Clinical trial results:
A Phase III, Randomized, Multicenter, Open-Label, Two-Arm Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Subcutaneous Administration of the Fixed-Dose Combination of Pertuzumab and Trastuzumab in Combination With Chemotherapy in Patients With HER2-Positive Early Breast Cancer

Summary

EudraCT number	2017-004897-32
Trial protocol	GB DE ES BE CZ PL IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	10 July 2020
First version publication date	10 July 2020

Trial information

Trial identification

Sponsor protocol code	WO40324

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03493854
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +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	04 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the non-inferiority of the Cycle 7 (pre-dose Cycle 8) serum trough concentration (Ctrough) of pertuzumab by subcutaneous (SC) injection within the pertuzumab and trastuzumab fixed-dose combination (FDC) SC compared with pertuzumab by intravenous (IV) infusion.

Protection of trial subjects:

This study is conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. All participants are required to read and sign an informed consent form prior to participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 8
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Brazil: 27
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 35
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Korea, Republic of: 35
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	Poland: 61
Country: Number of subjects enrolled	Russian Federation: 64
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	Ukraine: 21
Country: Number of subjects enrolled	United Kingdom: 22

Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	500
EEA total number of subjects	243

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)	441
From 65 to 84 years	59
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 607 patients were screened, 500 of whom were randomized.

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 IV + Trastuzumab IV + Chemotherapy

Arm description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab was given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

Arm type	Active comparator
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	Pertuzumab IV; Perjeta
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pertuzumab is administered as a fixed non-weight-based dose of 840-milligram (mg) intravenous (IV) loading dose and then 420-mg IV maintenance dose once every 3 weeks (Q3W).

Investigational medicinal product name	Trastuzumab IV
Investigational medicinal product code	RO0452317
Other name	Herceptin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab is administered as an 8-milligram per kilogram (mg/kg) intravenous (IV) loading dose and then 6-mg/kg IV maintenance dose once every 3 weeks (Q3W).

Investigational medicinal product name	Trastuzumab SC
Investigational medicinal product code	
Other name	Trastuzumab and hyaluronidase-oysk; Herceptin Hylecta
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

After surgery (from Cycle 9 onwards), participants in Arm A will be allowed to switch from trastuzumab intravenous (IV) to trastuzumab subcutaneous (SC), at the discretion of the investigator, in the countries where trastuzumab SC is routinely used. For participants who switch, a fixed dose of 600 mg trastuzumab SC (irrespective of the patient’s weight) will be administered in the adjuvant phase.

Arm title	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy

Arm description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

Arm type	Experimental
Investigational medicinal product name	Fixed dose combination of pertuzumab and trastuzumab
Investigational medicinal product code	RO7198574
Other name	PH FDC SC
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The fixed-dose combinatinon (FDC) of pertuzumab and trastuzumab is administered subcutaneously (SC) at a fixed non-weight-based dose. A loading dose of 1200 mg SC pertuzumab and 600 mg SC trastuzumab is then followed by a maintenance dose of 600 mg SC pertuzumab and 600 mg SC trastuzumab once every 3 weeks (Q3W).

Number of subjects in period 1	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy
Started	252	248
Received at Least One Dose of Study Drug	252	248
Completed Neoadjuvant Phase	242	234
Completed Surgery	239	234
Completed Adjuvant Treatment Phase	0	0
Started Treatment-Free Follow-Up	19	17
Completed	0	0
Not completed	252	248
Adverse event, serious fatal	1	1
Consent withdrawn by subject	4	3
Ongoing Adjuvant Treatment	229	228
Ongoing in Follow-Up	18	16

Baseline characteristics

Reporting groups

Reporting group title	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab was given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

Reporting group title	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

Reporting group values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy	Total
Number of subjects	252	248	500
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	219	222	441
From 65-84 years	33	26	59
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	50.3	51.7	
standard deviation	± 10.8	± 10.7	-
Sex: Female, Male Units: Participants			
Female	250	248	498
Male	2	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	32	42	74
Not Hispanic or Latino	200	189	389

Unknown or Not Reported	20	17	37
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	10	10	20
Asian	54	51	105
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	164	165	329
More than one race	2	3	5
Unknown or Not Reported	19	16	35
Randomization Stratification Factors: Hormone Receptor Status			
Hormone receptor status was based on central assessment of participant samples for estrogen receptor (ER) and progesterone receptor (PgR) negativity or positivity.			
Units: Subjects			
ER Negative and PgR Negative	97	96	193
ER Positive and PgR Positive	155	151	306
Unknown	0	1	1
Randomization Stratification Factors: Clinical Stage at Presentation Units: Subjects			
Stage II-IIIA	201	198	399
Stage IIIB-IIIC	51	50	101
Randomization Stratification Factors: Neoadjuvant Chemotherapy Regimen			
AC = doxorubicin plus cyclophosphamide; ddAC = dose-dense doxorubicin plus cyclophosphamide			
Units: Subjects			
ddAC Followed by Paclitaxel	120	120	240
AC Followed by Docetaxel	132	128	260

End points

End points reporting groups

Reporting group title	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab was given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

Reporting group title	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

Primary: Trough Serum Concentration (Ctrough) of Pertuzumab During Cycle 7 (Pre-Dose Cycle 8)

End point title	Trough Serum Concentration (Ctrough) of Pertuzumab During Cycle 7 (Pre-Dose Cycle 8)

End point description:

The observed pertuzumab trough serum concentration (Ctrough) at Cycle 7 was assessed following 3 cycles of pertuzumab IV and trastuzumab IV or the fixed-dose combination (FDC) of pertuzumab and trastuzumab SC. The Per Protocol Pharmacokinetics (PK) analysis population includes all enrolled participants who adhered to the protocol. Exclusions from the Per Protocol PK analysis population were made for the following reasons: participants were missing the Ctrough pre-dose Cycle 8 PK sample, participants with a Ctrough sample collected with at least 2 days deviation from the planned date on Day 21 (i.e., before Day 19 or after Day 23), participants given a dose amount that deviated from the planned dose by >20% within 3 cycles (from Cycle 5), participants with a dose delay of more than 7 days, a subcutaneous injection site other than thigh was used, if the Cycle 8 pre-dose and post-dose samples were switched, and an assay error impacting Ctrough measurement.

End point type	Primary

End point timeframe:

Pre-dose on Cycle 8, Day 1 (up to 21 weeks)

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[1]	206[2]		
Units: micrograms per millilitre (µg/mL)				
geometric mean (geometric coefficient	72.4 (± 34.1)	88.7 (± 33.6)		

of variation)

Notes:

[1] - Per Protocol PK analysis population

[2] - Per Protocol PK analysis population

Statistical analyses

Statistical analysis title	Non-inferiority of Ctrough Pertuzumab SC vs. IV

Statistical analysis description:

The null hypothesis was that the pertuzumab Arm A SC dose is inferior to the pertuzumab Arm B IV dose (i.e., the CtroughSC/CtroughIV geometric mean ratio of the SC dose of pertuzumab relative to the IV dose is not greater than 0.8).

Comparison groups	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric Mean Ratio
Point estimate	1.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.14
upper limit	1.31

Secondary: Ctrough of Trastuzumab During Cycle 7 (Pre-Dose Cycle 8)

End point title	Ctrough of Trastuzumab During Cycle 7 (Pre-Dose Cycle 8)

End point description:

The observed trastuzumab trough serum concentration (Ctrough) at Cycle 7 was assessed following 3 cycles of pertuzumab IV and trastuzumab IV or the fixed-dose combination (FDC) of pertuzumab and trastuzumab SC. The Per Protocol Pharmacokinetics (PK) analysis population includes all enrolled participants who adhered to the protocol. Exclusions from the Per Protocol PK analysis population were made for the following reasons: participants were missing the Ctrough pre-dose Cycle 8 PK sample, participants with a Ctrough sample collected with at least 2 days deviation from the planned date on Day 21 (i.e., before Day 19 or after Day 23), participants given a dose amount that deviated from the planned dose by >20% within 3 cycles (from Cycle 5), participants with a dose delay of more than 7 days, a subcutaneous injection site other than thigh was used, if the Cycle 8 pre-dose and post-dose samples were switched, and an assay error impacting Ctrough measurement.

