



Clinical trial results:

A Multicenter, Multinational, Phase II Study to Evaluate Perjeta in Combination With Herceptin and Standard Neoadjuvant Anthracycline-Based Chemotherapy in Patients With HER2-Positive, Locally Advanced, Inflammatory, or Early-Stage Breast Cancer

Summary

EudraCT number	2014-000156-28
Trial protocol	DE GB ES IT PT FR PL DK
Global end of trial date	25 August 2020

Results information

Result version number	v2 (current)
This version publication date	03 September 2021
First version publication date	17 March 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	WO29217
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02132949
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 August 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a non-randomized, open-label, multicenter, multinational, phase 2 clinical trial including two parallel cohorts of participants. The primary objective of this study was to evaluate the cardiac safety of neoadjuvant treatment with the following regimens: A) dose-dense doxorubicin and cyclophosphamide (ddAC), followed by paclitaxel with pertuzumab and trastuzumab; B) 5-fluoracil, epirubicin and cyclophosphamide (FEC), followed by docetaxel with pertuzumab and trastuzumab. Secondary safety objectives of the study included evaluation of the cardiac and overall safety profiles of these 2 treatment regimens during the neoadjuvant, adjuvant, and treatment-free follow-up periods, as well as an assessment of anti-tumor activity in the form of pathological complete response (pCR), clinical response, event-free survival (EFS), invasive disease-free survival (iDFS), and overall survival (OS) of each cohort.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 91
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	France: 75
Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Norway: 12
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 31
Country: Number of subjects enrolled	Spain: 62
Worldwide total number of subjects	400
EEA total number of subjects	248

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)	352
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 401 participants were enrolled, 199 in Cohort A and 202 in Cohort B. One participant in Cohort B who was human epidermal growth factor receptor 2 (HER2) negative and was enrolled by error, was excluded from the study. Hence, 199 participants were included in Cohort A and 201 participants in Cohort B.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab

Arm description:

Subjects received neoadjuvant treatment with dose-dense doxorubicin and cyclophosphamide (ddAC), with administration of doxorubicin 60 milligrams per square meter (mg/m^2) intravenously (IV) once every 2 weeks (q2w) and cyclophosphamide $600\text{mg}/\text{m}^2$ IV q2w for 4 cycles, followed by paclitaxel $80\text{mg}/\text{m}^2$ IV once weekly (qw) for 12 weeks. Pertuzumab (840 milligrams [mg] IV loading dose then 420mg IV q3w) and trastuzumab (8 milligrams per kilogram [mg/kg] IV loading dose then $4\text{mg}/\text{kg}$ IV q3w) were administered along with paclitaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery). Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study. Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriamycin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received doxorubicin 60 milligrams per square meter (mg/m^2) as an intravenous (IV) bolus over 3-5 minutes (min) or as an infusion over 15-30min q2w for 4 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received cyclophosphamide $600\text{mg}/\text{m}^2$ IV bolus over 3-5min or as an infusion, in accordance with local policy, q2w for 4 cycles.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received paclitaxel $80\text{mg}/\text{m}^2$ IV infusion weekly once (qw) for 12 weeks.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received pertuzumab 840mg loading dose IV, then 420mg IV q3w for 17 cycles.

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

Dosage and administration details:

Participants received trastuzumab 8 milligrams per kilogram (mg/kg) loading dose IV, then 6mg/kg q3w for 17 cycles.

Arm title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
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Arm description:

Subjects received neoadjuvant treatment with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with administration of 5-fluorouracil 500mg/m² intravenously (IV) q3w, epirubicin 100mg/m² IV q3w, and cyclophosphamide 600mg/m² IV q3w for 4 cycles, followed by docetaxel (with starting dose of 75mg/m² in Cycle 5, then 100mg/m² for Cycles 6-8) q3w for 4 cycles. Pertuzumab (840 mg IV loading dose then 420mg IV q3w) and trastuzumab (8 mg/kg IV loading dose then 4mg/kg IV q3w) were given along with doctaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery). Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study. Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 5-fluorouracil 500mg/m² as an IV bolus or as an infusion, in accordance with local policy, q3w for 4 cycles.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received epirubicin 100mg/m² as an IV bolus over 3-5min or as an infusion over 3-5min, in accordance with local policy, q3w for 4 cycles.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received docetaxel with starting dose of 75mg/m² in Cycle 5, then 100mg/m² for Cycles 6-8 q3w for 4 cycles.

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	
Other name	Perjeta

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received pertuzumab 840mg loading dose IV, then 420mg IV q3w for 17 cycles.	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received trastuzumab 8 milligrams per kilogram (mg/kg) loading dose IV, then 6mg/kg q3w for 17 cycles.	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Participants received cyclophosphamide 600mg/m ² IV bolus over 3-5min or as an infusion, in accordance with local policy, q2w for 4 cycles.	

Number of subjects in period 1	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
Started	199	201
Received any Cohort A Treatment (Safety)	198	1 ^[1]
Received any Cohort B Treatment (Safety)	0 ^[2]	198
Underwent Surgery	187	194
Completed Neoadjuvant Treatment	182	189
Started Adjuvant Treatment	181	190
Completed Adjuvant Treatment	163	176
Started Treatment-Free Follow-Up	195	195
Completed	158	173
Not completed	41	28
Consent withdrawn by subject	6	5
Physician decision	3	1
Adverse event, non-fatal	2	1
Death	7	13
Withdrew Prior to Treatment	1	2
Lost to follow-up	14	4
Reason Unspecified	-	1
Disease Progression	3	-
Noncompliance	5	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: One subject who had enrolled in Cohort B received Cohort A treatment, and they were counted as part of the Cohort A safety analysis population.

[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: None of the subjects who had enrolled in Cohort A received any Cohort B treatment.

Baseline characteristics

Reporting groups

Reporting group title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Subjects received neoadjuvant treatment with dose-dense doxorubicin and cyclophosphamide (ddAC), with administration of doxorubicin 60 milligrams per square meter (mg/m²) intravenously (IV) once every 2 weeks (q2w) and cyclophosphamide 600mg/m² IV q2w for 4 cycles, followed by paclitaxel 80mg/m² IV once weekly (qw) for 12 weeks. Pertuzumab (840 milligrams [mg] IV loading dose then 420mg IV q3w) and trastuzumab (8 milligrams per kilogram [mg/kg] IV loading dose then 4mg/kg IV q3w) were administered along with paclitaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery). Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study. Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Reporting group title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Subjects received neoadjuvant treatment with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with administration of 5-fluorouracil 500mg/m² intravenously (IV) q3w, epirubicin 100mg/m² IV q3w, and cyclophosphamide 600mg/m² IV q3w for 4 cycles, followed by docetaxel (with starting dose of 75mg/m² in Cycle 5, then 100mg/m² for Cycles 6-8) q3w for 4 cycles. Pertuzumab (840 mg IV loading dose then 420mg IV q3w) and trastuzumab (8 mg/kg IV loading dose then 4mg/kg IV q3w) were given along with doectaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery). Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study. Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Reporting group values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab	Total
Number of subjects	199	201	400
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	49.8	49.5	-
standard deviation	± 11.7	± 11.5	-
Gender Categorical Units: Subjects			
Female	199	200	399
Male	0	1	1

End points

End points reporting groups

Reporting group title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Subjects received neoadjuvant treatment with dose-dense doxorubicin and cyclophosphamide (ddAC), with administration of doxorubicin 60 milligrams per square meter (mg/m^2) intravenously (IV) once every 2 weeks (q2w) and cyclophosphamide $600\text{mg}/\text{m}^2$ IV q2w for 4 cycles, followed by paclitaxel $80\text{mg}/\text{m}^2$ IV once weekly (qw) for 12 weeks. Pertuzumab (840 milligrams [mg] IV loading dose then 420mg IV q3w) and trastuzumab (8 milligrams per kilogram [mg/kg] IV loading dose then $4\text{mg}/\text{kg}$ IV q3w) were administered along with paclitaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery). Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study. Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Reporting group title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Subjects received neoadjuvant treatment with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with administration of 5-fluorouracil $500\text{mg}/\text{m}^2$ intravenously (IV) q3w, epirubicin $100\text{mg}/\text{m}^2$ IV q3w, and cyclophosphamide $600\text{mg}/\text{m}^2$ IV q3w for 4 cycles, followed by docetaxel (with starting dose of $75\text{mg}/\text{m}^2$ in Cycle 5, then $100\text{mg}/\text{m}^2$ for Cycles 6-8) q3w for 4 cycles. Pertuzumab (840 mg IV loading dose then 420mg IV q3w) and trastuzumab (8 mg/kg IV loading dose then $4\text{mg}/\text{kg}$ IV q3w) were given along with docetaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery). Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study. Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Primary: Percentage of Participants With at Least One Event of New York Heart Association (NYHA) Class III or IV Heart Failure During the Neoadjuvant Treatment Period

End point title	Percentage of Participants With at Least One Event of New York Heart Association (NYHA) Class III or IV Heart Failure During the Neoadjuvant Treatment Period ^[1]
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End point description:

Symptomatic left ventricular systolic dysfunction (otherwise referred to as heart failure) is a serious adverse event. The NYHA Functional Classification System for Heart Failure considers the patient's symptoms: Class III: Marked limitation of physical activity; Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: Unable to carry on any physical activity without discomfort; Symptoms of heart failure at rest; If any physical activity is undertaken, discomfort increases. The 95% CIs were calculated with the Clopper-Pearson method. Results included events with onset from first dose of pertuzumab/trastuzumab prior to surgery through the day before the first dose of any study drug after surgery. If participant withdrew without entering adjuvant period, results included all events with onset from first dose of pertuzumab/trastuzumab through 42 days after last dose of any study drug or on the day of target surgery whichever was later.

End point type	Primary
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End point timeframe:

From day of first dose of pertuzumab or trastuzumab until the end of the neoadjuvant treatment period (as defined in the description; up to 25 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No comparisons were planned to be made between the efficacy and safety results of the two treatment cohorts. All analyses were descriptive.

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Percentage of participants				
number (confidence interval 95%)	1.5 (0.31 to 4.34)	0 (0.00 to 1.85)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With at Least One Left Ventricular Ejection Fraction (LVEF) Significant Decline, Defined as a Drop in LVEF of at Least 10 Percentage Points From Baseline and to Below 50%, During the Neoadjuvant Treatment Period

End point title	Percentage of Participants With at Least One Left Ventricular Ejection Fraction (LVEF) Significant Decline, Defined as a Drop in LVEF of at Least 10 Percentage Points From Baseline and to Below 50%, During the Neoadjuvant Treatment Period ^[2]
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End point description:

LVEF significant decline was defined as the decline in LVEF of $\geq 10\%$ -points from baseline to an LVEF of $< 50\%$. A Confirmed LVEF Significant Decline was defined as at least two consecutive readings of significant declines in LVEF. A Single LVEF Significant Decline was defined as only one reading of a significant decline (no consecutive readings) in LVEF. The category of 'At Least one LVEF Significant Decline Event' was defined as the total of confirmed and single LVEF significant declines. The 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. Results include events with onset from the first dose of pertuzumab or trastuzumab prior to surgery through the day before the first dose of any study drug after surgery. If participant withdrew without entering adjuvant period, results included all events with onset from first dose of pertuzumab or trastuzumab through 42 days after last dose of any study drug or on the day of target surgery whichever is later.

End point type	Primary
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End point timeframe:

From day of first dose of pertuzumab or trastuzumab until the end of the neoadjuvant treatment period (as defined in the description; up to 25 weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No comparisons were planned to be made between the efficacy and safety results of the two treatment cohorts. All analyses were descriptive.

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Percentage of participants				
number (confidence interval 95%)				
At Least 1 LVEF Significant Decline Event (Total)	6.5 (3.5 to 10.9)	2.0 (0.6 to 5.1)		
At Least 1 Confirmed LVEF Significant Decline	1.0 (0.1 to 3.6)	0.5 (0.0 to 2.8)		

At Least 1 Single LVEF Significant Decline	5.5 (2.8 to 9.7)	1.5 (0.3 to 4.4)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Event of New York Heart Association (NYHA) Class III or IV Heart Failure During the Adjuvant Treatment Period

End point title	Percentage of Participants With at Least One Event of New York Heart Association (NYHA) Class III or IV Heart Failure During the Adjuvant Treatment Period
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End point description:

Symptomatic left ventricular systolic dysfunction (otherwise referred to as heart failure) is a serious adverse event. The NYHA Functional Classification System for Heart Failure considers the patient's symptoms: Class III: Marked limitation of physical activity; Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: Unable to carry on any physical activity without discomfort; Symptoms of heart failure at rest; If any physical activity is undertaken, discomfort increases. The 95% CIs were calculated with the Clopper-Pearson method. Results included events with onset from the first dose of any study drug after surgery through 42 days after the last dose of any study drug.

End point type	Secondary
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End point timeframe:

From the first dose of any study drug after surgery through 42 days after the last dose of any study drug (during the adjuvant treatment period; up to approximately 39 weeks)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181 ^[3]	190 ^[4]		
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.00 to 2.02)	0.5 (0.01 to 2.90)		

Notes:

[3] - Includes subjects that started adjuvant treatment.

[4] - Includes subjects that started adjuvant treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Left Ventricular Ejection Fraction (LVEF) Significant Decline, Defined as a Drop in LVEF of at Least 10 Percentage Points From Baseline and to Below 50%, During the Adjuvant Treatment Period

End point title	Percentage of Participants With at Least One Left Ventricular Ejection Fraction (LVEF) Significant Decline, Defined as a Drop
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End point description:

LVEF significant decline was defined as the decline in LVEF of $\geq 10\%$ -points from baseline to an LVEF of $< 50\%$. A Confirmed LVEF Significant Decline was defined as at least two consecutive readings of significant declines in LVEF. A Single LVEF Significant Decline was defined as only one reading of a significant decline (no consecutive readings) in LVEF. The category of 'At Least one LVEF Significant Decline Event' was defined as the total of confirmed and single LVEF significant declines. The 95% confidence intervals were calculated using the Clopper-Pearson method. Results included events with onset from the first dose of any study drug after surgery through 42 days after the last dose of any study drug.

End point type Secondary

End point timeframe:

From the first dose of any study drug after surgery through 42 days after the last dose of any study drug (during the adjuvant treatment period; up to approximately 39 weeks)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181 ^[5]	190 ^[6]		
Units: Percentage of participants				
number (confidence interval 95%)				
At Least 1 LVEF Significant Decline Event (Total)	7.7 (4.3 to 12.6)	10.5 (6.5 to 15.8)		
At Least 1 Confirmed LVEF Significant Decline	2.8 (0.9 to 6.3)	3.2 (1.2 to 6.7)		
At Least 1 Single LVEF Significant Decline	5.0 (2.3 to 9.2)	7.4 (4.1 to 12.1)		

Notes:

[5] - Includes subjects that started adjuvant treatment.

[6] - Includes subjects that started adjuvant treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Event of New York Heart Association (NYHA) Class III or IV Heart Failure During the Treatment-Free Follow-Up Period

End point title Percentage of Participants With at Least One Event of New York Heart Association (NYHA) Class III or IV Heart Failure During the Treatment-Free Follow-Up Period

End point description:

Symptomatic left ventricular systolic dysfunction (otherwise referred to as heart failure) is a serious adverse event. The NYHA Functional Classification System for Heart Failure considers the patient's symptoms: Class III: Marked limitation of physical activity; Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV: Unable to carry on any physical activity without discomfort; Symptoms of heart failure at rest; If any physical activity is undertaken, discomfort increases. The 95% CIs were calculated with the Clopper-Pearson method.

End point type Secondary

End point timeframe:

From 42 days after the last dose of study treatment until the end of treatment-free follow-up (up to 5 years)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.00 to 1.84)	0.5 (0.01 to 2.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least One Left Ventricular Ejection Fraction (LVEF) Significant Decline, Defined as a Drop in LVEF of at Least 10 Percentage Points From Baseline and to Below 50%, During the Treatment-Free Follow-Up Period

End point title	Percentage of Participants With at Least One Left Ventricular Ejection Fraction (LVEF) Significant Decline, Defined as a Drop in LVEF of at Least 10 Percentage Points From Baseline and to Below 50%, During the Treatment-Free Follow-Up Period
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End point description:

LVEF significant decline was defined as the decline in LVEF of $\geq 10\%$ -points from baseline to an LVEF of $< 50\%$. A Confirmed LVEF Significant Decline was defined as at least two consecutive readings of significant declines in LVEF. A Single LVEF Significant Decline was defined as only one reading of a significant decline (no consecutive readings) in LVEF. The category of 'At Least one LVEF Significant Decline Event' was defined as the total of confirmed and single LVEF significant declines. The 95% confidence intervals were calculated using the Clopper-Pearson method.

End point type	Secondary
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End point timeframe:

From 42 days after the last dose of study treatment until the end of treatment-free follow-up (up to 5 years)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Percentage of participants				
number (confidence interval 95%)				
At Least 1 LVEF Significant Decline Event (Total)	6.0 (3.2 to 10.3)	3.5 (1.4 to 7.1)		
At Least 1 Confirmed LVEF Significant Decline	3.0 (1.1 to 6.4)	1.0 (0.1 to 3.6)		

At Least 1 Single LVEF Significant Decline	3.0 (1.1 to 6.4)	2.5 (0.8 to 5.8)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Overview of the Number of Participants With at Least One Adverse Event During the Neoadjuvant Treatment Period

End point title	Overview of the Number of Participants With at Least One Adverse Event During the Neoadjuvant Treatment Period
End point description:	An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous with respect to an AE. Severity refers to the intensity of an AE (rated according to NCI-CTCAE v4.0 criteria or, if not listed, the following scale: Grade 3 is severe, Grade 4 is life-threatening, and Grade 5 is death related to AE), whereas a serious AE (SAE) is a significant medical event (per standard criteria). Severity and seriousness needed to be independently assessed for each AE that was recorded. Selected AEs for reporting included heart failure (NYHA Class II/III/IV) and asymptomatic declines in LVEF (reported as an AE with the term of ejection fraction decreased). In the results table, multiple occurrences of the same AE in one individual were counted only once. Any AE includes all serious and non-serious AEs.
End point type	Secondary
End point timeframe:	From first dose of any study drug prior to surgery through the day before the first dose of study drug after surgery (up to 25 weeks)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Participants				
Any Adverse Event (AE)	198	198		
NCI-CTCAE Grade 3-5 AE	99	108		
Serious AE	45	52		
Deaths	0	0		
Ejection Fraction Decreased (Any Grade)	14	7		
Heart Failure (Any Grade)	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of the Number of Participants With at Least One Adverse Event

During the Adjuvant Treatment Period

End point title	Overview of the Number of Participants With at Least One Adverse Event During the Adjuvant Treatment Period
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End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous with respect to an AE. Severity refers to the intensity of an AE (rated according to NCI-CTCAE v4.0 criteria or, if not listed, the following scale: Grade 3 is severe, Grade 4 is life-threatening, and Grade 5 is death related to AE), whereas a serious AE (SAE) is a significant medical event (per standard criteria). Severity and seriousness needed to be independently assessed for each AE that was recorded. Selected AEs for reporting included heart failure (NYHA Class II/III/IV) and asymptomatic declines in LVEF (reported as an AE with the term of ejection fraction decreased). In the results table, multiple occurrences of the same AE in one individual were counted only once. Any AE includes all serious and non-serious AEs.

End point type	Secondary
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End point timeframe:

From the first dose of any study drug after surgery through 42 days after the last dose of any study drug (during the adjuvant treatment period; up to approximately 39 weeks)

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181 ^[7]	190 ^[8]		
Units: Participants				
Any Adverse Event (AE)	171	171		
NCI-CTCAE Grade 3-5 AE	23	40		
Serious AE	15	17		
Deaths	0	0		
Ejection Fraction Decreased (Any Grade)	15	20		
Heart Failure (Any Grade)	0	2		

Notes:

[7] - Includes subjects that started adjuvant treatment.

[8] - Includes subjects that started adjuvant treatment.

Statistical analyses

No statistical analyses for this end point

Secondary: Overview of the Number of Participants With at Least One Adverse Event During the Treatment-Free Follow-Up Period

End point title	Overview of the Number of Participants With at Least One Adverse Event During the Treatment-Free Follow-Up Period
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End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated according to NCI-CTCAE v4.0 criteria or, if not listed, the following scale: Grade 3 is severe, Grade 4 is life-threatening, and Grade 5 is death related to AE), and a serious AE (SAE) is a significant medical event (per standard criteria). Severity and seriousness were independently assessed for each AE. Selected AEs for reporting included heart failure (NYHA Class II/III/IV) and asymptomatic declines in LVEF (reported as ejection fraction decreased). During TFFU, only heart failure, pregnancies, and non-breast-related second primary malignancies, irrespective of causal relationship with study treatment, and drug-related SAEs were reported. Multiple occurrences of the same AE in 1 subject were counted only once.

End point type	Secondary
End point timeframe:	
From 42 days after the last dose of study treatment until the end of treatment-free follow-up (TFFU; up to 5 years)	

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	198		
Units: Participants				
Any Adverse Event (AE)	3	7		
NCI-CTCAE Grade 3-5 AE	2	5		
Serious AE	3	7		
Deaths	7	13		
Ejection Fraction Decreased (Any Grade)	1	1		
Heart Failure (Any Grade)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Positive for Anti-Therapeutic Antibodies (ATAs) to Pertuzumab at Baseline and Anytime Post-Baseline

End point title	Percentage of Participants Positive for Anti-Therapeutic Antibodies (ATAs) to Pertuzumab at Baseline and Anytime Post-Baseline
End point description:	
ATAs to pertuzumab in serum samples were detected using a validated bridging enzyme-linked immunosorbent assay (ELISA) method. This analysis only included participants with an ATA assay result from a baseline sample and/or at least one post-baseline sample.	
End point type	Secondary
End point timeframe:	
Screening (baseline) then prior to pertuzumab infusion (Hour 0) in Cycles 5, 14, 18 thereafter anytime between Cycle 8 Day 21 and surgery, up to treatment completion visit (cycle length=2-3 weeks; up to approximately 1 year, 3 months)	

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: Percentage of participants				
number (not applicable)				

At Baseline (n = 190, 191)	1.6	2.1		
Anytime Post-Baseline (n = 195, 197)	4.6	3.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Total Pathologic Complete Response (tpCR), Evaluated After Surgery

End point title	Percentage of Participants With Total Pathologic Complete Response (tpCR), Evaluated After Surgery
End point description:	
Total pathologic complete response (tpCR) was the pCR based on tumor and nodal staging (i.e., histological confirmation of pCR in breast and nodes at surgery) and was defined as the absence of any residual invasive cancer in the breast and the absence of any metastatic cells in the regional lymph nodes (i.e., ypT0/is ypN0 tpCR). Participants who did not undergo surgery or did not have a valid pCR assessment were considered non-responders in the analysis. The 95% CIs were calculated using the Clopper-Pearson method. ITT population: included all participants who were enrolled regardless of whether they received any study treatment, grouped according to the arm to which a participant was enrolled.	
End point type	Secondary
End point timeframe:	
After completion of neoadjuvant treatment and surgery (up to 25 weeks)	

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: Percentage of participants				
number (confidence interval 95%)	61.8 (54.67 to 68.59)	60.7 (53.58 to 67.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Response as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 During the Neoadjuvant Treatment Period

End point title	Percentage of Participants With Clinical Response as Determined by the Investigator According to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 During the Neoadjuvant Treatment Period
End point description:	
The clinical response rate was defined as the percentage of participants in the ITT population who	

achieved a complete response (CR) or partial response (PR) prior to surgery, according to RECIST v1.1. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of the longest diameter compared to Baseline. Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient (20%) increase to qualify for disease progression, in addition to no new target lesions. Progressive Disease (PD): at least a 20% increase in the sum of the longest diameter, taking as reference the smallest sum of the longest diameter observed at previous tumor assessment, or the appearance of any new lesions. Participants were classified as missing or unevaluable if no assessments were measured prior to surgery on the ipsilateral breast. The 95% CIs were calculated using the Clopper-Pearson method; they were only calculated for responses (not for missing or unevaluable data).

End point type	Secondary
End point timeframe:	
Baseline until disease progression or death due to any cause up to 24 weeks (assessed on Day 1 of Cycles 1-8 [cycle length=2-3 weeks])	

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: percentage of participants				
number (confidence interval 95%)				
Clinical Response Rate (CR+PR)	67.3 (60.35 to 73.80)	60.2 (53.07 to 67.02)		
Complete Response (CR)	39.7 (32.85 to 46.86)	23.9 (18.16 to 30.39)		
Partial Response (PR)	27.6 (21.55 to 34.41)	36.3 (29.67 to 43.38)		
Stable Disease (SD)	7.0 (3.90 to 11.52)	10.0 (6.18 to 14.95)		
Progressive Disease (PD)	0.5 (0.01 to 2.77)	1.0 (0.12 to 3.55)		
Missing or Unevaluable	25.1 (-999999 to 999999)	28.9 (-999999 to 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Event-Free for Event-Free Survival at 1 to 5 Years, Determined by the Investigator According to RECIST v1.1

End point title	Kaplan-Meier Estimate of the Percentage of Participants Event-Free for Event-Free Survival at 1 to 5 Years, Determined by the Investigator According to RECIST v1.1
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End point description:

The Kaplan-Meier method was used to estimate the percentage of participants who were event-free at landmark timepoints. Event-free survival (EFS) was defined as the time from enrollment to the first occurrence of progressive disease (PD), relapse, or death from any cause, with tumor evaluations performed by the investigator according to RECIST v1.1. Ipsilateral or contralateral in situ disease and second primary non-breast cancers (including in situ carcinomas and non-melanoma skin cancers) were not counted as progressive disease or relapse. Participants who withdrew from the study without documented progression or relapse and for whom there existed evidence that evaluations had been made, were censored at the date of the last assessment at which the participant was known to be free

from progressive disease or relapse. Participants with no tumor evaluations after baseline were censored at the date of enrollment plus 1 day.

End point type	Secondary
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End point timeframe:

At 1, 2, 3, 4, and 5 years

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199 ^[9]	201 ^[10]		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
1 Year (n = 191, 190)	98.47 (96.75 to 100.00)	97.48 (95.29 to 99.66)		
2 Years (n = 176, 180)	95.80 (92.94 to 98.65)	92.86 (89.25 to 96.46)		
3 Years (n = 163, 174)	93.58 (90.06 to 97.10)	90.78 (86.72 to 94.84)		
4 Years (n = 154, 172)	92.39 (88.55 to 96.23)	89.73 (85.47 to 94.00)		
5 Years (n = 96, 141)	90.84 (86.48 to 95.20)	89.20 (84.84 to 93.57)		

Notes:

[9] - ITT Population. 'n' represents the number remaining at risk at each timepoint.

[10] - ITT Population. 'n' represents the number remaining at risk at each timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Event-Free for Invasive Disease-Free Survival (iDFS) at 1 to 4 Years, Determined by the Investigator According to RECIST v1.1

End point title	Kaplan-Meier Estimate of the Percentage of Participants Event-Free for Invasive Disease-Free Survival (iDFS) at 1 to 4 Years, Determined by the Investigator According to RECIST v1.1
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End point description:

The Kaplan-Meier method was used to estimate the percentage of subjects event-free at landmark timepoints. Invasive disease-free survival (iDFS) was defined as the time from the first date of no disease (date of surgery) to the first documentation of progressive invasive disease, relapse, or death, with tumor evaluations made by the investigator according to RECISTv1.1. Ipsilateral or contralateral in situ disease and second primary non-breast cancers were not counted as events. Subjects who withdrew from study without documented progression or relapse and for whom evidence existed that evaluations had been made, were censored at the date of the last assessment they were known to be alive and disease-free. Subjects with no postbaseline information and those who did not undergo surgery were excluded from analysis.

End point type	Secondary
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End point timeframe:

At 1, 2, 3, and 4 years

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187 ^[11]	194 ^[12]		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				
1 Year (n = 180, 184)	98.91 (97.41 to 100.00)	96.34 (93.68 to 99.00)		
2 Years (n = 167, 178)	95.57 (92.57 to 98.57)	94.25 (90.94 to 97.55)		
3 Years (n = 158, 171)	94.42 (91.06 to 97.78)	91.06 (87.00 to 95.11)		
4 Years (n = 131, 168)	92.60 (88.72 to 96.48)	91.06 (87.00 to 95.11)		

Notes:

[11] - ITT Population. 'n' represents the number remaining at risk at each timepoint.

[12] - ITT Population. 'n' represents the number remaining at risk at each timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of the Percentage of Participants Event-Free for Overall Survival (OS) at 1 to 5 Years

End point title	Kaplan-Meier Estimate of the Percentage of Participants Event-Free for Overall Survival (OS) at 1 to 5 Years
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End point description:

The Kaplan-Meier method was used to estimate the percentage of participants who were event-free at landmark timepoints. Overall survival (OS) was defined as the time from enrollment to death from any cause. Participants who were alive or lost to follow-up were censored at their last known date in the study. Participants with no post-baseline assessments were censored at the date of enrollment plus 1 day.

End point type	Secondary
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End point timeframe:

At 1, 2, 3, 4, and 5 years

End point values	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199 ^[13]	201 ^[14]		
Units: Estimate of percentage of participants				
number (confidence interval 95%)				

1 Year (n = 193, 194)	99.48 (98.48 to 100.00)	100.00 (100.00 to 100.00)		
2 Years (n = 183, 190)	98.96 (97.52 to 100.00)	97.94 (95.94 to 99.94)		
3 Years (n = 176, 185)	97.86 (95.78 to 99.94)	96.38 (93.74 to 99.01)		
4 Years (n = 171, 180)	97.86 (95.78 to 99.94)	94.81 (91.68 to 97.94)		
5 Years (n = 158, 177)	96.10 (93.26 to 98.94)	93.75 (90.33 to 97.17)		

Notes:

[13] - ITT Population. 'n' represents the number remaining at risk at each timepoint.

[14] - ITT Population. 'n' represents the number remaining at risk at each timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of any study drug until the end of treatment-free follow-up (up to 6 years, 1 month)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Subjects received neoadjuvant treatment with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), with administration of 5-fluorouracil 500mg/m² intravenously (IV) q3w, epirubicin 100mg/m² IV q3w, and cyclophosphamide 600mg/m² IV q3w for 4 cycles, followed by docetaxel (with starting dose of 75mg/m² in Cycle 5, then 100mg/m² for Cycles 6-8) q3w for 4 cycles. Pertuzumab (840 mg IV loading dose then 420mg IV q3w) and trastuzumab (8 mg/kg IV loading dose then 4mg/kg IV q3w) were given along with doectaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery).

Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study.

Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Reporting group title	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab
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Reporting group description:

Subjects received neoadjuvant treatment with dose-dense doxorubicin and cyclophosphamide (ddAC), with administration of doxorubicin 60 milligrams per square meter (mg/m²) intravenously (IV) once every 2 weeks (q2w) and cyclophosphamide 600mg/m² IV q2w for 4 cycles, followed by paclitaxel 80mg/m² IV once weekly (qw) for 12 weeks. Pertuzumab (840 milligrams [mg] IV loading dose then 420mg IV q3w) and trastuzumab (8 milligrams per kilogram [mg/kg] IV loading dose then 4mg/kg IV q3w) were administered along with paclitaxel for 4 cycles (8 cycles of chemotherapy in total prior to surgery). Following surgery, subjects received adjuvant treatment with pertuzumab and trastuzumab IV q3w (up to 13 cycles), for a total of 17 cycles of pertuzumab and trastuzumab therapy during the study. Radiotherapy and adjuvant hormonal therapy were also given as clinically indicated. Following treatment completion/discontinuation, subjects were followed for safety and efficacy for up to 5 years.

Serious adverse events	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 198 (33.33%)	56 / 199 (28.14%)	
number of deaths (all causes)	13	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA OF COLON			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			

subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLON CANCER			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-HODGKIN'S LYMPHOMA			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLASMA CELL MYELOMA			
subjects affected / exposed	2 / 198 (1.01%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL CANCER			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
HAEMATOMA			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
ABORTION INDUCED			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
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			
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	4 / 198 (2.02%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
BREAST HAEMATOMA			
subjects affected / exposed	1 / 198 (0.51%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			

subjects affected / exposed	1 / 198 (0.51%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAINFUL RESPIRATION			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EJECTION FRACTION DECREASED			
subjects affected / exposed	5 / 198 (2.53%)	5 / 199 (2.51%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

TRANSAMINASES INCREASED			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	2 / 198 (1.01%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEROMA			
subjects affected / exposed	1 / 198 (0.51%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND DECOMPOSITION			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (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	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			

subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL THROMBOSIS			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	4 / 198 (2.02%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIOGENIC SHOCK			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBELLAR SYNDROME			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	1 / 198 (0.51%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			

subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
AGRANULOCYTOSIS			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE MARROW FAILURE			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	27 / 198 (13.64%)	11 / 199 (5.53%)	
occurrences causally related to treatment / all	28 / 28	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			

subjects affected / exposed	2 / 198 (1.01%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 198 (0.51%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
COLITIS			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	11 / 198 (5.56%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	9 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC COLITIS			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ODYNOPHAGIA			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			

subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCTALGIA			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
ERYTHEMA MULTIFORME			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN NECROSIS			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (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			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
MYALGIA			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BREAST CELLULITIS			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 198 (0.00%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			
subjects affected / exposed	0 / 198 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	7 / 198 (3.54%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 198 (0.51%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL INFECTION			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAL BACTERAEMIA			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
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 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 198 (0.00%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DEVICE INFECTION			
subjects affected / exposed	3 / 198 (1.52%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	1 / 198 (0.51%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 198 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort B: FEC, Docetaxel, Pertuzumab, Trastuzumab	Cohort A: ddAC, Paclitaxel, Pertuzumab, Trastuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 198 (100.00%)	197 / 199 (98.99%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	12 / 198 (6.06%)	14 / 199 (7.04%)	
occurrences (all)	14	14	
HOT FLUSH			
subjects affected / exposed	48 / 198 (24.24%)	69 / 199 (34.67%)	
occurrences (all)	55	77	

LYMPHOEDEMA subjects affected / exposed occurrences (all)	16 / 198 (8.08%) 17	14 / 199 (7.04%) 15	
General disorders and administration site conditions			
ASTHENIA subjects affected / exposed occurrences (all)	85 / 198 (42.93%) 130	41 / 199 (20.60%) 72	
CHILLS subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 4	12 / 199 (6.03%) 14	
FATIGUE subjects affected / exposed occurrences (all)	81 / 198 (40.91%) 119	125 / 199 (62.81%) 151	
INFLUENZA LIKE ILLNESS subjects affected / exposed occurrences (all)	21 / 198 (10.61%) 24	7 / 199 (3.52%) 8	
MUCOSAL INFLAMMATION subjects affected / exposed occurrences (all)	77 / 198 (38.89%) 106	46 / 199 (23.12%) 55	
OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	28 / 198 (14.14%) 35	22 / 199 (11.06%) 25	
OEDEMA subjects affected / exposed occurrences (all)	10 / 198 (5.05%) 10	5 / 199 (2.51%) 5	
PAIN subjects affected / exposed occurrences (all)	6 / 198 (3.03%) 6	16 / 199 (8.04%) 18	
PYREXIA subjects affected / exposed occurrences (all)	39 / 198 (19.70%) 53	39 / 199 (19.60%) 45	
Reproductive system and breast disorders			
BREAST PAIN subjects affected / exposed occurrences (all)	20 / 198 (10.10%) 21	27 / 199 (13.57%) 28	
AMENORRHOEA			

subjects affected / exposed occurrences (all)	10 / 198 (5.05%) 10	9 / 199 (4.52%) 10	
VULVOVAGINAL DRYNESS subjects affected / exposed occurrences (all)	14 / 198 (7.07%) 14	22 / 199 (11.06%) 22	
Respiratory, thoracic and mediastinal disorders			
COUGH subjects affected / exposed occurrences (all)	27 / 198 (13.64%) 30	50 / 199 (25.13%) 64	
DYSPNOEA subjects affected / exposed occurrences (all)	37 / 198 (18.69%) 38	29 / 199 (14.57%) 33	
NASAL CONGESTION subjects affected / exposed occurrences (all)	4 / 198 (2.02%) 4	21 / 199 (10.55%) 23	
EPISTAXIS subjects affected / exposed occurrences (all)	41 / 198 (20.71%) 45	54 / 199 (27.14%) 61	
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	21 / 198 (10.61%) 23	26 / 199 (13.07%) 31	
UPPER-AIRWAY COUGH SYNDROME subjects affected / exposed occurrences (all)	0 / 198 (0.00%) 0	12 / 199 (6.03%) 13	
RHINORRHOEA subjects affected / exposed occurrences (all)	22 / 198 (11.11%) 22	21 / 199 (10.55%) 23	
Psychiatric disorders			
ANXIETY subjects affected / exposed occurrences (all)	18 / 198 (9.09%) 20	23 / 199 (11.56%) 24	
DEPRESSION subjects affected / exposed occurrences (all)	11 / 198 (5.56%) 11	23 / 199 (11.56%) 23	
INSOMNIA			

subjects affected / exposed occurrences (all)	35 / 198 (17.68%) 38	45 / 199 (22.61%) 52	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	13 / 198 (6.57%)	15 / 199 (7.54%)	
occurrences (all)	15	19	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	11 / 198 (5.56%)	14 / 199 (7.04%)	
occurrences (all)	12	18	
EJECTION FRACTION DECREASED			
subjects affected / exposed	22 / 198 (11.11%)	22 / 199 (11.06%)	
occurrences (all)	27	27	
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 198 (0.00%)	12 / 199 (6.03%)	
occurrences (all)	0	15	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	19 / 198 (9.60%)	18 / 199 (9.05%)	
occurrences (all)	26	22	
WEIGHT DECREASED			
subjects affected / exposed	13 / 198 (6.57%)	19 / 199 (9.55%)	
occurrences (all)	13	19	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	6 / 198 (3.03%)	22 / 199 (11.06%)	
occurrences (all)	6	29	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	35 / 198 (17.68%)	38 / 199 (19.10%)	
occurrences (all)	50	42	
PROCEDURAL PAIN			
subjects affected / exposed	12 / 198 (6.06%)	17 / 199 (8.54%)	
occurrences (all)	14	18	
RADIATION SKIN INJURY			
subjects affected / exposed	58 / 198 (29.29%)	36 / 199 (18.09%)	
occurrences (all)	59	36	

Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	11 / 198 (5.56%)	10 / 199 (5.03%)	
occurrences (all)	12	12	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	20 / 198 (10.10%)	33 / 199 (16.58%)	
occurrences (all)	22	37	
DYSGEUSIA			
subjects affected / exposed	35 / 198 (17.68%)	37 / 199 (18.59%)	
occurrences (all)	44	41	
HEADACHE			
subjects affected / exposed	41 / 198 (20.71%)	70 / 199 (35.18%)	
occurrences (all)	48	85	
HYPOAESTHESIA			
subjects affected / exposed	10 / 198 (5.05%)	10 / 199 (5.03%)	
occurrences (all)	10	10	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	34 / 198 (17.17%)	56 / 199 (28.14%)	
occurrences (all)	37	60	
PARAESTHESIA			
subjects affected / exposed	27 / 198 (13.64%)	35 / 199 (17.59%)	
occurrences (all)	31	44	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	21 / 198 (10.61%)	40 / 199 (20.10%)	
occurrences (all)	23	44	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	64 / 198 (32.32%)	56 / 199 (28.14%)	
occurrences (all)	78	65	
FEBRILE NEUTROPENIA			
subjects affected / exposed	10 / 198 (5.05%)	3 / 199 (1.51%)	
occurrences (all)	10	3	
LYMPHOPENIA			
subjects affected / exposed	11 / 198 (5.56%)	5 / 199 (2.51%)	
occurrences (all)	16	5	
NEUTROPENIA			

subjects affected / exposed occurrences (all)	31 / 198 (15.66%) 43	43 / 199 (21.61%) 54	
Ear and labyrinth disorders VERTIGO subjects affected / exposed occurrences (all)	10 / 198 (5.05%) 11	4 / 199 (2.01%) 4	
Eye disorders LACRIMATION INCREASED subjects affected / exposed occurrences (all)	37 / 198 (18.69%) 37	20 / 199 (10.05%) 20	
DRY EYE subjects affected / exposed occurrences (all)	13 / 198 (6.57%) 13	13 / 199 (6.53%) 13	
VISION BLURRED subjects affected / exposed occurrences (all)	2 / 198 (1.01%) 2	13 / 199 (6.53%) 16	
Gastrointestinal disorders ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	31 / 198 (15.66%) 33	15 / 199 (7.54%) 17	
ABDOMINAL PAIN subjects affected / exposed occurrences (all)	27 / 198 (13.64%) 38	12 / 199 (6.03%) 12	
CONSTIPATION subjects affected / exposed occurrences (all)	78 / 198 (39.39%) 90	73 / 199 (36.68%) 87	
DIARRHOEA subjects affected / exposed occurrences (all)	141 / 198 (71.21%) 238	143 / 199 (71.86%) 207	
DYSPEPSIA subjects affected / exposed occurrences (all)	35 / 198 (17.68%) 42	40 / 199 (20.10%) 46	
DRY MOUTH subjects affected / exposed occurrences (all)	17 / 198 (8.59%) 18	13 / 199 (6.53%) 13	
HAEMORRHOIDS			

subjects affected / exposed	22 / 198 (11.11%)	19 / 199 (9.55%)
occurrences (all)	26	20
GASTROESOPHAGEAL REFLUX DISEASE		
subjects affected / exposed	6 / 198 (3.03%)	27 / 199 (13.57%)
occurrences (all)	6	27
NAUSEA		
subjects affected / exposed	142 / 198 (71.72%)	144 / 199 (72.36%)
occurrences (all)	196	181
MOUTH ULCERATION		
subjects affected / exposed	15 / 198 (7.58%)	5 / 199 (2.51%)
occurrences (all)	16	5
ODYNOPHAGIA		
subjects affected / exposed	10 / 198 (5.05%)	7 / 199 (3.52%)
occurrences (all)	13	7
STOMATITIS		
subjects affected / exposed	56 / 198 (28.28%)	49 / 199 (24.62%)
occurrences (all)	73	53
VOMITING		
subjects affected / exposed	71 / 198 (35.86%)	46 / 199 (23.12%)
occurrences (all)	107	57
Skin and subcutaneous tissue disorders		
ALOPECIA		
subjects affected / exposed	117 / 198 (59.09%)	127 / 199 (63.82%)
occurrences (all)	119	127
DERMATITIS		
subjects affected / exposed	12 / 198 (6.06%)	9 / 199 (4.52%)
occurrences (all)	12	11
DERMATITIS ACNEIFORM		
subjects affected / exposed	9 / 198 (4.55%)	15 / 199 (7.54%)
occurrences (all)	10	18
DRY SKIN		
subjects affected / exposed	28 / 198 (14.14%)	31 / 199 (15.58%)
occurrences (all)	29	32
ERYTHEMA		

subjects affected / exposed	32 / 198 (16.16%)	19 / 199 (9.55%)
occurrences (all)	36	20
NAIL DISCOLOURATION		
subjects affected / exposed	4 / 198 (2.02%)	31 / 199 (15.58%)
occurrences (all)	4	31
NAIL DISORDER		
subjects affected / exposed	21 / 198 (10.61%)	13 / 199 (6.53%)
occurrences (all)	22	13
ONYCHOCLASIS		
subjects affected / exposed	10 / 198 (5.05%)	3 / 199 (1.51%)
occurrences (all)	10	3
NAIL TOXICITY		
subjects affected / exposed	6 / 198 (3.03%)	10 / 199 (5.03%)
occurrences (all)	6	12
ONYCHOLYSIS		
subjects affected / exposed	15 / 198 (7.58%)	14 / 199 (7.04%)
occurrences (all)	15	16
ONYCHOMADESIS		
subjects affected / exposed	5 / 198 (2.53%)	19 / 199 (9.55%)
occurrences (all)	5	20
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME		
subjects affected / exposed	23 / 198 (11.62%)	11 / 199 (5.53%)
occurrences (all)	26	11
PRURITUS		
subjects affected / exposed	44 / 198 (22.22%)	36 / 199 (18.09%)
occurrences (all)	49	42
RASH		
subjects affected / exposed	40 / 198 (20.20%)	46 / 199 (23.12%)
occurrences (all)	47	52
RASH MACULO-PAPULAR		
subjects affected / exposed	3 / 198 (1.52%)	19 / 199 (9.55%)
occurrences (all)	3	19
SKIN HYPERPIGMENTATION		
subjects affected / exposed	7 / 198 (3.54%)	11 / 199 (5.53%)
occurrences (all)	8	11

Renal and urinary disorders			
POLLAKIURIA			
subjects affected / exposed	2 / 198 (1.01%)	13 / 199 (6.53%)	
occurrences (all)	2	14	
DYSURIA			
subjects affected / exposed	5 / 198 (2.53%)	15 / 199 (7.54%)	
occurrences (all)	5	16	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	67 / 198 (33.84%)	73 / 199 (36.68%)	
occurrences (all)	81	96	
BACK PAIN			
subjects affected / exposed	22 / 198 (11.11%)	30 / 199 (15.08%)	
occurrences (all)	25	36	
BONE PAIN			
subjects affected / exposed	13 / 198 (6.57%)	24 / 199 (12.06%)	
occurrences (all)	18	27	
MUSCLE SPASMS			
subjects affected / exposed	16 / 198 (8.08%)	32 / 199 (16.08%)	
occurrences (all)	16	37	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	6 / 198 (3.03%)	13 / 199 (6.53%)	
occurrences (all)	6	13	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	27 / 198 (13.64%)	17 / 199 (8.54%)	
occurrences (all)	28	18	
MYALGIA			
subjects affected / exposed	76 / 198 (38.38%)	49 / 199 (24.62%)	
occurrences (all)	95	57	
PAIN IN EXTREMITY			
subjects affected / exposed	30 / 198 (15.15%)	27 / 199 (13.57%)	
occurrences (all)	36	29	
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	16 / 198 (8.08%)	10 / 199 (5.03%)	
occurrences (all)	18	10	

INFLUENZA			
subjects affected / exposed	14 / 198 (7.07%)	8 / 199 (4.02%)	
occurrences (all)	16	9	
NASOPHARYNGITIS			
subjects affected / exposed	33 / 198 (16.67%)	21 / 199 (10.55%)	
occurrences (all)	40	30	
ORAL CANDIDIASIS			
subjects affected / exposed	10 / 198 (5.05%)	1 / 199 (0.50%)	
occurrences (all)	10	1	
PHARYNGITIS			
subjects affected / exposed	13 / 198 (6.57%)	8 / 199 (4.02%)	
occurrences (all)	14	8	
SINUSITIS			
subjects affected / exposed	9 / 198 (4.55%)	11 / 199 (5.53%)	
occurrences (all)	9	12	
RHINITIS			
subjects affected / exposed	18 / 198 (9.09%)	7 / 199 (3.52%)	
occurrences (all)	19	8	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	6 / 198 (3.03%)	25 / 199 (12.56%)	
occurrences (all)	7	28	
URINARY TRACT INFECTION			
subjects affected / exposed	10 / 198 (5.05%)	32 / 199 (16.08%)	
occurrences (all)	11	36	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	49 / 198 (24.75%)	40 / 199 (20.10%)	
occurrences (all)	59	42	
DEHYDRATION			
subjects affected / exposed	1 / 198 (0.51%)	10 / 199 (5.03%)	
occurrences (all)	1	14	
HYPOKALAEMIA			
subjects affected / exposed	6 / 198 (3.03%)	16 / 199 (8.04%)	
occurrences (all)	10	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2014	It was amended to extend the duration of reporting pregnancy and the time of prohibition of breast feeding to 7 months after receipt of the final dose of study drug.
17 June 2014	The protocol was updated to specify that anti-HER2 treatment should not start if the LVEF is <50% after anthracycline treatment for participants in both Cohorts A and B. The echocardiogram (ECHO)/multiple gated acquisition scan (MUGA) assessment at Cycle 3 or 4 has been removed to be more in line with clinical practice.
26 May 2016	A minor modification of the exclusion criterion regarding history of malignancy has been made for alignment with current clinical practice. Clarification that participants with prior breast malignancies within 5 years of study entry should be excluded was made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported