt of intravenous antibiotics to 7 days, and to specify that use of chronic steroids referred to a period of ≥3 months and concurrent participation in a clinical study referred to therapeutic clinical studies 4. The sponsor would continue to provide pertuzumab for those participants who were still receiving the IMP at the end of the study and who are willing and considered suitable to enter an extension study for the purpose of collecting safety data and pre-specified efficacy measures 5. The dosing schedule of pertuzumab was amended (from Day 1 to Day 1 or Day 2) and an instruction was included to permit pertuzumab, trastuzumab and taxanes to be administered in any order (apart from Cycle 1) to allow more flexibility in the timing and order of administration of study medication 6. The interval duration for the scheduling of tumor assessments after 36 months was extended to reduce the burden of assessments for participants at this stage of the study 7. An IDMC was established to review safety
28 April 2016	1. Treatment of participants with initially inoperable locally advanced breast cancer at inclusion which subsequently became resectable was at the investigator's discretion 2. The follow-up period for the evaluation of OS was extended from 24 months to 60 months 3. For this protocol, mortality was an efficacy endpoint. It was clarified that death should be considered an outcome and not a distinct event. An independent monitoring committee was to monitor the frequency of deaths from all causes 4. Participants with limited liver abnormalities were allowed in the study
20 September 2016	1. The definition for abnormal liver function test AEs reverted to the definition used for Version 2.0 of the protocol. This amendment was introduced following a request from the Medicines and Healthcare products Regulatory Agency in the United Kingdom (UK) and to ensure that there was consistency within the PERTAIN (EudraCT number 2011-002132-10) study assessments over time and globally 2. The Schedule of Assessments was revised to reflect the fact that an increased follow-up visit tolerance of an additional 5 weeks, 18 weeks in total, was now permitted for participants who were progression-free for >36 months

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported