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	02 June 2023

Results information

Result version number	v4 (current)
This version publication date	18 July 2024
First version publication date	10 July 2020
Version creation reason	

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	Final
Date of interim/final analysis	02 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 June 2023
Was the trial ended prematurely?	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	Czechia: 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	221

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 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.

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).

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	209 [1]	217 [2]
Started Treatment-Free Follow-Up	247	241
Completed	223	219
Not completed	29	29
Consent withdrawn by subject	13	15
Death	12	13
Lost to follow-up	4	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number of subjects represents those who completed adjuvant treatment. Subjects who withdrew prematurely from treatment remained in the study by entering into the follow-up period.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number of subjects represents those who completed adjuvant treatment. Subjects who withdrew prematurely from treatment remained in the study by entering into the follow-up period.

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). The null hypothesis could be rejected and non-inferiority concluded if the lower bound of the 90% confidence interval of the geometric mean ratio was ≥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	non-inferiority[3]
Parameter estimate	Geometric Mean Ratio
Point estimate	1.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.14
upper limit	1.31

Notes:

[3] - The null hypothesis could be rejected and non-inferiority concluded if the lower bound of the 90% confidence interval of the geometric mean ratio was ≥0.8.

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[4]	206[5]		
Units: micrograms per milllilitre (µg/mL)				
geometric mean (geometric coefficient of variation)	43.2 (± 34.7)	57.5 (± 37.0)		

Notes:

[4] - Per Protocol PK analysis population

[5] - 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). The null hypothesis could be rejected and non-inferiority concluded if the lower bound of the 90% confidence interval of the geometric mean ratio was ≥0.8. Non-inferiority was tested in hierarchical order after the primary outcome measure.

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	non-inferiority[6]
Parameter estimate	Geometric Mean Ratio
Point estimate	1.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.24
upper limit	1.43

Notes:

[6] - The null hypothesis could be rejected and non-inferiority concluded if the lower bound of the 90% confidence interval of the geometric mean ratio was ≥0.8. Non-inferiority was tested in hierarchical order after the primary outcome measure, to adjust for multiple statistical testing and control the type I error at one sided 5% significance level.

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	other[7]
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

Notes:

[7] - Descriptive analysis only. tpCR was analyzed outside of a hypothesis-testing framework and according to the methodology outlined in the outcome measure description.

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. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

End point type	Secondary

End point timeframe:

At 1, 2, 3, and 4 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	239[8]	234[9]		
Units: Percentage of participants				
number (confidence interval 95%)				
1 Year (n = 219, 222)	96.07 (93.55 to 98.59)	97.37 (95.30 to 99.45)		
2 Years (n = 208, 205)	92.98 (89.66 to 96.30)	90.75 (86.98 to 94.52)		
3 Years (n = 194, 199)	90.71 (86.93 to 94.50)	89.86 (85.93 to 93.79)		
4 Years (n = 31, 23)	89.60 (85.54 to 93.65)	88.50 (84.34 to 92.66)		

Notes:

[8] - The analysis includes subjects who completed surgery.

[9] - The analysis includes subjects who completed surgery.

Statistical analyses

Statistical analysis title	iDFS - Log Rank
Statistical analysis description: Descriptive analysis only	
Comparison groups	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5216
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.11

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). The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

End point type	Secondary
End point timeframe:	
At 1, 2, 3, and 4 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	239[10]	234[11]		
Units: Percentage of participants				
number (confidence interval 95%)				
1 Year (n = 218, 221)	95.63 (92.99 to 98.28)	96.94 (94.70 to 99.17)		
2 Years (n = 206, 202)	92.10 (88.60 to 95.60)	89.44 (85.44 to 93.43)		
3 Years (n = 191, 196)	89.39 (85.37 to 93.40)	88.54 (84.40 to 92.69)		
4 Years (n = 31, 23)	88.27 (84.01 to 92.53)	87.64 (83.35 to 91.93)		

Notes:

[10] - The analysis includes subjects who completed surgery.

[11] - The analysis includes subjects who completed surgery.

Statistical analyses

Statistical analysis title	iDFS (+SPNBC) - Log Rank
Statistical analysis description:	
Descriptive analysis only	
Comparison groups	Arm A: Pertuzumab IV + Trastuzumab IV + Chemotherapy v Arm B: Pertuzumab and Trastuzumab FDC SC + Chemotherapy
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5992
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.97

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. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

End point type	Secondary

End point timeframe:

At 1, 2, 3, and 4 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	252	248		
Units: Percentage of participants				
number (confidence interval 95%)				
1 Year (n = 237, 235)	96.79 (94.60 to 98.98)	97.95 (96.18 to 99.73)		
2 Years (n = 224, 218)	92.29 (88.96 to 95.62)	91.67 (88.17 to 95.16)		
3 Years (n = 212, 209)	89.77 (85.96 to 93.57)	88.29 (84.21 to 92.37)		
4 Years (n = 191, 198)	88.47 (84.44 to 92.49)	86.57 (82.24 to 90.90)		

Statistical analyses

Statistical analysis title	EFS - Log Rank

Statistical analysis description:

Descriptive analysis only

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	other
P-value	= 0.4844
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.98

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). The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

End point type	Secondary

End point timeframe:

At 1, 2, 3, and 4 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	252	248		
Units: Percentage of participants				
number (confidence interval 95%)				
1 Year (n = 236, 234)	96.38 (94.06 to 98.70)	97.54 (95.59 to 99.48)		
2 Years (n = 222, 215)	91.47 (87.98 to 94.96)	90.41 (86.69 to 94.14)		
3 Years (n = 209, 206)	88.53 (84.52 to 92.53)	87.04 (82.78 to 91.30)		
4 Years (n = 188, 196)	87.22 (83.02 to 91.43)	85.75 (81.31 to 90.18)		

Statistical analyses

Statistical analysis title	EFS (+SPNBC) - Log Rank

Statistical analysis description:

Descriptive analysis only

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	other
P-value	= 0.5474
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.88

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. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.

End point type	Secondary

End point timeframe:

At 1, 2, 3, and 4 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	252	248		
Units: Percentage of participants				
number (confidence interval 95%)				
1 Year (n = 244, 239)	99.59 (98.80 to 100.00)	99.58 (98.77 to 100.00)		
2 Years (n = 231, 224)	95.88 (93.39 to 98.38)	95.37 (92.70 to 98.04)		
3 Years (n = 221, 216)	93.77 (90.72 to 96.82)	93.23 (90.02 to 96.43)		
4 Years (n = 212, 210)	92.49 (89.15 to 95.83)	91.92 (88.44 to 95.41)		

Statistical analyses

Statistical analysis title	DRFI - Log Rank
Statistical analysis description: Descriptive analysis only	
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	other
P-value	= 0.6291
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	2.24

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. The number analyzed at each landmark timepoint represents the number of participants who were remaining at risk for an event.	
End point type	Secondary
End point timeframe: At 1, 2, 3, and 4 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	252	248		
Units: Percentage of participants				
number (confidence interval 95%)				
1 Year (n = 245, 240)	99.60 (98.82 to 100.00)	99.19 (98.06 to 100.00)		
2 Years (n = 241, 230)	98.38 (96.80 to 99.95)	96.68 (94.42 to 98.94)		
3 Years (n = 232, 226)	96.73 (94.50 to 98.96)	95.83 (93.30 to 98.36)		
4 Years (n = 223, 221)	95.47 (92.86 to 98.09)	94.13 (91.14 to 97.11)		

Statistical analyses

Statistical analysis title	OS - Log Rank
Statistical analysis description: Descriptive analysis only.	
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	other
P-value	= 0.5609
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	2.72

Secondary: 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 4.0 (NCI CTCAE v4.0), Over the Course of the Entire Study

End point title	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 4.0 (NCI CTCAE v4.0), Over the Course of the Entire Study

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 first dose of study treatment until 28 days after last dose of study treatment (up to 1 year, 6 months)

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		
AE with Fatal Outcome (Grade 5)	2	2		
Any AE: Grades 3 to 5	149	132		
Serious AE	52	49		
Related Serious AE	29	29		
Anaphylaxis and Hypersensitivity AEs, Any Grade	3	3		
Anaphylaxis and Hypersensitivity AEs, Grade ≥3	1	0		
Infusion/Admin.-Rel. Reactions in 24 hrs, Any Gr.	39	54		
Infusion/Admin.-Rel. Reactions in 24 hrs, Gr. ≥3	3	0		
Serious Rash/Skin Reactions, Any Grade	0	1		
Serious Rash/Skin Reactions, Grade ≥3	0	0		
Diarrhoea, Any Grade	149	153		
Diarrhoea, Grade ≥3	13	16		
Cardiac Dysfunction, Any Grade	65	52		
Cardiac Dysfunction, Grade ≥3	12	3		
Interstitial Lung Disease, Any Grade	3	5		
Interstitial Lung Disease, Grade ≥3	0	0		
Neutropenia/Febrile Neutropenia, Any Grade	142	123		
Neutropenia/Febrile Neutropenia, Grade ≥3	92	82		
Serious Mucositis, Any Grade	3	3		
Serious Mucositis, Grade ≥3	3	2		
Pregnancy- and Neonatal-Related AEs, Any Grade	0	0		
AE Leading to Study Drug Discontinuation	32	22		
AE Leading to Anti-HER2 Therapy Discontinuation	15	12		
AE Leading to Any Chemo. Drug Discontinuation	23	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Primary Cardiac Event During the Neoadjuvant Phase

End point title	Number of Participants With a Primary Cardiac Event During the Neoadjuvant Phase

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 first dose of study treatment until the completion of neoadjuvant therapy (24 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				
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 During the Neoadjuvant Phase

End point title	Number of Participants With a Secondary Cardiac Event During the Neoadjuvant Phase

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 first dose of study treatment until the completion of neoadjuvant therapy (24 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				
Any Secondary Cardiac Event	4	1		
Identified by Initial LVEF Assessments	4	1		
Confirmed by Second LVEF Assessment	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Primary Cardiac Event During the Adjuvant Phase

End point title	Number of Participants With a Primary Cardiac Event During the Adjuvant Phase

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 surgery until 28 days after the last dose of adjuvant treatment (42 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				
Any Primary Cardiac Event	1	2		
Heart Failure and Significant LVEF Decline	1	2		
Cardiac Death (Definite or Probable)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a Secondary Cardiac Event During the Adjuvant

End point title	Number of Participants With a Secondary Cardiac Event During the Adjuvant

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 surgery until 28 days after the last dose of adjuvant treatment (42 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				
Any Secondary Cardiac Event	15	8		
Identified by Initial LVEF Assessment	15	8		
Confirmed by Second LVEF Assessment	0	0		

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 Over the Course of the Entire Study

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

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.

End point type	Secondary

End point timeframe:

From first dose of study treatment until 28 days after last dose of study treatment (up to 1 year, 6 months)

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 (n=251,247)	50	39		
Albumin, Low - Grade 1 (n=251,247)	41	34		
Albumin, Low - Grade 2 (n=251,247)	8	5		
Albumin, Low - Grade 3 (n=251,247)	1	0		
Alkaline Phosphatase, High - Any Grade (n=234,225)	80	71		
Alkaline Phosphatase, High - Grade 1 (n=234,225)	78	70		
Alkaline Phosphatase, High - Grade 2 (n=234,225)	2	1		
SGPT/ALT, High - Any Grade	172	149		
SGPT/ALT, High - Grade 1	145	132		
SGPT/ALT, High - Grade 2	18	13		
SGPT/ALT, High - Grade 3	9	4		
SGOT/AST, High - Any Grade	149	130		
SGOT/AST, High - Grade 1	137	125		
SGOT/AST, High - Grade 2	7	3		
SGOT/AST, High - Grade 3	5	2		
Creatinine, High - Any Grade	225	217		
Creatinine, High - Grade 1	214	204		
Creatinine, High - Grade 2	9	13		
Creatinine, High - Grade 3	2	0		
Glucose, Low - Any Grade (n=251,247)	23	22		
Glucose, Low - Grade 1 (n=251,247)	20	22		
Glucose, Low - Grade 2 (n=251,247)	3	0		
Glucose, High - Any Grade (n=251,247)	3	4		
Glucose, High - Grade 3 (n=251,247)	3	4		
Hemoglobin, Low - Any Grade	233	223		
Hemoglobin, Low - Grade 1	129	139		
Hemoglobin, Low - Grade 2	93	77		
Hemoglobin, Low - Grade 3	11	7		
Hemoglobin, High - Any Grade	12	6		
Hemoglobin, High - Grade 1	12	6		
Lymphocytes, Abs., Low -Any Grade (n=163,167)	144	150		
Lymphocytes, Abs., Low - Grade 1 (n=163,167)	23	22		
Lymphocytes, Abs., Low - Grade 2 (n=163,167)	59	68		
Lymphocytes, Abs., Low - Grade 3 (n=163,167)	55	56		
Lymphocytes, Abs., Low - Grade 4 (n=163,167)	7	4		

Lymphocytes, Abs., High - Any Grade (n=163,167)	4	3		
Lymphocytes, Abs., High - Grade 2 (n=163,167)	4	3		
Neutrophils, Total,Abs., Low -Any Grade(n=163,167)	110	114		
Neutrophils, Total,Abs., Low - Grade 1(n=163,167)	27	42		
Neutrophils, Total,Abs., Low - Grade 2(n=163,167)	30	23		
Neutrophils, Total,Abs., Low - Grade 3(n=163,167)	17	24		
Neutrophils, Total,Abs., Low - Grade 4(n=163,167)	36	25		
Platelets, Low - Any Grade	72	67		
Platelets, Low - Grade 1	68	65		
Platelets, Low - Grade 2	3	2		
Platelets, Low - Grade 3	1	0		
Potassium, Low - Any Grade	45	41		
Potassium, Low - Grade 2	38	28		
Potassium, Low - Grade 3	6	11		
Potassium, Low - Grade 4	1	2		
Potassium, High - Any Grade	24	32		
Potassium, High - Grade 1	17	26		
Potassium, High - Grade 2	7	3		
Potassium, High - Grade 3	0	2		
Potassium, High - Grade 4	0	1		
Sodium, Low - Any Grade	27	33		
Sodium, Low - Grade 1	22	32		
Sodium, Low - Grade 3	4	0		
Sodium, Low - Grade 4	1	1		
Sodium, High - Any Grade	25	16		
Sodium, High - Grade 1	19	13		
Sodium, High - Grade 2	4	1		
Sodium, High - Grade 3	0	1		
Sodium, High - Grade 4	2	1		
Bilirubin, High - Any Grade	24	22		
Bilirubin, High - Grade 1	16	17		
Bilirubin, High - Grade 2	7	5		
Bilirubin, High - Grade 3	1	0		
Total Leukocyte Count, Low - Any Grade	199	203		
Total Leukocyte Count, Low - Grade 1	57	64		
Total Leukocyte Count, Low - Grade 2	81	78		
Total Leukocyte Count, Low - Grade 3	41	43		
Total Leukocyte Count, Low - Grade 4	20	18		
Total Leukocyte Count, High - Any Grade	0	1		
Total Leukocyte Count, High - Grade 1	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs): From first dose of study treatment until 28 days after last dose of study treatment (up to 1 year, 6 months); All-cause mortality: From first dose of study treatment until end of follow-up (up to 4 years, 11 months)

Adverse event reporting additional description:

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	26.0

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	49 / 248 (19.76%)	52 / 252 (20.63%)	
number of deaths (all causes)	14	12	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma			
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	

Clear cell 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	
Endometrial cancer			
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	
Pancreatic 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	
Thyroid cancer			
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	
Gastric cancer stage I			
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	
Gastric cancer			
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	
Vascular disorders			
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	
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	
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	
General disorders and administration site conditions			
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	
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	
Pyrexia			
subjects affected / exposed	2 / 248 (0.81%)	3 / 252 (1.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
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	
Death			
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	
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	
Reproductive system and breast disorders			

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	
Uterine 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	
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	
Intermenstrual bleeding			
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			
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	
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	
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	
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	

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	
Acute respiratory 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	
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			
Neutrophil count decreased			
subjects affected / exposed	3 / 248 (1.21%)	1 / 252 (0.40%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
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	
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	
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	
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%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
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	
Cardiomyopathy			
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	4 / 248 (1.61%)	6 / 252 (2.38%)	
occurrences causally related to treatment / all	5 / 5	6 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
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	
Nervous system disorders			

Syncope			
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	
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	
Immune thrombocytopenia			
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	
Febrile neutropenia			
subjects affected / exposed	9 / 248 (3.63%)	10 / 252 (3.97%)	
occurrences causally related to treatment / all	9 / 9	10 / 11	
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			
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	
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	

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	
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	
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	
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	
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	
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			
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	
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	
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	
Pneumonia			
subjects affected / exposed	0 / 248 (0.00%)	3 / 252 (1.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
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	
Herpes zoster			

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	
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	
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	
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	
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	
Postoperative 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	
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	
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	
Skin 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	
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	2 / 248 (0.81%)	2 / 252 (0.79%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngopharyngitis			
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	
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	
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	
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	
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	

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%)	251 / 252 (99.60%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 248 (4.84%)	16 / 252 (6.35%)	
occurrences (all)	13	19	
Hot flush			
subjects affected / exposed	41 / 248 (16.53%)	39 / 252 (15.48%)	
occurrences (all)	44	44	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	40 / 248 (16.13%)	2 / 252 (0.79%)	
occurrences (all)	174	2	
Asthenia			
subjects affected / exposed	79 / 248 (31.85%)	84 / 252 (33.33%)	
occurrences (all)	160	142	
Mucosal inflammation			
subjects affected / exposed	39 / 248 (15.73%)	49 / 252 (19.44%)	
occurrences (all)	53	66	
Oedema			
subjects affected / exposed	6 / 248 (2.42%)	13 / 252 (5.16%)	
occurrences (all)	6	13	
Malaise			
subjects affected / exposed	14 / 248 (5.65%)	16 / 252 (6.35%)	
occurrences (all)	20	20	
Pyrexia			
subjects affected / exposed	32 / 248 (12.90%)	41 / 252 (16.27%)	
occurrences (all)	41	56	
Fatigue			
subjects affected / exposed	71 / 248 (28.63%)	62 / 252 (24.60%)	
occurrences (all)	113	114	

Influenza like illness			
subjects affected / exposed	15 / 248 (6.05%)	11 / 252 (4.37%)	
occurrences (all)	21	17	
Oedema peripheral			
subjects affected / exposed	23 / 248 (9.27%)	26 / 252 (10.32%)	
occurrences (all)	25	28	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	15 / 248 (6.05%)	13 / 252 (5.16%)	
occurrences (all)	17	13	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	31 / 248 (12.50%)	37 / 252 (14.68%)	
occurrences (all)	36	43	
Dyspnoea			
subjects affected / exposed	29 / 248 (11.69%)	15 / 252 (5.95%)	
occurrences (all)	32	18	
Oropharyngeal pain			
subjects affected / exposed	15 / 248 (6.05%)	14 / 252 (5.56%)	
occurrences (all)	16	21	
Rhinorrhoea			
subjects affected / exposed	17 / 248 (6.85%)	13 / 252 (5.16%)	
occurrences (all)	22	15	
Cough			
subjects affected / exposed	41 / 248 (16.53%)	40 / 252 (15.87%)	
occurrences (all)	44	43	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 248 (6.05%)	8 / 252 (3.17%)	
occurrences (all)	17	8	
Insomnia			
subjects affected / exposed	44 / 248 (17.74%)	35 / 252 (13.89%)	
occurrences (all)	50	45	
Investigations			
Neutrophil count decreased			

subjects affected / exposed	40 / 248 (16.13%)	54 / 252 (21.43%)	
occurrences (all)	97	141	
Weight decreased			
subjects affected / exposed	26 / 248 (10.48%)	15 / 252 (5.95%)	
occurrences (all)	27	16	
Ejection fraction decreased			
subjects affected / exposed	16 / 248 (6.45%)	24 / 252 (9.52%)	
occurrences (all)	17	28	
Aspartate aminotransferase increased			
subjects affected / exposed	29 / 248 (11.69%)	40 / 252 (15.87%)	
occurrences (all)	37	54	
White blood cell count decreased			
subjects affected / exposed	19 / 248 (7.66%)	35 / 252 (13.89%)	
occurrences (all)	58	108	
Alanine aminotransferase increased			
subjects affected / exposed	39 / 248 (15.73%)	50 / 252 (19.84%)	
occurrences (all)	50	61	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	29 / 248 (11.69%)	25 / 252 (9.92%)	
occurrences (all)	31	26	
Infusion related reaction			
subjects affected / exposed	9 / 248 (3.63%)	36 / 252 (14.29%)	
occurrences (all)	9	53	
Radiation skin injury			
subjects affected / exposed	50 / 248 (20.16%)	54 / 252 (21.43%)	
occurrences (all)	51	55	
Nervous system disorders			
Dizziness			
subjects affected / exposed	34 / 248 (13.71%)	32 / 252 (12.70%)	
occurrences (all)	39	39	
Headache			
subjects affected / exposed	45 / 248 (18.15%)	68 / 252 (26.98%)	
occurrences (all)	72	84	
Dysgeusia			

subjects affected / exposed	43 / 248 (17.34%)	35 / 252 (13.89%)	
occurrences (all)	53	45	
Paraesthesia			
subjects affected / exposed	25 / 248 (10.08%)	23 / 252 (9.13%)	
occurrences (all)	30	26	
Neuropathy peripheral			
subjects affected / exposed	33 / 248 (13.31%)	40 / 252 (15.87%)	
occurrences (all)	38	53	
Peripheral sensory neuropathy			
subjects affected / exposed	42 / 248 (16.94%)	40 / 252 (15.87%)	
occurrences (all)	45	44	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	90 / 248 (36.29%)	109 / 252 (43.25%)	
occurrences (all)	117	148	
Leukopenia			
subjects affected / exposed	25 / 248 (10.08%)	36 / 252 (14.29%)	
occurrences (all)	42	58	
Neutropenia			
subjects affected / exposed	58 / 248 (23.39%)	64 / 252 (25.40%)	
occurrences (all)	109	119	
Eye disorders			
Dry eye			
subjects affected / exposed	14 / 248 (5.65%)	9 / 252 (3.57%)	
occurrences (all)	14	11	
Lacrimation increased			
subjects affected / exposed	14 / 248 (5.65%)	14 / 252 (5.56%)	
occurrences (all)	15	15	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	63 / 248 (25.40%)	61 / 252 (24.21%)	
occurrences (all)	85	90	
Dyspepsia			
subjects affected / exposed	35 / 248 (14.11%)	31 / 252 (12.30%)	
occurrences (all)	42	34	
Vomiting			

subjects affected / exposed	50 / 248 (20.16%)	50 / 252 (19.84%)	
occurrences (all)	71	73	
Abdominal pain upper			
subjects affected / exposed	20 / 248 (8.06%)	21 / 252 (8.33%)	
occurrences (all)	31	25	
Abdominal pain			
subjects affected / exposed	22 / 248 (8.87%)	15 / 252 (5.95%)	
occurrences (all)	29	17	
Haemorrhoids			
subjects affected / exposed	22 / 248 (8.87%)	11 / 252 (4.37%)	
occurrences (all)	22	11	
Diarrhoea			
subjects affected / exposed	152 / 248 (61.29%)	148 / 252 (58.73%)	
occurrences (all)	293	309	
Nausea			
subjects affected / exposed	151 / 248 (60.89%)	157 / 252 (62.30%)	
occurrences (all)	308	327	
Constipation			
subjects affected / exposed	57 / 248 (22.98%)	54 / 252 (21.43%)	
occurrences (all)	75	79	
Gastritis			
subjects affected / exposed	13 / 248 (5.24%)	5 / 252 (1.98%)	
occurrences (all)	14	6	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	46 / 248 (18.55%)	56 / 252 (22.22%)	
occurrences (all)	56	75	
Onycholysis			
subjects affected / exposed	11 / 248 (4.44%)	13 / 252 (5.16%)	
occurrences (all)	11	13	
Dry skin			
subjects affected / exposed	38 / 248 (15.32%)	34 / 252 (13.49%)	
occurrences (all)	43	39	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	17 / 248 (6.85%)	13 / 252 (5.16%)	
occurrences (all)	17	13	
Alopecia			
subjects affected / exposed	196 / 248 (79.03%)	184 / 252 (73.02%)	
occurrences (all)	196	188	
Nail disorder			
subjects affected / exposed	16 / 248 (6.45%)	17 / 252 (6.75%)	
occurrences (all)	18	17	
Nail discolouration			
subjects affected / exposed	23 / 248 (9.27%)	17 / 252 (6.75%)	
occurrences (all)	23	17	
Dermatitis			
subjects affected / exposed	19 / 248 (7.66%)	14 / 252 (5.56%)	
occurrences (all)	20	14	
Erythema			
subjects affected / exposed	22 / 248 (8.87%)	14 / 252 (5.56%)	
occurrences (all)	26	14	
Pruritus			
subjects affected / exposed	29 / 248 (11.69%)	25 / 252 (9.92%)	
occurrences (all)	35	29	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	25 / 248 (10.08%)	15 / 252 (5.95%)	
occurrences (all)	32	20	
Pain in extremity			
subjects affected / exposed	22 / 248 (8.87%)	25 / 252 (9.92%)	
occurrences (all)	26	30	
Arthralgia			
subjects affected / exposed	71 / 248 (28.63%)	82 / 252 (32.54%)	
occurrences (all)	91	106	
Bone pain			
subjects affected / exposed	20 / 248 (8.06%)	13 / 252 (5.16%)	
occurrences (all)	24	19	
Musculoskeletal pain			

subjects affected / exposed	8 / 248 (3.23%)	13 / 252 (5.16%)	
occurrences (all)	9	18	
Myalgia			
subjects affected / exposed	67 / 248 (27.02%)	52 / 252 (20.63%)	
occurrences (all)	80	63	
Muscle spasms			
subjects affected / exposed	21 / 248 (8.47%)	18 / 252 (7.14%)	
occurrences (all)	23	20	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	34 / 248 (13.71%)	24 / 252 (9.52%)	
occurrences (all)	43	37	
Nasopharyngitis			
subjects affected / exposed	33 / 248 (13.31%)	36 / 252 (14.29%)	
occurrences (all)	40	39	
Rhinitis			
subjects affected / exposed	14 / 248 (5.65%)	13 / 252 (5.16%)	
occurrences (all)	15	17	
Urinary tract infection			
subjects affected / exposed	18 / 248 (7.26%)	16 / 252 (6.35%)	
occurrences (all)	22	20	
Paronychia			
subjects affected / exposed	20 / 248 (8.06%)	12 / 252 (4.76%)	
occurrences (all)	21	14	
Cystitis			
subjects affected / exposed	8 / 248 (3.23%)	13 / 252 (5.16%)	
occurrences (all)	8	14	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	16 / 248 (6.45%)	22 / 252 (8.73%)	
occurrences (all)	17	24	
Decreased appetite			
subjects affected / exposed	43 / 248 (17.34%)	51 / 252 (20.24%)	
occurrences (all)	50	70	

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