End point type	Secondary

End point timeframe:

Pre-dose on Cycle 8, Day 1 (up to 21 weeks)

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[3]	206[4]		
Units: micrograms per milllilitre (µg/mL)				
geometric mean (geometric coefficient of variation)	44.1 (± 34.9)	58.7 (± 37.0)		

Notes:

[3] - Per Protocol PK analysis population

[4] - Per Protocol PK analysis population

Statistical analyses

Statistical analysis title	Non-inferiority of Ctrough Trastuzumab SC vs. IV

Statistical analysis description:

The null hypothesis was that the trastuzumab Arm B SC dose is inferior to the Arm A trastuzumab IV dose (i.e., the CtroughSC/CtroughIV geometric mean ratio of the SC dose of trastuzumab relative to the IV dose is not greater than 0.8).

Comparison groups	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric Mean Ratio
Point estimate	1.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.24
upper limit	1.43

Secondary: Percentage of Participants with Total Pathological Complete Response (tpCR), According to Local Pathologist Assessment

End point title	Percentage of Participants with Total Pathological Complete Response (tpCR), According to Local Pathologist Assessment

End point description:

Total pCR (tpCR) was defined as eradication of invasive disease in the breast and axilla; that is, ypT0/is ypN0, according to the local pathologists' assessment. Pathologic response to therapy was determined at the time of surgery. The tpCR rate is the percentage of participants in the ITT population who achieved a tpCR. Participants with missing data for tpCR (i.e., do not undergo surgery or have an invalid pCR assessment) were included in the analysis and classified as non-responders. Rates of tpCR were calculated in each treatment arm and were assessed using the difference between the Arm B: Pertuzumab and Trastuzumab FDC SC and the Arm A: Pertuzumab IV and Trastuzumab IV tpCR rates and corresponding 95% Clopper-Pearson confidence intervals (CIs). The difference between the tpCR rates along with corresponding 95% Hauck-Anderson CIs were calculated. The lower bound of the CI will reliably reflect the largest tpCR difference that can be considered unlikely.

End point type	Secondary

End point timeframe:

Following completion of surgery (up to 33 weeks)

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	248		
Units: Percentage of participants				
number (confidence interval 95%)	59.5 (53.2 to 65.6)	59.7 (53.3 to 65.8)		

Statistical analyses

Statistical analysis title	Difference in tpCR Rates SC vs. IV
Comparison groups	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in tpCR Rate
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.67
upper limit	8.97

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Invasive Disease-Free Survival (iDFS; Excluding Second Primary Non-Breast Cancer [SPNBC]) Criteria

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Invasive Disease-Free Survival (iDFS; Excluding Second Primary Non-Breast Cancer [SPNBC]) Criteria

End point description:

iDFS (excluding SPNBC) is defined as the time from the first date of no disease (i.e., the date of primary surgery) to the first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence; ipsilateral local-regional invasive breast cancer reccurrence; distant recurrence; contralateral invasive breast cancer; or death attributable to any cause. Ipsilateral or contralateral in situ disease and SPNBC (including in situ carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or relapse.

End point type	Secondary

End point timeframe:

Up to 5.5 years

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[5] - There are no results to report at this time because data collection is ongoing.

[6] - There are no results to report at this time because data collection is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to iDFS (Including SPNBC) Criteria

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to iDFS (Including SPNBC) Criteria

End point description:

Invasive disease-free survival (iDFS) including second primary non-breast cancer (SPNBC) is defined as the time from the first date of no disease (i.e., the date of primary surgery) to the first occurrence of one of the following events: ipsilateral invasive breast tumor recurrence; ipsilateral local-regional invasive breast cancer reccurrence; distant recurrence; contralateral invasive breast cancer; or death attributable to any cause. It also includes SPNBC as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site).

End point type	Secondary

End point timeframe:

Up to 5.5 years

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[7] - There are no results to report at this time because data collection is ongoing.

[8] - There are no results to report at this time because data collection is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Event-Free Survival (EFS; Excluding SPNBC) Criteria

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Event-Free Survival (EFS; Excluding SPNBC) Criteria

End point description:

Event-free survival (EFS) excluding second primary non-breast cancer (SPNBC) is defined as the time from enrollment to the first occurrence of one of the following events: breast cancer progression; breast cancer recurrence; or death from any cause. Ipsilateral or contralateral in situ disease and SPNBC (including in situ carcinomas and non-melanoma skin cancers) will not be counted as progressive disease or relapse.

End point type	Secondary

End point timeframe:

Up to 5.5 years

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[9] - There are no results to report at this time because data collection is ongoing.

[10] - There are no results to report at this time because data collection is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to EFS (Including SPNBC) Criteria

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to EFS (Including SPNBC) Criteria

End point description:

Event-free survival (EFS) including second primary non-breast cancer (SPNBC) is defined as the time from enrollment to the first occurrence of one of the following events: breast cancer progression; breast cancer recurrence; or death from any cause. It also includes SPNBC as an event (with the exception of non-melanoma skin cancers and in situ carcinoma of any site).

End point type	Secondary

End point timeframe:

Up to 5.5 years

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[11] - There are no results to report at this time because data collection is ongoing.

[12] - There are no results to report at this time because data collection is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Distant Recurrence-Free Interval (DRFI) Criteria

End point title	Kaplan-Meier Estimate of the Percentage of Participants Who Are Event-Free According to Distant Recurrence-Free Interval (DRFI) Criteria

End point description:

The distant recurrence-free interval (DRFI) is defined as the time between randomization and the date of distant breast cancer recurrence.

End point type	Secondary

End point timeframe:

Up to 5.5 years

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[13] - There are no results to report at this time because data collection is ongoing.

[14] - There are no results to report at this time because data collection is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants in Overall Survival

End point title	Kaplan-Meier Estimate of the Percentage of Participants in Overall Survival

End point description:

Overall survival is defined as the time from randomization to death from any cause.

End point type	Secondary

End point timeframe:

Up to 5.5 years

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: Percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[15] - There are no results to report at this time because data collection is ongoing.

[16] - There are no results to report at this time because data collection is ongoing.

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Summary of the Number of Participants With at Least One Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (NCI CTCAE v4)

End point title	Safety Summary of the Number of Participants With at Least One Adverse Event, Severity Determined According to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (NCI CTCAE v4)

End point description:

The adverse event (AE) severity grading scale for the NCI CTCAE v4.0 was used for assessing AE severity. Any AEs that were not specifically listed in the NCI CTCAE, v4.0 were graded per the following 5 grades: Grade 1 = mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated. Grade 2 = moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living. Grade 3 = severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. Grade 4 = life-threatening consequences or urgent intervention indicated. Grade 5 = death related to AE. The terms "severe" and "serious" are not synonymous and are independently assessed for each AE. Multiple occurrences of AEs were counted only once per participant at the highest (worst) grade.

End point type	Secondary

End point timeframe:

From Baseline until 28 days after last dose of study drug; up to the primary completion date (up to 1 year, 1 month)

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	248		

Units: Participants				
Any Adverse Event (AE): Any Grade	251	248		
Any AE: Grade 1	11	9		
Any AE: Grade 2	107	118		
Any AE: Grade 3	87	79		
Any AE: Grade 4	45	41		
Any AE: Grade 5	1	1		
Any AE: Grades 3 to 5	133	121		
Any Serious AE	45	40		
Anaphylaxis and Hypersensitivity AEs	5	4		
Infusion/Admin.-Related Reactions Within 24 hrs	34	43		
Serious Rash/Skin Reactions	0	1		
Diarrhoea	139	145		
Cardiac Dysfunction	41	41		
Interstitial Lung Disease	2	3		
Neutropenia/Febrile Neutropenia	133	119		
Serious Mucositis	4	3		
Pregnancy- and Neonatal-Related AEs	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Primary Cardiac Event

End point title	Number of Participants With a Primary Cardiac Event

End point description:

A primary cardiac event is defined as the occurrence of either of the following events: - Incidence of a symptomatic ejection fraction decrease (heart failure) of New York Heart Association (NYHA) Class III or IV and a drop in left ventricular ejection fraction (LVEF) of at least 10-percentage points from baseline and to below 50%; or - Cardiac death, defined as: Definite cardiac death (due to heart failure, myocardial infarction, or documented primary arrhythmia); or, Probable cardiac death (sudden unexpected death within 24 hours of a definite or probable cardiac event [e.g., syncope, cardiac arrest, chest pain, infarction, arrhythmia] without documented etiology).

End point type	Secondary

End point timeframe:

From Baseline until 28 days after last dose of study drug; up to the primary completion date (up to 1 year, 1 month)

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	248		
Units: Participants				
Any Primary Cardiac Event	0	2		

Heart Failure and Significant LVEF Decline	0	1		
Cardiac Death (Definite or Probable)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Secondary Cardiac Event

End point title	Number of Participants With a Secondary Cardiac Event

End point description:

A secondary cardiac event is defined as asymptomatic or mildly symptomatic Left Ventricular Systolic Dysfunction (LVSD) of NYHA Class II, defined as a left ventricular ejection fraction (LVEF) decrease of at least 10-percentage points below the baseline measurement to an absolute LVEF value of <50% confirmed by a second assessment within approximately 3 weeks

End point type	Secondary

End point timeframe:

From Baseline until 28 days after last dose of study drug; up to the primary completion date (up to 1 year, 1 month)

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	248		
Units: Participants				
Any Secondary Cardiac Event	9	4		
Identified by Initial LVEF Assessments	9	4		
Confirmed by Second LVEF Assessment	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Laboratory Test Abnormalities at the Highest NCI CTCAE v4 Grade Post-Baseline

End point title	Number of Participants with Laboratory Test Abnormalities at the Highest NCI CTCAE v4 Grade Post-Baseline

End point description:

Clinical laboratory tests were performed at local laboratories; any abnormal values (High or Low) were based on local laboratory normal ranges. Laboratory abnormalities are presented by the highest (worst) severity grade (according to NCI-CTCAE v4.0) post-baseline. Not every abnormal laboratory value qualified as an adverse event, only if it met any of the following criteria: clinically significant (per investigator); accompanied by clinical symptoms; resulted in a change in study treatment; or required a medical intervention or a change in concomitant therapy. For a participant with multiple post-baseline

abnormalities, only the highest (worst) grade for a given laboratory test is reported. 'Any Grade' indicates the total number of participants with a post-baseline abnormality of any grade for the specified test. Abs. = absolute count; SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate transaminase; SGPT/ALT = serum glutamic-pyruvic transaminase/alanine transaminase

End point type	Secondary

End point timeframe:

Day 1 of Cycles 1 to 8 (up to 21 weeks)

End point values	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	248		
Units: Participants				
Albumin, Low - Any Grade	49	39		
Albumin, Low - Grade 1	40	34		
Albumin, Low - Grade 2	8	5		
Albumin, Low - Grade 3	1	0		
Alkaline Phosphatase, High - Any Grade	34	41		
Alkaline Phosphatase, High - Grade 1	32	40		
Alkaline Phosphatase, High - Grade 2	2	1		
SGPT/ALT, High - Any Grade	166	138		
SGPT/ALT, High - Grade 1	146	123		
SGPT/ALT, High - Grade 2	14	12		
SGPT/ALT, High - Grade 3	6	3		
SGOT/AST, High - Any Grade	137	113		
SGOT/AST, High - Grade 1	129	110		
SGOT/AST, High - Grade 2	6	1		
SGOT/AST, High - Grade 3	2	2		
Creatinine, High - Any Grade	193	194		
Creatinine, High - Grade 1	187	186		
Creatinine, High - Grade 2	5	8		
Creatinine, High - Grade 3	1	0		
Glucose, Low - Any Grade	22	21		
Glucose, Low - Grade 1	18	21		
Glucose, Low - Grade 2	3	0		
Glucose, Low - Grade 3	1	0		
Glucose, High - Any Grade	3	4		
Glucose, High - Grade 3	3	4		
Hemoglobin, Low - Any Grade	231	220		
Hemoglobin, Low - Grade 1	131	138		
Hemoglobin, Low - Grade 2	90	76		
Hemoglobin, Low - Grade 3	10	6		
Hemoglobin, High - Any Grade	10	4		
Hemoglobin, High - Grade 1	10	4		
Lymphocytes, Abs., Low - Any Grade	140	138		
Lymphocytes, Abs., Low - Grade 1	29	19		
Lymphocytes, Abs., Low - Grade 2	59	67		

Lymphocytes, Abs., Low - Grade 3	45	48		
Lymphocytes, Abs., Low - Grade 4	7	4		
Lymphocytes, Abs., High - Any Grade	3	3		
Lymphocytes, Abs., High - Grade 1	3	3		
Neutrophils, Total, Abs., Low - Any Grade	108	106		
Neutrophils, Total, Abs., Low - Grade 1	27	35		
Neutrophils, Total, Abs., Low - Grade 2	29	22		
Neutrophils, Total, Abs., Low - Grade 3	16	24		
Neutrophils, Total, Abs., Low - Grade 4	36	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until 28 days after last dose of study drug; up to the primary completion date (up to 1 year, 1 month)

Adverse event reporting additional description:

After informed consent but prior to first dose, only serious adverse events (AEs) caused by protocol-mandated intervention were reported. After initiation of study drug, all AEs were reported until 28 days after the last dose of study drug. After this period, only drug-related serious AEs, heart failure, pregnancies, and malignancies were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of ddAC Q2W (given with G-CSF support as needed according to local guidelines) followed by paclitaxel once every week (QW) for 12 weeks; or 2) 4 cycles of AC Q3W followed by docetaxel Q3W for 4 cycles. The fixed-dose combination (FDC) of pertuzumab and trastuzumab was given subcutaneously (SC) for 4 cycles (Q3W) concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of the FDC of pertuzumab and trastuzumab SC for a total of 18 cycles.

Reporting group title	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy

Reporting group description:

Participants received 8 cycles of investigator's choice of neoadjuvant chemotherapy. This included either: 1) 4 cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) once every 2 weeks (Q2W) (given with granulocyte colony-stimulating factor [G-CSF] support as needed according to local guidelines) followed by paclitaxel QW for 12 weeks; or 2) 4 cycles of doxorubicin plus cyclophosphamide (AC) once every 3 weeks (Q3W) followed by docetaxel Q3W for 4 cycles. Pertuzumab and trastuzumab were given intravenously (IV) for 4 cycles Q3W concurrently with the taxane component of chemotherapy. After completing their neoadjuvant therapy, participants underwent surgery. Thereafter, participants received an additional 14 cycles of pertuzumab IV and trastuzumab IV for a total of 18 cycles.

Serious adverse events	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 248 (16.13%)	45 / 252 (17.86%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
RENAL CELL CARCINOMA			

subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
EMBOLISM			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILIAC ARTERY OCCLUSION			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
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 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LITHIASIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

MUCOSAL INFLAMMATION			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	2 / 248 (0.81%)	4 / 252 (1.59%)	
occurrences causally related to treatment / all	1 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
BREAST HAEMATOMA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST INFLAMMATION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METRORRHAGIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			

subjects affected / exposed	2 / 248 (0.81%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 248 (0.81%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (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	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
CLOSTRIDIUM TEST POSITIVE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	3 / 248 (1.21%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (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			
FEMUR FRACTURE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLAP NECROSIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION RELATED REACTION			
subjects affected / exposed	0 / 248 (0.00%)	3 / 252 (1.19%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ARRHYTHMIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	2 / 248 (0.81%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
SEIZURE			
subjects affected / exposed	1 / 248 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 248 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	9 / 248 (3.63%)	10 / 252 (3.97%)	
occurrences causally related to treatment / all	9 / 9	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 248 (0.40%)	3 / 252 (1.19%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL INCONTINENCE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	1 / 248 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			

subjects affected / exposed	1 / 248 (0.40%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS HAEMORRHAGIC			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL TOXICITY			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ERYTHEMA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL FAILURE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
GOITRE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
PERIOSTITIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ANAL ABSCESS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	1 / 248 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA BACTERAEMIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 248 (0.40%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (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	1 / 248 (0.40%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	3 / 248 (1.21%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGITIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 248 (0.00%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAS INFECTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 252 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			

subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 248 (0.40%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	248 / 248 (100.00%)	250 / 252 (99.21%)	
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	19 / 248 (7.66%)	26 / 252 (10.32%)	
occurrences (all)	19	26	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	70 / 248 (28.23%)	76 / 252 (30.16%)	
occurrences (all)	131	122	
FATIGUE			
subjects affected / exposed	69 / 248 (27.82%)	56 / 252 (22.22%)	
occurrences (all)	98	97	
INJECTION SITE REACTION			
subjects affected / exposed	32 / 248 (12.90%)	2 / 252 (0.79%)	
occurrences (all)	63	2	
MALAISE			

subjects affected / exposed	15 / 248 (6.05%)	13 / 252 (5.16%)	
occurrences (all)	21	18	
MUCOSAL INFLAMMATION			
subjects affected / exposed	36 / 248 (14.52%)	48 / 252 (19.05%)	
occurrences (all)	47	65	
OEDEMA PERIPHERAL			
subjects affected / exposed	17 / 248 (6.85%)	20 / 252 (7.94%)	
occurrences (all)	19	21	
PYREXIA			
subjects affected / exposed	28 / 248 (11.29%)	35 / 252 (13.89%)	
occurrences (all)	35	44	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	33 / 248 (13.31%)	30 / 252 (11.90%)	
occurrences (all)	34	30	
DYSPNOEA			
subjects affected / exposed	24 / 248 (9.68%)	11 / 252 (4.37%)	
occurrences (all)	25	13	
EPISTAXIS			
subjects affected / exposed	27 / 248 (10.89%)	34 / 252 (13.49%)	
occurrences (all)	31	39	
RHINORRHOEA			
subjects affected / exposed	14 / 248 (5.65%)	9 / 252 (3.57%)	
occurrences (all)	15	10	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	37 / 248 (14.92%)	28 / 252 (11.11%)	
occurrences (all)	40	33	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	35 / 248 (14.11%)	48 / 252 (19.05%)	
occurrences (all)	40	55	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	26 / 248 (10.48%)	37 / 252 (14.68%)	
occurrences (all)	31	45	

EJECTION FRACTION DECREASED			
subjects affected / exposed	9 / 248 (3.63%)	14 / 252 (5.56%)	
occurrences (all)	9	15	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	40 / 248 (16.13%)	49 / 252 (19.44%)	
occurrences (all)	85	108	
WEIGHT DECREASED			
subjects affected / exposed	23 / 248 (9.27%)	13 / 252 (5.16%)	
occurrences (all)	24	13	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	16 / 248 (6.45%)	31 / 252 (12.30%)	
occurrences (all)	49	77	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	9 / 248 (3.63%)	32 / 252 (12.70%)	
occurrences (all)	9	47	
PROCEDURAL PAIN			
subjects affected / exposed	30 / 248 (12.10%)	23 / 252 (9.13%)	
occurrences (all)	30	24	
RADIATION SKIN INJURY			
subjects affected / exposed	20 / 248 (8.06%)	18 / 252 (7.14%)	
occurrences (all)	20	18	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	21 / 248 (8.47%)	22 / 252 (8.73%)	
occurrences (all)	23	27	
DYSGEUSIA			
subjects affected / exposed	41 / 248 (16.53%)	35 / 252 (13.89%)	
occurrences (all)	51	42	
HEADACHE			
subjects affected / exposed	36 / 248 (14.52%)	50 / 252 (19.84%)	
occurrences (all)	58	58	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	28 / 248 (11.29%)	31 / 252 (12.30%)	
occurrences (all)	31	40	
PARAESTHESIA			

subjects affected / exposed	22 / 248 (8.87%)	19 / 252 (7.54%)	
occurrences (all)	27	22	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	38 / 248 (15.32%)	34 / 252 (13.49%)	
occurrences (all)	39	37	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	83 / 248 (33.47%)	103 / 252 (40.87%)	
occurrences (all)	99	129	
LEUKOPENIA			
subjects affected / exposed	18 / 248 (7.26%)	34 / 252 (13.49%)	
occurrences (all)	25	47	
NEUTROPENIA			
subjects affected / exposed	51 / 248 (20.56%)	61 / 252 (24.21%)	
occurrences (all)	85	106	
Eye disorders			
DRY EYE			
subjects affected / exposed	13 / 248 (5.24%)	8 / 252 (3.17%)	
occurrences (all)	13	9	
LACRIMATION INCREASED			
subjects affected / exposed	13 / 248 (5.24%)	13 / 252 (5.16%)	
occurrences (all)	14	13	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	18 / 248 (7.26%)	13 / 252 (5.16%)	
occurrences (all)	22	15	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	18 / 248 (7.26%)	14 / 252 (5.56%)	
occurrences (all)	25	17	
CONSTIPATION			
subjects affected / exposed	54 / 248 (21.77%)	52 / 252 (20.63%)	
occurrences (all)	67	66	
DIARRHOEA			
subjects affected / exposed	144 / 248 (58.06%)	138 / 252 (54.76%)	
occurrences (all)	235	256	
DYSPEPSIA			

subjects affected / exposed	31 / 248 (12.50%)	26 / 252 (10.32%)	
occurrences (all)	36	29	
HAEMORRHOIDS			
subjects affected / exposed	21 / 248 (8.47%)	9 / 252 (3.57%)	
occurrences (all)	21	9	
NAUSEA			
subjects affected / exposed	146 / 248 (58.87%)	152 / 252 (60.32%)	
occurrences (all)	274	301	
STOMATITIS			
subjects affected / exposed	62 / 248 (25.00%)	60 / 252 (23.81%)	
occurrences (all)	84	84	
VOMITING			
subjects affected / exposed	48 / 248 (19.35%)	45 / 252 (17.86%)	
occurrences (all)	66	64	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	191 / 248 (77.02%)	177 / 252 (70.24%)	
occurrences (all)	191	179	
DERMATITIS			
subjects affected / exposed	16 / 248 (6.45%)	11 / 252 (4.37%)	
occurrences (all)	16	11	
DRY SKIN			
subjects affected / exposed	33 / 248 (13.31%)	31 / 252 (12.30%)	
occurrences (all)	34	33	
ERYTHEMA			
subjects affected / exposed	15 / 248 (6.05%)	12 / 252 (4.76%)	
occurrences (all)	17	12	
NAIL DISCOLOURATION			
subjects affected / exposed	22 / 248 (8.87%)	16 / 252 (6.35%)	
occurrences (all)	22	16	
NAIL DISORDER			
subjects affected / exposed	15 / 248 (6.05%)	14 / 252 (5.56%)	
occurrences (all)	16	14	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			

subjects affected / exposed	15 / 248 (6.05%)	12 / 252 (4.76%)	
occurrences (all)	15	12	
PRURITUS			
subjects affected / exposed	8 / 248 (3.23%)	18 / 252 (7.14%)	
occurrences (all)	10	21	
RASH			
subjects affected / exposed	30 / 248 (12.10%)	44 / 252 (17.46%)	
occurrences (all)	36	55	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	38 / 248 (15.32%)	45 / 252 (17.86%)	
occurrences (all)	44	50	
BACK PAIN			
subjects affected / exposed	19 / 248 (7.66%)	10 / 252 (3.97%)	
occurrences (all)	22	13	
BONE PAIN			
subjects affected / exposed	18 / 248 (7.26%)	11 / 252 (4.37%)	
occurrences (all)	22	16	
MYALGIA			
subjects affected / exposed	53 / 248 (21.37%)	43 / 252 (17.06%)	
occurrences (all)	61	52	
PAIN IN EXTREMITY			
subjects affected / exposed	13 / 248 (5.24%)	16 / 252 (6.35%)	
occurrences (all)	14	18	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	19 / 248 (7.66%)	21 / 252 (8.33%)	
occurrences (all)	23	21	
PARONYCHIA			
subjects affected / exposed	15 / 248 (6.05%)	6 / 252 (2.38%)	
occurrences (all)	15	6	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	24 / 248 (9.68%)	22 / 252 (8.73%)	
occurrences (all)	27	26	
URINARY TRACT INFECTION			

subjects affected / exposed	13 / 248 (5.24%)	12 / 252 (4.76%)	
occurrences (all)	15	15	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	40 / 248 (16.13%)	46 / 252 (18.25%)	
occurrences (all)	45	63	
HYPOKALAEMIA			
subjects affected / exposed	15 / 248 (6.05%)	18 / 252 (7.14%)	
occurrences (all)	15	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2018	Protocol version 2 provided additional clarifications and corrected inconsistencies regarding the inclusion criteria, observation periods following IMPs administration, management of hypersensitivity, tumor staging, PK sampling process, reasons for discontinuation, and LVEF assessments. None of these updates constituted a major change to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported