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	14 November 2019

Results information

Result version number	v2 (current)
This version publication date	12 November 2020
First version publication date	27 May 2017
Version creation reason	

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	Final
Date of interim/final analysis	14 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2016
Global end of trial reached?	Yes
Global end of trial date	14 November 2019
Was the trial ended prematurely?	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	0

months)	
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.

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 +/- Chemotherapy

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 +/- Chemotherapy

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 +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy
Started	129	129
Received at Least One Dose of Study Drug	127	124
Entered Follow-Up (Post-Treatment)	120	116
Completed	0	0
Not completed	129	129
Consent withdrawn by subject	20	17
Death	63	57
Reason not specified	8	9
Lost to follow-up	2	10
Study Termination by Sponsor	36	36

Baseline characteristics

Reporting groups

Reporting group title	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy

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 +/- Chemotherapy

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 +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy	Total
Number of subjects	129	129	258
Age categorical Units: Subjects			
18-64 Years	86	86	172
65-84 Years	42	39	81
85+ Years	1	4	5
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
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	10	18	28
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	5	9
White	104	93	197
More Than One Race	0	0	0
Unknown or Not Reported	11	12	23
Ethnicity Units: Subjects			
Hispanic/Latino	45	40	85
Chinese	0	0	0

Indian (Indian subcontinent)	10	16	26
Japanese	0	1	1
Mixed Ethnicity	0	0	0
Other	63	60	123
Missing	11	12	23
Number of Subjects by IXRS Stratification Factors			
Subjects were stratified at randomization according to the following factors: -Chosen to receive induction chemotherapy? (Yes vs. No); -Time since adjuvant hormone therapy (<12 months vs. ≥12 months), or no prior hormone therapy. IXRS = interactive response system			
Units: Subjects			
Chemo - Yes and <12 Months Since Hormone Therapy	12	12	24
Chemo - Yes and ≥12 Months Since Hormone Therapy	24	23	47
Chemo - Yes and No Prior Hormone Therapy	39	38	77
Chemo - No and <12 Months Since Hormone Therapy	12	12	24
Chemo - No and ≥12 Months Since Hormone Therapy	18	19	37
Chemo - No and No Prior Hormone Therapy	24	25	49

End points

End points reporting groups

Reporting group title	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy

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 +/- Chemotherapy

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:

Progression-free survival (PFS) was 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 and 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). The sum of target lesion diameters 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. The primary analysis of PFS was planned to be performed when a total of 165 PFS events had occurred, and the final analysis after at least 60 months follow-up.

End point type	Primary

End point timeframe:

Median [full range] of follow-up time on study for: Primary Analysis: 31.7 [0.0-44.3] months vs. 30.4 [0.0-45.8] months in Arm A vs. Arm B; Final Analysis: 73.20 [0.03-88.34] months vs. 71.06 [0.03-88.97] months in Arm A vs. Arm B

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: Months				
median (confidence interval 95%)				
Primary Analysis	18.89 (14.09 to 27.66)	15.80 (11.04 to 18.56)		

Final Analysis	20.63 (14.39 to 28.35)	15.80 (11.04 to 18.66)		

Statistical analyses

Statistical analysis title	PFS Primary Analysis

Statistical analysis description:

Log Rank tested the following: Null Hypothesis (H0): the distribution of the PFS time was the same in Arms A & B; The Alternative Hypothesis (H1): the distribution of the PFS time was different in Arms A & B. A Cox proportional hazards model tested the HR. If the HR of investigational arm (Arm A) compared with control arm (Arm B) with respect to PFS was assumed to be constant over time (λ) then the null (H0) and alternative hypotheses (H1) were: H0: λ =1; H1: λ ≠1.

Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.007 [2]
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

Notes:

[1] - Stratified log-rank test based upon Kaplan-Meier including the induction chemotherapy and prior adjuvant hormone therapy stratification factors. Hazard ratio comparing Arm A vs. B from stratified Cox proportional hazards model including stratification factors.
[2] - Test was performed at 2-sided alpha of 5%.

Statistical analysis title	PFS Final Analysis
Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.0059
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.89

Notes:

[3] - Exploratory. Stratified log-rank test based upon Kaplan-Meier including the induction chemotherapy and prior adjuvant hormone therapy stratification factors. Hazard ratio comparing Arm A vs. B from stratified Cox proportional hazards model including stratification factors.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) was defined as the time from the date of randomization to the date of death, regardless of the cause of death. Participants who were alive at the time of the analysis were censored at the date of the last follow-up assessment. Participants without follow-up assessment were censored at the day of last study medication (pertuzumab, trastuzumab, AI or induction chemotherapy), and participants with no post-baseline information were censored at the date of randomization. The primary analysis of OS was planned to be performed at the same time as for PFS (when a total of 165 PFS events had occurred), and the final analysis was planned after at least 60 months follow-up for all participants. Here, 999999 indicates median and/or lower and/or upper limits of the 95% confidence interval were not reached because not enough events had occurred at the time of analysis.

End point type	Secondary

End point timeframe:

Median [full range] of follow-up time on study for: Primary Analysis: 31.7 [0.0-44.3] months vs. 30.4 [0.0-45.8] months in Arm A vs. Arm B; Final Analysis: 73.20 [0.03-88.34] months vs. 71.06 [0.03-88.97] months in Arm A vs. Arm B

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: Months				
median (confidence interval 95%)				
Primary Analysis	999999 (999999 to 999999)	999999 (41.40 to 999999)		
Final Analysis	60.16 (47.21 to 79.01)	57.17 (45.44 to 999999)		

Statistical analyses

Statistical analysis title	OS Primary Analysis

Statistical analysis description:

Exploratory. This study was not powered for overall survival (OS), so adequately powered statistical testing for this outcome measure was not possible.

Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[4]
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

Notes:

[4] - Stratified log-rank test based upon Kaplan-Meier including the induction chemotherapy and prior adjuvant hormone therapy stratification factors. Hazard ratio comparing Arm A vs. B from stratified Cox proportional hazards model including stratification factors.

Statistical analysis title	OS Final Analysis

Statistical analysis description:

Exploratory. This study was not powered for overall survival (OS), so adequately powered statistical testing for this outcome measure was not possible.

Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.7833
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.52

Notes:

[5] - Stratified log-rank test based upon Kaplan-Meier including the induction chemotherapy and prior adjuvant hormone therapy stratification factors. Hazard ratio comparing Arm A vs. B from stratified Cox proportional hazards model including stratification factors.

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

The overall response rate (ORR) was defined as the percentage of participants with best (confirmed) overall response (BOR) of either complete response (CR) or partial response (PR) from start of study treatment until progressive disease (PD)/recurrence or death, as assessed by the investigator 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 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. Participants needed to have two consecutive assessments of PR or CR at least 4 weeks apart to be a responder. Analysis of this outcome measure was only planned to occur at the time of primary analysis.

End point type	Secondary

End point timeframe:

Median [full range] of follow-up time on study for Primary Analysis: 31.7 [0.0-44.3] months vs. 30.4 [0.0-45.8] months in Arm A vs. Arm B

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[6]	106[7]		
Units: Percentage of participants				
number (confidence interval 95%)				
ORR (CR + PR)	63.3 (53.5 to 72.3)	55.7 (45.7 to 65.3)		
Non-responders (SD + PD + NE)	36.7 (27.7 to 46.5)	44.3 (34.7 to 54.3)		
Complete Response (CR)	7.3 (3.2 to 14.0)	0.9 (0.0 to 5.1)		
Partial Response (PR)	56.0 (46.1 to 65.5)	54.7 (44.8 to 64.4)		
Stable Disease (SD)	26.6 (18.6 to 35.9)	27.4 (19.1 to 36.9)		
Progressive Disease (PD)	5.5 (2.0 to 11.6)	12.3 (6.7 to 20.1)		
Not Evaluable (NE)	4.5 (1.5 to 10.4)	4.7 (1.5 to 10.7)		

Notes:

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

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

Statistical analyses

Statistical analysis title	ORR for Arm A vs. Arm B
Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2537 [8]
Method	Chi-squared
Parameter estimate	Difference in ORR
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	21.3

Notes:

[8] - Test was performed at 2-sided alpha of 5%. There was no multiplicity adjustment.

Secondary: Clinical Benefit Response (CBR)

End point title	Clinical Benefit Response (CBR)

End point description:

Clinical Benefit Rate (CBR) was defined as the percentage of participants with best (confirmed) partial response (PR) or complete response (CR) or stable disease (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; 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. The ITT population included all randomized participants; this

analysis only included participants with measurable disease at baseline. Analysis of this outcome measure was only planned to occur at the time of primary analysis.

End point type	Secondary

End point timeframe:

Median [full range] of follow-up time on study for Primary Analysis: 31.7 [0.0-44.3] months vs. 30.4 [0.0-45.8] months in Arm A vs. Arm B

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[9]	106[10]		
Units: Percentage of participants				
number (confidence interval 95%)				
CBR (CR + PR + SD for ≥6 Months)	68.8 (59.2 to 77.3)	67.0 (57.2 to 75.8)		
Complete Response (CR)	7.3 (3.2 to 14.0)	0.9 (0.0 to 5.1)		
Partial Response (PR)	56.0 (46.1 to 65.5)	54.7 (44.8 to 64.4)		
Stable Disease (SD) for ≥6 Months	5.5 (2.0 to 11.6)	11.3 (6.0 to 18.9)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CBR for Arm A vs. Arm B
Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7743 [11]
Method	Chi-squared
Parameter estimate	Difference in CBR
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	14.8

Notes:

[11] - Test was performed at 2-sided alpha of 5%. There was no multiplicity adjustment.

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response (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. Participants 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. The primary analysis of DOR was planned to be performed at the same time as for PFS (when a total of 165 PFS events had occurred), and the final analysis was planned after at least 60 months follow-up for all participants. Here, 999999 indicates the upper limit of CI was not reached.

End point type	Secondary

End point timeframe:

Median [full range] of follow-up time on study for: Primary Analysis: 31.7 [0.0-44.3] months vs. 30.4 [0.0-45.8] months in Arm A vs. Arm B; Final Analysis: 73.20 [0.03-88.34] months vs. 71.06 [0.03-88.97] months in Arm A vs. Arm B

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[12]	61[13]		
Units: Months				
median (confidence interval 95%)				
Primary Analysis (n = 69, 59)	27.10 (14.13 to 999999)	15.11 (12.09 to 20.96)		
Final Analysis (n = 69, 61)	27.40 (15.24 to 44.35)	16.36 (12.09 to 20.96)		

Notes:

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

Statistical analyses

Statistical analysis title	DOR Primary Analysis

Statistical analysis description:

Log Rank tested the following: Null Hypothesis (H0): the distribution of the DOR time was the same in Arms A & B; The Alternative Hypothesis (H1): the distribution of the DOR time was different in Arms A & B. A Cox proportional hazards model tested the HR. If the HR of investigational arm (Arm A) compared with control arm (Arm B) with respect to DOR was assumed to be constant over time (λ) then the null (H0) and alternative hypotheses (H1) were: H0: $\lambda = 1$; H1: $\lambda \neq 1$.

Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.0181 [15]
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

Notes:

[14] - Stratified log-rank test based upon Kaplan-Meier including the induction chemotherapy and prior adjuvant hormone therapy stratification factors. Hazard ratio comparing Arm A vs. B from stratified Cox proportional hazards model including stratification factors.
[15] - Test was performed at 2-sided alpha of 5%. There was no multiplicity adjustment.

Statistical analysis title	DOR Final Analysis

Statistical analysis description:

Exploratory

Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0205
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.93

Notes:

[16] - Stratified log-rank test based upon Kaplan-Meier including the induction chemotherapy and prior adjuvant hormone therapy stratification factors. Hazard ratio comparing Arm A vs. B from stratified Cox proportional hazards model including stratification factors.

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

Time to Response (TTR) was defined as the time from the date of randomization to the date of first complete response (CR) or partial response (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. For participants who did not have a confirmed response, a censored TTR was calculated at the date of the last adequate tumor assessment. 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 randomization). Analysis of this outcome measure was only planned to occur at the time of primary analysis.

End point type	Secondary

End point timeframe:

Median [full range] of follow-up time on study for Primary Analysis: 31.7 [0.0-44.3] months vs. 30.4 [0.0-45.8] months in Arm A vs. Arm B

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[17]	106[18]		
Units: Months				
median (confidence interval 95%)	2.53 (2.10 to 4.37)	3.91 (2.10 to 4.17)		

Notes:

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

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

Statistical analyses

Statistical analysis title	TTR

Statistical analysis description:

Log Rank tested the following: Null Hypothesis (H0): the distribution of the TTR time was the same in Arms A & B; The Alternative Hypothesis (H1): the distribution of the TTR time was different in Arms A & B. A Cox proportional hazards model tested the HR. If the HR of investigational arm (Arm A) compared with control arm (Arm B) with respect to TTR was assumed to be constant over time (λ) then the null (H0) and alternative hypotheses (H1) were: H0: λ =1; H1: λ ≠1.

Comparison groups	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy v Arm B: Trastuzumab + AI +/- Chemotherapy
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.5597 [20]
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

Notes:

[19] - The log-rank test from unstratified analysis was based upon Kaplan-Meier approach. Hazard ratio from stratified Cox proportional hazards model including the induction chemotherapy and prior adjuvant hormone therapy stratification factors.

[20] - Test was performed at 2-sided alpha of 5%. There was no multiplicity adjustment.

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:

The EQ-5D VAS is a participant-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. The ITT population included all randomised subjects, and only those with non-missing assessments at each timepoint were included in the analysis. In the data table below, 'n' indicates the number of subjects who were evaluated at a specified time point; '999999' indicates that the standard deviation could not be calculated because only 1 subject was evaluated at a given timepoint; '9999999' indicates that the mean and standard deviation were not reported because no subjects were evaluated at a given timepoint.

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 +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	129		
Units: EQ-5D VAS				
arithmetic mean (standard deviation)				
Baseline (BL) - Value at Visit (n= 98,101)	73.0 (± 19.34)	72.8 (± 18.83)		
Change from BL at Cycle 3 (n= 87, 87)	3.3 (± 14.90)	1.9 (± 15.67)		
Change from BL at Cycle 6 (n= 82, 75)	3.5 (± 18.91)	0.5 (± 13.63)		
Change from BL at Cycle 9 (n= 68, 66)	5.3 (± 18.80)	2.1 (± 15.20)		
Change from BL at Cycle 12 (n= 58, 52)	10.7 (± 17.91)	4.0 (± 15.34)		
Change from BL at Cycle 15 (n= 54, 50)	9.1 (± 17.25)	1.4 (± 22.16)		
Change from BL at Cycle 18 (n= 47, 43)	7.5 (± 12.85)	3.5 (± 15.76)		
Change from BL at Cycle 21 (n= 44, 39)	5.8 (± 13.68)	3.5 (± 19.70)		
Change from BL at Cycle 24 (n= 39, 38)	6.2 (± 14.30)	3.2 (± 16.66)		
Change from BL at Cycle 27 (n= 35, 34)	7.5 (± 14.01)	3.9 (± 22.00)		
Change from BL at Cycle 30 (n= 33, 29)	8.3 (± 14.25)	4.9 (± 16.98)		
Change from BL at Cycle 33 (n= 34, 24)	5.1 (± 14.70)	4.3 (± 15.59)		
Change from BL at Cycle 36 (n= 30, 21)	7.3 (± 15.19)	5.9 (± 15.13)		
Change from BL at Cycle 39 (n= 30, 18)	8.1 (± 16.33)	2.4 (± 29.68)		
Change from BL at Cycle 42 (n= 25, 15)	6.4 (± 19.18)	9.0 (± 17.55)		
Change from BL at Cycle 45 (n= 22, 14)	9.7 (± 15.01)	9.9 (± 19.52)		
Change from BL at Cycle 48 (n= 19, 13)	8.8 (± 12.50)	6.8 (± 17.22)		
Change from BL at Cycle 51 (n= 18, 13)	7.2 (± 14.81)	9.1 (± 19.11)		
Change from BL at Cycle 54 (n= 16, 12)	4.7 (± 23.48)	7.6 (± 17.85)		
Change from BL at Cycle 57 (n= 16, 11)	6.8 (± 18.08)	10.5 (± 16.81)		
Change from BL at Cycle 60 (n= 16, 11)	8.2 (± 15.88)	10.9 (± 18.27)		
Change from BL at Cycle 63 (n= 16, 10)	4.0 (± 20.88)	8.8 (± 14.64)		
Change from BL at Cycle 66 (n= 14, 8)	10.4 (± 16.92)	4.1 (± 15.69)		
Change from BL at Cycle 69 (n= 13, 7)	7.5 (± 17.35)	5.0 (± 16.77)		
Change from BL at Cycle 72 (n= 13, 8)	6.2 (± 16.10)	5.8 (± 16.10)		
Change from BL at Cycle 75 (n= 11, 7)	8.6 (± 19.12)	5.1 (± 15.50)		
Change from BL at Cycle 78 (n= 11, 7)	12.8 (± 17.45)	6.9 (± 14.58)		
Change from BL at Cycle 81 (n= 11, 6)	11.5 (± 18.39)	8.0 (± 14.76)		
Change from BL at Cycle 84 (n= 11, 6)	11.2 (± 19.71)	1.3 (± 18.13)		
Change from BL at Cycle 87 (n= 11, 4)	11.2 (± 18.17)	-3.0 (± 11.22)		
Change from BL at Cycle 90 (n= 11, 4)	10.9 (± 18.28)	-3.0 (± 12.36)		
Change from BL at Cycle 93 (n= 11, 5)	7.1 (± 15.43)	6.6 (± 13.89)		
Change from BL at Cycle 96 (n= 8, 5)	7.5 (± 16.04)	8.6 (± 12.64)		
Change from BL at Cycle 99 (n= 9, 5)	4.4 (± 17.22)	5.6 (± 16.71)		
Change from BL at Cycle 102 (n= 8, 3)	5.6 (± 16.35)	10.0 (± 17.32)		
Change from BL at Cycle 105 (n= 8, 1)	4.4 (± 16.35)	0.0 (± 999999)		
Change from BL at Cycle 108 (n= 7, 1)	4.0 (± 14.39)	0.0 (± 999999)		

Change from BL at Cycle 111 (n= 4, 0)	3.3 (± 21.50)	9999999 (± 9999999)		
Change from BL at Cycle 114 (n= 4, 0)	-1.3 (± 17.97)	9999999 (± 9999999)		
Change from BL at Cycle 117 (n= 1, 0)	-5.0 (± 999999)	9999999 (± 9999999)		
Change from BL at Cycle 120 (n= 1, 0)	-5.0 (± 999999)	9999999 (± 9999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of the Percentage of Participants With Adverse Events, Severity Determined According to NCI-CTCAE version 4.03

End point title	Overview of the Percentage of Participants With Adverse Events, Severity Determined According to NCI-CTCAE version 4.03

End point description:

The safety population was analyzed for all adverse events (AEs) occurring during the study and until the post-treatment safety follow-up visit approximately 28 days after last study medication; thereafter, only study drug-related serious adverse events (SAEs) continued to be collected. The investigator graded all AEs for severity per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03; if not listed, the AE was assessed as follows: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening/disabling; Grade 5 = death. The investigator determined whether an AE was related to study drug and independently assessed severity and seriousness of each AE. AEs suggestive of congestive heart failure (CHF) were identified by the SMQ (wide) "Cardiac Failure" with a status of "serious", which included the preferred terms cardiac failure, left ventricular dysfunction, and pulmonary oedema.

End point type	Secondary

End point timeframe:

From Baseline until the end of post-treatment follow-up (up to 89 months)

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	124		
Units: percentage of subjects				
number (not applicable)				
Any Adverse Event (AE)	96.1	98.4		
Any AE, Grade ≥3	56.7	41.1		
Any Serious Adverse Event (SAE), Grade ≥3	27.6	17.7		
Any AE, Grade 5	0.8	0.8		
Any SAE	36.2	22.6		
SAE Related to Pertuzumab	7.9	0		
SAE Related to Trastuzumab	7.1	1.6		
SAE Related to Docetaxel (n = 74, 69)	8.1	5.8		
SAE Related to Paclitaxel (n = 74, 69)	4.1	0		

Any AE Leading to Discontinuation of Any Treatment	15.7	8.1		
Any AE Leading to Pertuzumab Discontinuation	12.6	0		
Any AE Leading to Trastuzumab Discontinuation	12.6	4.8		
Any AE Leading to Interruption of Any Treatment	46.5	21.0		
Any AE Leading to Pertuzumab Interruption	34.6	0		
Any AE Leading to Trastuzumab Interruption	37.8	12.9		
Any AE Related to Pertuzumab	64.6	0		
Any AE Related to Trastuzumab	63.8	50		
AE Suggestive of Congestive Heart Failure	3.9	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died Over the Course of the Study by Reported Cause of Death and Time of Death Relative to First or Last Dose of Study Treatment

End point title	Number of Participants Who Died Over the Course of the Study by Reported Cause of Death and Time of Death Relative to First or Last Dose of Study Treatment

End point description:

The causes of death over the course of the study, regardless of whether the death was related to study treatment, are listed by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), version 22.1.

End point type	Secondary

End point timeframe:

From Baseline until the end of post-treatment follow-up (up to 89 months)

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	124		
Units: Participants				
Total Number of Deaths	62	57		
Deaths Related to Any Study Treatment	0	0		
Cause of Death: Cardiac Arrest	1	0		
Cause of Death: Craniocerebral Injury	1	0		
Cause of Death: Dyspnoea	1	0		
Cause of Death: High-grade B-cell Lymphoma	1	0		
Cause of Death: Sudden Death	0	1		
Cause of Death: Unevaluable Event	2	1		

Cause of Death: Progressive Disease	56	55		
Total Deaths Within 30 Days After First Dose	0	0		
Total Deaths Within 28 Days After Last Dose	1	2		
Total Deaths Within 60 Days After Last Dose	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Values Over the Course of the Study

End point title	Change from Baseline in Left Ventricular Ejection Fraction (LVEF) Values Over the Course of the Study

End point description:

Left ventricular ejection fraction (LVEF) is the measurement of how much blood is being pumped out of the left ventricle of the heart (the main pumping chamber) with each contraction. A normal LVEF ranges from 55% to 70%, as measured by echocardiogram or multiple-gated acquisition (MUGA) scan. All participants must have had a baseline LVEF of at least (≥)50% to enroll in the study; patients with clinically significant cardiovascular disease or baseline LVEF below 50% were not eligible for this study.

End point type	Secondary

End point timeframe:

Baseline and every 3 cycles until treatment discontinuation (up to Cycle 120; 1 cycle is 21 days)

End point values	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	124		
Units: Percentage points of LVEF				
arithmetic mean (standard deviation)				
Baseline (BL) - Absolute LVEF at Visit (n=127,123)	63.8 (± 6.23)	63.9 (± 6.12)		
Change from BL at Cycle 3 (n=114,114)	-1.0 (± 6.25)	-1.4 (± 6.23)		
Change from BL at Cycle 6 (n=101,101)	-2.3 (± 6.66)	-1.3 (± 6.03)		
Change from BL at Cycle 9 (n=87,84)	-2.5 (± 6.80)	-2.2 (± 6.52)		
Change from BL at Cycle 12 (n=75,69)	-2.4 (± 8.05)	-2.8 (± 6.99)		
Change from BL at Cycle 15 (n=64,61)	-2.9 (± 8.67)	-2.5 (± 6.94)		
Change from BL at Cycle 18 (n=62,54)	-1.9 (± 6.42)	-1.3 (± 6.19)		
Change from BL at Cycle 21 (n=53,48)	-1.1 (± 6.01)	-1.1 (± 6.64)		
Change from BL at Cycle 24 (n=52,46)	-2.1 (± 6.82)	-0.6 (± 6.19)		
Change from BL at Cycle 27 (n=46,39)	-1.6 (± 5.05)	-1.3 (± 5.87)		
Change from BL at Cycle 30 (n=43,34)	-1.4 (± 5.20)	-0.3 (± 6.03)		
Change from BL at Cycle 33 (n=44,28)	-2.8 (± 5.60)	1.2 (± 6.71)		
Change from BL at Cycle 36 (n=37,24)	-2.5 (± 5.50)	-0.2 (± 5.41)		
Change from BL at Cycle 39 (n=38,23)	-2.6 (± 5.72)	1.4 (± 4.87)		

Change from BL at Cycle 42 (n=35,18)	-2.1 (± 5.91)	1.9 (± 6.12)		
Change from BL at Cycle 45 (n=31,17)	-1.0 (± 5.54)	3.0 (± 5.27)		
Change from BL at Cycle 48 (n=28,18)	-3.3 (± 6.56)	-0.2 (± 7.50)		
Change from BL at Cycle 51 (n=27,18)	-1.4 (± 5.82)	1.0 (± 4.19)		
Change from BL at Cycle 54 (n=26,13)	-1.3 (± 6.17)	-1.0 (± 6.23)		
Change from BL at Cycle 57 (n=26,15)	-1.7 (± 6.43)	0.8 (± 5.68)		
Change from BL at Cycle 60 (n=25,14)	-2.5 (± 5.54)	-0.9 (± 3.91)		
Change from BL at Cycle 63 (n=26,14)	-2.1 (± 6.10)	0.8 (± 5.99)		
Change from BL at Cycle 66 (n=22,13)	-2.9 (± 7.80)	-0.4 (± 5.17)		
Change from BL at Cycle 69 (n=19,9)	-2.1 (± 7.23)	-1.5 (± 7.68)		
Change from BL at Cycle 72 (n=18,12)	-3.0 (± 4.97)	-1.0 (± 5.75)		
Change from BL at Cycle 75 (n=17,12)	-3.3 (± 6.59)	-1.1 (± 6.97)		
Change from BL at Cycle 78 (n=17,9)	-3.3 (± 5.58)	-1.1 (± 7.82)		
Change from BL at Cycle 81 (n=17,9)	-2.9 (± 6.83)	-2.6 (± 6.00)		
Change from BL at Cycle 84 (n=15,9)	-2.5 (± 7.66)	-4.5 (± 3.59)		
Change from BL at Cycle 87 (n=15,8)	-3.8 (± 5.76)	-1.4 (± 5.12)		
Change from BL at Cycle 90 (n=16,7)	-2.4 (± 7.69)	0.4 (± 6.77)		
Change from BL at Cycle 93 (n=14,7)	-1.8 (± 6.57)	-3.9 (± 6.00)		
Change from BL at Cycle 96 (n=12,7)	-0.7 (± 7.45)	-3.2 (± 5.50)		
Change from BL at Cycle 99 (n=11,7)	-3.4 (± 5.78)	-2.8 (± 8.41)		
Change from BL at Cycle 102 (n=13,5)	-1.3 (± 6.12)	-1.6 (± 9.68)		
Change from BL at Cycle 105 (n=12,3)	-0.4 (± 7.05)	-2.0 (± 12.17)		
Change from BL at Cycle 108 (n=9,3)	-3.4 (± 5.32)	-3.3 (± 8.33)		
Change from BL at Cycle 111 (n=4,1)	-6.3 (± 5.91)	-5.5 (± 999999)		
Change from BL at Cycle 114 (n=4,1)	-4.0 (± 5.35)	9999999 (± 9999999)		
Change from BL at Cycle 117 (n=1,0)	-11.0 (± 999999)	9999999 (± 9999999)		
Change from BL at Cycle 120 (n=1,0)	-11.0 (± 999999)	9999999 (± 9999999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until end of post-treatment follow-up (up to 89 months)

Adverse event reporting additional description:

All adverse events that occurred during the study and until the post-treatment safety follow-up visit approximately 28 days after last study medication were to be recorded. Thereafter, only serious adverse events thought to be related to study drug were collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy

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 +/- Chemotherapy

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 +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 127 (36.22%)	28 / 124 (22.58%)	
number of deaths (all causes)	62	57	
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	
High-grade 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 / 1	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	
Tumour exudation			
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	
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	
Sudden death			
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 / 1	
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	2 / 127 (1.57%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	1 / 2	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	
Painful respiration			
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	
Confusional state			

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	
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	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	
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	
Fall			
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	4 / 127 (3.15%)	0 / 124 (0.00%)	
occurrences causally related to treatment / all	4 / 4	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	
Myocardial infarction			
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	
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	
Spinal cord compression			
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	2 / 127 (1.57%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 127 (1.57%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
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	
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	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	
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	0 / 127 (0.00%)	2 / 124 (1.61%)	
occurrences causally related to treatment / all	0 / 0	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%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
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	6 / 127 (4.72%)	1 / 124 (0.81%)	
occurrences causally related to treatment / all	1 / 7	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	
Vascular device 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	
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	
Dehydration			

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	

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

Non-serious adverse events	Arm A: Pertuzumab + Trastuzumab + AI +/- Chemotherapy	Arm B: Trastuzumab + AI +/- Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 127 (94.49%)	116 / 124 (93.55%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	9 / 127 (7.09%)	9 / 124 (7.26%)	
occurrences (all)	14	17	
Hypertension			
subjects affected / exposed	22 / 127 (17.32%)	24 / 124 (19.35%)	
occurrences (all)	54	65	
Lymphoedema			
subjects affected / exposed	7 / 127 (5.51%)	5 / 124 (4.03%)	
occurrences (all)	10	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 127 (30.71%)	32 / 124 (25.81%)	
occurrences (all)	76	77	
Chest pain			
subjects affected / exposed	9 / 127 (7.09%)	9 / 124 (7.26%)	
occurrences (all)	11	11	
Chills			
subjects affected / exposed	8 / 127 (6.30%)	7 / 124 (5.65%)	
occurrences (all)	8	8	
Fatigue			
subjects affected / exposed	21 / 127 (16.54%)	25 / 124 (20.16%)	
occurrences (all)	33	43	
Influenza like illness			

subjects affected / exposed	10 / 127 (7.87%)	7 / 124 (5.65%)	
occurrences (all)	17	10	
Mucosal inflammation			
subjects affected / exposed	14 / 127 (11.02%)	13 / 124 (10.48%)	
occurrences (all)	20	15	
Oedema peripheral			
subjects affected / exposed	34 / 127 (26.77%)	23 / 124 (18.55%)	
occurrences (all)	53	34	
Pyrexia			
subjects affected / exposed	17 / 127 (13.39%)	13 / 124 (10.48%)	
occurrences (all)	22	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 127 (19.69%)	18 / 124 (14.52%)	
occurrences (all)	36	27	
Dyspnoea			
subjects affected / exposed	20 / 127 (15.75%)	13 / 124 (10.48%)	
occurrences (all)	22	17	
Epistaxis			
subjects affected / exposed	14 / 127 (11.02%)	13 / 124 (10.48%)	
occurrences (all)	18	20	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	14 / 127 (11.02%)	5 / 124 (4.03%)	
occurrences (all)	15	6	
Depression			
subjects affected / exposed	13 / 127 (10.24%)	5 / 124 (4.03%)	
occurrences (all)	14	6	
Insomnia			
subjects affected / exposed	15 / 127 (11.81%)	18 / 124 (14.52%)	
occurrences (all)	18	23	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	13 / 127 (10.24%)	8 / 124 (6.45%)	
occurrences (all)	19	9	
Weight decreased			

subjects affected / exposed	14 / 127 (11.02%)	11 / 124 (8.87%)	
occurrences (all)	16	12	
Weight increased			
subjects affected / exposed	11 / 127 (8.66%)	5 / 124 (4.03%)	
occurrences (all)	13	10	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 127 (16.54%)	12 / 124 (9.68%)	
occurrences (all)	32	12	
Headache			
subjects affected / exposed	22 / 127 (17.32%)	14 / 124 (11.29%)	
occurrences (all)	33	24	
Neuropathy peripheral			
subjects affected / exposed	18 / 127 (14.17%)	17 / 124 (13.71%)	
occurrences (all)	26	19	
Paraesthesia			
subjects affected / exposed	13 / 127 (10.24%)	11 / 124 (8.87%)	
occurrences (all)	19	13	
Peripheral sensory neropathy			
subjects affected / exposed	10 / 127 (7.87%)	9 / 124 (7.26%)	
occurrences (all)	12	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 127 (22.05%)	18 / 124 (14.52%)	
occurrences (all)	53	30	
Neutropenia			
subjects affected / exposed	11 / 127 (8.66%)	13 / 124 (10.48%)	
occurrences (all)	14	23	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	9 / 127 (7.09%)	7 / 124 (5.65%)	
occurrences (all)	9	8	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 127 (7.87%)	16 / 124 (12.90%)	
occurrences (all)	11	18	
Abdominal pain upper			

subjects affected / exposed	12 / 127 (9.45%)	6 / 124 (4.84%)	
occurrences (all)	17	6	
Constipation			
subjects affected / exposed	18 / 127 (14.17%)	19 / 124 (15.32%)	
occurrences (all)	27	25	
Diarrhoea			
subjects affected / exposed	70 / 127 (55.12%)	45 / 124 (36.29%)	
occurrences (all)	213	88	
Dyspepsia			
subjects affected / exposed	8 / 127 (6.30%)	9 / 124 (7.26%)	
occurrences (all)	9	11	
Nausea			
subjects affected / exposed	47 / 127 (37.01%)	34 / 124 (27.42%)	
occurrences (all)	68	56	
Stomatitis			
subjects affected / exposed	17 / 127 (13.39%)	11 / 124 (8.87%)	
occurrences (all)	24	22	
Vomiting			
subjects affected / exposed	31 / 127 (24.41%)	21 / 124 (16.94%)	
occurrences (all)	42	33	
Haemorrhoids			
subjects affected / exposed	7 / 127 (5.51%)	2 / 124 (1.61%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	38 / 127 (29.92%)	40 / 124 (32.26%)	
occurrences (all)	40	50	
Dry skin			
subjects affected / exposed	8 / 127 (6.30%)	6 / 124 (4.84%)	
occurrences (all)	10	7	
Nail disorder			
subjects affected / exposed	9 / 127 (7.09%)	5 / 124 (4.03%)	
occurrences (all)	13	7	
Pruritus			
subjects affected / exposed	20 / 127 (15.75%)	14 / 124 (11.29%)	
occurrences (all)	42	19	

Rash			
subjects affected / exposed	23 / 127 (18.11%)	12 / 124 (9.68%)	
occurrences (all)	35	17	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	9 / 127 (7.09%)	2 / 124 (1.61%)	
occurrences (all)	14	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	38 / 127 (29.92%)	31 / 124 (25.00%)	
occurrences (all)	60	49	
Back pain			
subjects affected / exposed	23 / 127 (18.11%)	21 / 124 (16.94%)	
occurrences (all)	29	27	
Bone pain			
subjects affected / exposed	16 / 127 (12.60%)	10 / 124 (8.06%)	
occurrences (all)	25	12	
Muscle spasms			
subjects affected / exposed	14 / 127 (11.02%)	5 / 124 (4.03%)	
occurrences (all)	17	6	
Musculoskeletal chest pain			
subjects affected / exposed	11 / 127 (8.66%)	4 / 124 (3.23%)	
occurrences (all)	13	6	
Musculoskeletal pain			
subjects affected / exposed	11 / 127 (8.66%)	6 / 124 (4.84%)	
occurrences (all)	11	8	
Myalgia			
subjects affected / exposed	12 / 127 (9.45%)	9 / 124 (7.26%)	
occurrences (all)	16	9	
Pain in extremity			
subjects affected / exposed	22 / 127 (17.32%)	16 / 124 (12.90%)	
occurrences (all)	44	23	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 127 (10.24%)	7 / 124 (5.65%)	
occurrences (all)	21	8	

Upper respiratory tract infection			
subjects affected / exposed	13 / 127 (10.24%)	15 / 124 (12.10%)	
occurrences (all)	36	23	
Urinary tract infection			
subjects affected / exposed	17 / 127 (13.39%)	16 / 124 (12.90%)	
occurrences (all)	25	20	
Influenza			
subjects affected / exposed	6 / 127 (4.72%)	7 / 124 (5.65%)	
occurrences (all)	10	12	
Paronychia			
subjects affected / exposed	7 / 127 (5.51%)	3 / 124 (2.42%)	
occurrences (all)	12	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 127 (18.11%)	10 / 124 (8.06%)	
occurrences (all)	27	14	
Hyperglycaemia			
subjects affected / exposed	8 / 127 (6.30%)	5 / 124 (4.03%)	
occurrences (all)	17	9	

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