Clinical trial results:
A randomised, multicenter, multinational Phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer

Summary

EudraCT number	2007-001105-13
Trial protocol	ES AT IT PL GB SE
Global end of trial date	22 September 2014

Results information

Result version number	v1
This version publication date	19 March 2016
First version publication date	19 March 2016

Trial information

Trial identification

Sponsor protocol code	WO20697

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00545688
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse124, Basel, Switzerland, CH-4070
Public contact	F.Hoffmann-LaRocheAG, Roche Trial Information Hotline, +41 616878333, global.trial_information@roche.com
Scientific contact	F.Hoffmann-LaRocheAG, Roche Trial Information Hotline, +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	20 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to make a preliminary assessment of the efficacy of neoadjuvant treatment with trastuzumab plus docetaxel (T+D), as compared to trastuzumab, pertuzumab plus docetaxel (Ptz+T+D), or to pertuzumab plus trastuzumab (Ptz+T), and to compare pertuzumab plus docetaxel (Ptz+D) with trastuzumab, pertuzumab plus docetaxel (Ptz+T+D), in participants with T2-4d human epidermal growth factor receptor 2 (HER2) -positive breast cancer.

Protection of trial subjects:

This study was conducted in full conformance with the principles of the 'Declaration of Helsinki' (and its subsequent amendments) or with the local laws and regulations of the country in which the research was conducted; whichever provided greater protection to the individual. In countries in which good clinical practice (GCP) guidelines exist, sponsor and the investigators strictly adhered to the stated provisions in these guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	Poland: 54
Country: Number of subjects enrolled	Spain: 48
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Italy: 58
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 39
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Peru: 9
Country: Number of subjects enrolled	China: 39
Country: Number of subjects enrolled	Korea, Republic of: 37
Country: Number of subjects enrolled	Russian Federation: 61

Country: Number of subjects enrolled	Thailand: 19
Worldwide total number of subjects	417
EEA total number of subjects	177

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)	385
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 107, 107, 107, and 96 participants (total 417) were randomized to Arms Trastuzumab plus (+) Docetaxel (T+ D), Trastuzumab+Pertuzumab+Docetaxel (T+Ptz+D), Trastuzumab+Pertuzumab (T+Ptz), and Pertuzumab+Docetaxel (Ptz+D), respectively and were included in intent-to-treat population (as randomized).

Pre-assignment

Screening details:

3 participants did not receive correct treatment, as randomized, and 1 (in Arm T + D) did not receive any treatment. Safety population (as treated) included 107, 107, 108, and 94 participants in Arms 'T+D', 'T+Ptz+D', 'T+Ptz', and 'Ptz+D', respectively. Participant flow was available for "As Treated" participants.

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Trastuzumab + Docetaxel

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab intravenous (IV) infusion at a loading dose of 8 milligrams per kilogram (mg/kg) on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 and docetaxel IV infusion at a starting dose of 75 milligrams per square meter (mg/m^2) on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by 5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV (FEC) on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Trastuzumab+Pertuzumab+Docetaxel

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Arm type	Experimental

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Trastuzumab+Pertuzumab

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV on Day 1 of Cycle 5 followed by docetaxel 100 mg/m^2 for three cycles (Cycles 6−8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles. Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 12 until Cycle 17.

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

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Pertuzumab+Docetaxel

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received pertuzumab IV at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 420 mg on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 21.

Arm type	Active comparator

Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Number of subjects in period 1	Trastuzumab + Docetaxel	Trastuzumab+Pertuzumab+Docetaxel	Trastuzumab+Pertuzumab
Started	107	107	107
Completed	107	107	108
Not completed	1	0	0
Received wrong dosage	-	-	-
Unknown reason	1	-	-
Joined	1	0	1
Received wrong dosage	1	-	1

Number of subjects in period 1	Pertuzumab+Docetaxel
Started	96
Completed	94
Not completed	2
Received wrong dosage	2
Unknown reason	-
Joined	0
Received wrong dosage	-

Period 2

Period 2 title	Neo-Adjuvant Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab + Docetaxel

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab intravenous (IV) infusion at a loading dose of 8 milligrams per kilogram (mg/kg) on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 and docetaxel IV infusion at a starting dose of 75 milligrams per square meter (mg/m^2) on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by 5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV (FEC) on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Trastuzumab+Pertuzumab+Docetaxel

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Trastuzumab+Pertuzumab

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-

4.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV on Day 1 of Cycle 5 followed by docetaxel 100 mg/m^2 for three cycles (Cycles 6−8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles. Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 12 until Cycle 17.

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

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Pertuzumab+Docetaxel

Arm description:

Neoadjuvant (Pre-Operative) Treatment: Participants received pertuzumab IV at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 420 mg on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 21.

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

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Number of subjects in period 2	Trastuzumab + Docetaxel	Trastuzumab+Pertuzumab+Docetaxel	Trastuzumab+Pertuzumab
Started	107	107	108
Completed	103	102	94
Not completed	4	5	14
Disease progression	-	1	7
Death	-	1	-
Refused treatment	1	1	4
Adverse event	-	-	2
Unknown reason	1	-	-
Lost to follow-up	1	-	-
Protocol deviation	1	2	1

Number of subjects in period 2	Pertuzumab+Docetaxel
Started	94
Completed	88
Not completed	6
Disease progression	2
Death	-
Refused treatment	1
Adverse event	2
Unknown reason	-
Lost to follow-up	-
Protocol deviation	1

Period 3	
Period 3 title	Adjuvant Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Trastuzumab + Docetaxel

Arm description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by 5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV (FEC) on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Arm type	Experimental

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Trastuzumab+Pertuzumab+Docetaxel

Arm description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Arm type	Experimental
Investigational medicinal product name	Pertuzumab
Investigational medicinal product code	RO4368451
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Trastuzumab+Pertuzumab

Arm description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV on Day 1 of Cycle 5 followed by docetaxel 100 mg/m^2 for three cycles (Cycles 6−8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles. Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 12 until Cycle 17.

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

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Arm title	Pertuzumab+Docetaxel

Arm description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 21.

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

Dosage and administration details:

Loading dose of 840 mg on Day 1 of Cycle 1 and 420 mg on Day 1 of Cycles 2-4.

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

Dosage and administration details:

Loading dose of 8 mg/kg IV infusion on Day 1 of Cycle 1 and maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 during pre-operative period and 6 mg/kg IV on Day 1 of Cycles 5-18 in the T + D and T + Ptz + D arms. In the Ptz + D arm, 6 mg/kg IV on Day 1 of adjuvant period and every 3 weeks thereafter for Cycles 5-21.

Number of subjects in period 3	Trastuzumab + Docetaxel	Trastuzumab+Pertuzumab+Docetaxel	Trastuzumab+Pertuzumab
Started	103	102	94
Completed	98	94	90
Not completed	5	8	4
Disease progression	3	3	-
Refused treatment	1	1	1
Adverse event	-	3	2
Unknown reason	-	1	-
Lost to follow-up	1	-	1

Number of subjects in period 3	Pertuzumab+Docetaxel
Started	88
Completed	74
Not completed	14
Disease progression	7
Refused treatment	5

Adverse event	2
Unknown reason	-
Lost to follow-up	-

Period 4	
Period 4 title	Follow-Up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	No
Arm title	Trastuzumab + Docetaxel

Arm description:

During the post-treatment follow-up period no trial drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Trastuzumab+Pertuzumab+Docetaxe

Arm description:

During the post-treatment follow-up period no trial drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Trastuzumab+Pertuzumab

Arm description:

During the post-treatment follow-up period no trial drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Pertuzumab+Docetaxel

Arm description:

During the post-treatment follow-up period no trial drug was administered.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 4	Trastuzumab + Docetaxel	Trastuzumab+Pertuzumab+Docetaxe	Trastuzumab+Pertuzumab
Started	98	102	98
Completed	77	83	78
Not completed	21	19	20
Disease progression	6	5	9
Death	4	2	2

Refused treatment	6	2	-
Violation of selection criteria	-	2	-
Unspecified reason	2	5	6
Lost to follow-up	3	3	3

Number of subjects in period 4	Pertuzumab+Docetaxel
Started	87
Completed	60
Not completed	27
Disease progression	9
Death	6
Refused treatment	2
Violation of selection criteria	1
Unspecified reason	8
Lost to follow-up	1

Baseline characteristics

Reporting groups[1]	
Reporting group title	Baseline Period
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Subjects included in the Baseline period were the Safety Analysis Population.

Reporting group values	Baseline Period	Total	
Number of subjects	417	417	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	49.8		
standard deviation	± 10.4	-	
Gender categorical Units: Subjects			
Female	417	417	
Male	0	0	

End points reporting groups

Reporting group title	Trastuzumab + Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab intravenous (IV) infusion at a loading dose of 8 milligrams per kilogram (mg/kg) on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 and docetaxel IV infusion at a starting dose of 75 milligrams per square meter (mg/m^2) on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by 5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV (FEC) on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab+Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV on Day 1 of Cycle 5 followed by docetaxel 100 mg/m^2 for three cycles (Cycles 6−8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles. Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 12 until Cycle 17.

Reporting group title	Pertuzumab+Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received pertuzumab IV at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 420 mg on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 21.

Reporting group title	Trastuzumab + Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab intravenous (IV) infusion at a loading dose of 8 milligrams per kilogram (mg/kg) on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 and docetaxel IV infusion at a starting dose of 75 milligrams per square meter (mg/m^2) on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by 5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV (FEC) on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab+Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV on Day 1 of Cycle 5 followed by docetaxel 100 mg/m^2 for three cycles (Cycles 6−8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles. Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 12 until Cycle 17.

Reporting group title	Pertuzumab+Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received pertuzumab IV at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 420 mg on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 21.

Reporting group title	Trastuzumab + Docetaxel

Reporting group description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by 5-fluorouracil 600 mg/m^2 IV, epirubicin 90 mg/m^2 IV, and cyclophosphamide 600 mg/m^2 IV (FEC) on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab+Docetaxel

Reporting group description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab

Reporting group description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV on Day 1 of Cycle 5 followed by docetaxel 100 mg/m^2 for three cycles (Cycles 6−8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles. Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 12 until Cycle 17.

Reporting group title	Pertuzumab+Docetaxel

Reporting group description:

Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 21.

Reporting group title	Trastuzumab + Docetaxel

Reporting group description:

During the post-treatment follow-up period no trial drug was administered.

Reporting group title	Trastuzumab+Pertuzumab+Docetaxe

Reporting group description:

During the post-treatment follow-up period no trial drug was administered.

Reporting group title	Trastuzumab+Pertuzumab

Reporting group description:

During the post-treatment follow-up period no trial drug was administered.

Reporting group title	Pertuzumab+Docetaxel

Reporting group description:

During the post-treatment follow-up period no trial drug was administered.

Primary: Percentage of Participants Achieving Pathological Complete Response (pCR)

End point title	Percentage of Participants Achieving Pathological Complete Response (pCR)

End point description:

pCR was defined as an absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. Participants with invalid/missing pCR assessments were defined as non-responders. Intent-To-Treat (ITT) Population included all randomized participants who received any amount of study medication. Analysis was performed according to initial randomization.

End point type	Primary

End point timeframe:

Approximately 4 months from randomization following surgery or early withdrawal, whichever occurred first (Surgery was performed within 2 weeks after Cycle 4)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+Docetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+Docetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: percentage of participants				
number (confidence interval 95%)	29 (20.6 to 38.5)	45.8 (36.1 to 55.7)	16.8 (10.3 to 25.3)	24 (15.8 to 33.7)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab+Pertuzumab+Docetaxel
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0094 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response rates
Point estimate	16.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.5
upper limit	30.1

Notes:

[1] - Cochran-Mantel-Haenszel test stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen and or progesterone positivity (either positive versus both negative).

Statistical analysis title	Statistical Analysis 2
Comparison groups	Trastuzumab + Docetaxel v

	Trastuzumab+Pertuzumab+Docetaxel
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0141 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Cochran-Mantel-Haenszel test (with Simes multiplicity adjustment) stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen and or progesterone positivity (either positive versus both negative).

Statistical analysis title	Statistical Analysis 3
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab+Pertuzumab
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0198 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response rate
Point estimate	-12.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.8
upper limit	-0.5

Notes:

[3] - Cochran-Mantel-Haenszel test stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen and or progesterone positivity (either positive versus both negative).

Statistical analysis title	Statistical Analysis 4
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab+Pertuzumab
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0198 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - Cochran-Mantel-Haenszel test with Simes multiplicity adjustment was used.

Statistical analysis title	Statistical Analysis 5
Comparison groups	Trastuzumab+Pertuzumab+Docetaxel v Pertuzumab+Docetaxel
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response rates
Point estimate	-21.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.1
upper limit	-8.5

Notes:

[5] - Cochran-Mantel-Haenszel test stratified by breast cancer type (operable, locally advanced, or inflammatory) and estrogen and or progesterone positivity (either positive versus both negative).

Statistical analysis title	Statistical Analysis 6
Comparison groups	Trastuzumab+Pertuzumab+Docetaxel v Pertuzumab+Docetaxel
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Cochran-Mantel-Haenszel test with Simes multiplicity adjustment.

Primary: Percentage of Participants Achieving pCR by Breast Cancer Type

End point title	Percentage of Participants Achieving pCR by Breast Cancer Type[7]

End point description:

pCR was defined as an absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. Based on the type of breast cancer participants were categorized as those with 1. Operable breast cancer, 2. Inflammatory breast cancer and 3. Locally advanced breast cancer. Participants with invalid/missing pCR assessments were defined as non-responders.Analysis was performed on ITT population according to initial randomization. Number (n) equal (=) number of participants included in the specified type of breast cancer.

End point type	Primary

End point timeframe:

Approximately 4 months from randomization following surgery or early withdrawal, whichever occurred first (Surgery was performed within 2 weeks after Cycle 4)

Notes:

[7] - 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 statistical analysis was performed per protocol since this endpoint was sub-group analysis.

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: percentage of participants				
number (confidence interval 95%)				
Operable Breast Cancer (n=64,65,65,60)	23.4 (13.8 to 35.7)	47.7 (35.1 to 60.5)	16.9 (8.8 to 28.3)	26.7 (16.1 to 39.7)
Inflammatory Breast Cancer (n=7,10,7,5)	14.3 (0.4 to 57.9)	40 (12.2 to 73.8)	28.6 (3.7 to 71)	40 (5.3 to 85.3)
Locally Advance Breast Cancer (n=36,32,35,31)	41.7 (25.5 to 59.2)	43.8 (26.4 to 62.3)	14.3 (4.8 to 30.3)	16.1 (5.5 to 33.7)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Achieving pCR by Hormone Receptor Status

End point title	Percentage of Participants Achieving pCR by Hormone Receptor Status[8]

End point description:

pCR was defined as an absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. Participants were classified as Estrogen and/or Progesterone positive (+ve), Estrogen and/or Progesterone negative (-ve) or receptor status unknown. Participants with invalid/missing pCR assessments were defined as non-responders. 99999 to 99999= There were no participants in this category.Analysis was performed on ITT population according to initial randomization. n = number of participants included in the specified hormone receptor status.

End point type	Primary

End point timeframe:

Approximately 4 months from randomization following surgery or early withdrawal, whichever occurred first (Surgery was performed within 2 weeks after Cycle 4)

Notes:

[8] - 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 statistical analysis was performed per protocol since this endpoint was sub-group analysis.

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+Docetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+Docetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: percentage of participants				
number (confidence interval 95%)				
Estrogen and/or Progesterone +ve (n=50,50,51,46)	20 (10 to 33.7)	26 (14.6 to 40.3)	5.9 (1.2 to 16.2)	17.4 (7.8 to 31.4)
Estrogen and/or Progesterone -ve (n=57,57,55,50)	36.8 (24.4 to 50.7)	63.2 (49.3 to 75.6)	27.3 (16.1 to 41)	30 (17.9 to 44.6)
Receptor Status Unknown (0,0,1,0)	99999 (99999 to 99999)	99999 (99999 to 99999)	0 (0 to 97.5)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Achieving pCR by Lymph Node Status

End point title	Percentage of Participants Achieving pCR by Lymph Node Status[9]

End point description:

pCR was defined as an absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. Lymph node status was defined as either negative lymph node at surgery or positive lymph node at surgery. Participants with invalid/missing pCR assessments were defined as non-responders.Analysis was performed on ITT population according to initial randomization.

End point type	Primary

End point timeframe:

Approximately 4 months from randomization following surgery or early withdrawal, whichever occurred first (Surgery was performed within 2 weeks after Cycle 4)

Notes:

[9] - 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 statistical analysis was performed per protocol since this endpoint was sub-group analysis.

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: percentage of participants				
number (not applicable)				
pCR achieved and Negative Lymph Nodes at Surgery	21.5	39.3	11.2	17.7
pCR achieved and Positive Lymph Nodes at Surgery	7.5	6.5	5.6	6.3

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Achieving pCR by Presence or Absence of Residual Intraductal Carcinoma (DCIS) / Intalobular Carcinoma (LCIS)

End point title	Percentage of Participants Achieving pCR by Presence or Absence of Residual Intraductal Carcinoma (DCIS) / Intalobular Carcinoma (LCIS)[10]

End point description:

pCR was defined as an absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. Participants with invalid/missing pCR assessments were defined as non-responders.Analysis was performed on ITT population according to initial randomization.

End point type	Primary

End point timeframe:

Approximately 4 months from randomization following surgery or early withdrawal, whichever occurred first (Surgery was performed within 2 weeks after Cycle 4)

Notes:

[10] - 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 statistical analysis was performed per protocol since this endpoint was sub-group analysis.

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: percentage of participants				
number (not applicable)				
pCR Achieved and No residual DCIS/LCIS at Surgery	16.8	36.4	9.3	17.7
pCR Achieved and Residual DCIS/LCIS at Surgery	12.1	9.3	7.5	6.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Best Primary Tumor Response (Complete Response [CR], Partial Response [PR], Stable Disease [SD] or Disease Progression [PD]) During Neo-Adjuvant Treatment by X-Ray/Mammography

End point title	Percentage of Participants Achieving Best Primary Tumor Response (Complete Response [CR], Partial Response [PR], Stable Disease [SD] or Disease Progression [PD]) During Neo-Adjuvant Treatment by X-Ray/Mammography

End point description:

Tumor assessments were made based upon the Response Evaluation Criteria in Solid Tumors (RECIST) criteria - version 1.0. The clinical response at each cycle up to the last assessment prior to surgery was derived for primary breast tumor using the following algorithm: CR: if measurement of '0' is noted at a given cycle as compared to baseline measurement which is greater than (>)0 at screening or cycle 1 Day 1; PR: if measurement is at least a 30 percent (%) decreased compared to baseline levels . (Reference= baseline size or sum of sizes); SD: if measurement at a given cycle is not sufficient shrinkage to qualify for neither PR nor sufficient increase to qualify for PD compared to baseline levels. PD: if lesion is at least a 20 % increase from measurements at baseline.Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	58	61	47
Units: percentage of participants				
number (not applicable)				
CR	18.3	19	13.1	19.1
PR	49.3	46.6	36.1	46.8
SD	31	32.8	44.3	34
PD	1.4	1.7	6.6	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Best Overall Response (CR, PR, SD or PD) During Neo-Adjuvant Period by X-Ray/Mammography

End point title	Percentage of Participants Achieving Best Overall Response (CR, PR, SD or PD) During Neo-Adjuvant Period by X-Ray/Mammography

End point description:

Tumor assessments were made based on the RECIST criteria - version 1.0 The overall response at each cycle up to the last assessment prior to surgery was derived for: i) the primary breast lesion; (ii) across secondary breast lesions, (iii) across all breast lesions (iv) across axillary nodes (v) across supraclavicular nodes and (vi) across all nodes (vii) across all lesions (overall) using the following algorithm: CR: if measurement of '0' is noted at a given cycle as compared to baseline measurement which is >0 at screening or cycle 1 day 1; PR: if measurement is at least a 30% decreased compared to baseline levels . (Reference= baseline size or sum of sizes); SD: if measurement at a given cycle is not sufficient shrinkage to qualify for neither PR nor sufficient increase to qualify for PD compared to baseline levels. PD: if lesion is at least a 20 % increase from measurements at baseline. Overall response is derived based on the sum total of breast tumors and all nodes examined. Ana

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	53	55	43
Units: percentage of participants				
number (not applicable)				
CR	18.3	18.9	12.7	18.6
PR	49.3	49.1	34.5	46.5
SD	31	30.2	45.5	34.9
PD	1.4	1.9	7.3	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Best Primary Breast Tumor Response (CR, PR, SD or PD) During Neo-Adjuvant Period by Clinical Examination

End point title	Percentage of Participants Achieving Best Primary Breast Tumor Response (CR, PR, SD or PD) During Neo-Adjuvant Period by Clinical Examination

End point description:

Tumor assessments were made based on the RECIST criteria - version 1.0 The clinical response at each cycle up to the last assessment prior to surgery was derived for primary breast tumor using the following algorithm: CR: if measurement of '0' is noted at a given cycle as compared to baseline measurement which is >0 at screening or cycle 1 day 1; PR: if measurement is at least a 30% decreased compared to baseline levels. (Reference= baseline size or sum of sizes); SD: if measurement at a given cycle is not sufficient shrinkage to qualify for neither PR nor sufficient increase to qualify for PD compared to baseline levels. PD: if lesion is at least a 20 % increase from measurements at baseline. Overall response is derived based on the sum total of breast tumors and all nodes examined.Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	101	102	91
Units: percentage of participants				
number (not applicable)				
CR	23.2	30.7	16.7	20.9
PR	56.6	57.4	51	50.5
SD	20.2	11.9	30.4	28.6
PD	0	0	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Best Overall Response (CR, PR, SD or PD) During the Neo-Adjuvant Period by Clinical Examination

End point title	Percentage of Participants Achieving Best Overall Response (CR, PR, SD or PD) During the Neo-Adjuvant Period by Clinical Examination

End point description:

Clinical response was determined based on tumor measurements by sponsor in combination with tumor response assessment by investigator. Tumor assessments were made based on the RECIST criteria - version 1.0. The clinical response at each cycle up to the last assessment prior to surgery was derived using the following algorithm: CR: if measurement of '0' is noted at a given cycle as compared to baseline measurement which is >0 at screening or cycle 1 day 1; PR: if measurement is at least a 30% decreased compared to baseline levels. Clinical Responders are participants who have achieved CR or PR during the Neo-adjuvant treatment. Overall response is derived based on the sum total of breast tumors and all nodes examined. Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	100	98	88
Units: percentage of participants				
number (not applicable)				
CR	21.6	25	11.2	15.9
PR	59.8	63	55.1	58
SD	17.5	12	31.6	26.1
PD	1	0	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Clinical Response During Neo-Adjuvant Period by X-Ray/Mammography

End point title	Percentage of Participants Achieving Clinical Response During Neo-Adjuvant Period by X-Ray/Mammography

End point description:

Clinical response was determined based on tumor measurements by sponsor in combination with tumor response assessment by investigator. Tumor assessments were made based on the RECIST criteria - version 1.0. The clinical response at each cycle up to the last assessment prior to surgery was derived using the following algorithm: CR: if measurement of '0' is noted at a given cycle as compared to baseline measurement which is >0 at screening or cycle 1 day 1; PR: if measurement is at least a 30% decreased compared to baseline levels. Clinical Responders are participants who have achieved CR or PR during the Neo-adjuvant treatment. Overall response is derived based on the sum total of breast tumors and all nodes examined. Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome and n = number participants analyzed in the specified category.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+Docetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+Docetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	58	61	47
Units: percentage of participants				
number (confidence interval 95%)				
Primary Breast Tumor (n=71,58,61,47)	67.6 (55.5 to 78.2)	65.5 (51.9 to 77.5)	49.2 (36.1 to 62.3)	66 (50.7 to 79.1)
Overall Response (n=71,53,55,43)	67.6 (55.5 to 78.2)	67.9 (53.7 to 80.1)	47.3 (33.7 to 61.2)	65.1 (49.1 to 79)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Clinical Response During Neo-Adjuvant Period by Clinical Examination

End point title	Percentage of Participants Achieving Clinical Response During Neo-Adjuvant Period by Clinical Examination

End point description:

Tumor assessments were made based on the RECIST criteria - version 1.0 The clinical response at each cycle up to the last assessment prior to surgery was derived using the following algorithm: CR: if measurement of '0' is noted at a given cycle as compared to baseline measurement which is >0 at screening or cycle 1 day 1; PR: if measurement is at least a 30% decreased compared to baseline levels . (Reference= baseline size or sum of sizes). Clinical Responders are participants who have achieved CR or PR during the Neo-adjuvant treatment. Primary breast tumor clinical response is based on primary breast tumor assessment. Overall response is derived based on the sum total of breast tumors and all nodes examined.Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome and n = number participants analyzed in the specified category.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	101	102	91
Units: percentage of participants				
number (confidence interval 95%)				
Primary Breast Tumor (n=99,101,102,91)	79.8 (70.5 to 87.2)	88.1 (80.2 to 93.7)	67.6 (57.7 to 76.6)	71.4 (61 to 80.4)
Overall Response (n=97,100,98,88)	81.4 (72.3 to 88.6)	88 (80 to 93.6)	66.3 (56.1 to 75.6)	73.9 (63.4 to 82.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Clinical Response During Neo-Adjuvant Treatment Period

End point title	Time to Clinical Response During Neo-Adjuvant Treatment Period

End point description:

Time to clinical response was defined as the time from the date of first dose received to the date of assessment of clinical response. Time to Clinical response was determined by Kaplan-Meier estimates. Tumor assessments were made based on the RECIST criteria - version 1.0. The clinical response at each cycle up to the last assessment prior to surgery was derived using the following algorithm: CR: if measurement of '0' is noted at a given cycle as compared to baseline measurement which is >0 at screening or cycle 1 day 1; PR: if measurement is at least a 30% decreased compared to baseline levels . (Reference= baseline size or sum of sizes). Clinical Responders are participants who have achieved CR or PR during the Neo-adjuvant treatment.Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	101	102	91
Units: months				
median (confidence interval 80%)	6.3 (6 to 7)	6.3 (4 to 7)	6.9 (6 to 9)	7.3 (6 to 9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Progressive Disease During Neo-Adjuvant Treatment Period

End point title	Percentage of Participants With Progressive Disease During Neo-Adjuvant Treatment Period

End point description:

Tumor assessments were made based upon the Response Evaluation Criteria in Solid Tumors (RECIST) criteria - version 1.0. The clinical response at each cycle up to the last assessment prior to surgery was derived for: i) the primary breast lesion; (ii) across secondary breast lesions, (iii) across all breast lesions (iv) across axillary nodes (v) across supraclavicular nodes and (vi) across all nodes (vii) across all lesions (overall) using the following algorithm: PD: if lesion is at least a 20 % increased from measurements at baseline. Percentage of participants along with 95% Confidence Interval (CI) for one sample binomial using Pearson-Clopper method were reported. Missing investigator assessments were considered as no progressive disease. Analysis was performed on ITT population according to initial randomization.

End point type	Secondary

End point timeframe:

Baseline up to Cycle 4 (assessed at baseline, Day 1 of Cycles 1-4 Pre-Surgery)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: percentage of participants				
number (confidence interval 80%)	0 (0 to 3.4)	0.9 (0 to 5.1)	7.5 (3.3 to 14.2)	2.1 (0.3 to 7.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Breast Conserving Surgery For Whom Mastectomy Was Planned

End point title	Percentage of Participants Achieving Breast Conserving Surgery For Whom Mastectomy Was Planned

End point description:

Breast Conserving Surgery (BCS) was defined as quadrantectomy, lumpectomy, no surgery, sentinel node biopsy, axillary surgical resection or other method of avoiding mastectomy. Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome.

End point type	Secondary

End point timeframe:

Surgery (Within 2 weeks after Cycle 4)

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	56	61	60
Units: percentage of participants				
number (confidence interval 95%)	22.6 (12.9 to 35)	23.2 (13 to 36.4)	18 (9.4 to 30)	31.7 (20.3 to 45)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were Progression Free and Disease Free

End point title	Percentage of Participants Who Were Progression Free and Disease Free

End point description:

Disease-free survival (DFS) was defined as time from first date of no disease to first documentation of PD or death. Participants without progression after surgery were considered Disease Free. Progression-free survival (PFS) was defined as time from date of randomization to first documentation of PD or death. Any evidence of contralateral disease in-situ was not considered as PD. Participants who were withdrawn from study without documented progression and for whom evaluations were made, were censored at date of last assessment when the participant was known to be free from progressive disease or were disease free. Participants without post baseline assessments but known to be alive were censored at the time of randomization. Analysis was performed on ITT population according to initial randomization. Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome.

End point type	Secondary

End point timeframe:

Randomization up to a maximum of 329 weeks

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: percentage of participants				
number (not applicable)				
Progression Free	82.2	84.1	74.8	75
Disease Free	82.5	85.1	80.2	76.1

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free and Disease Free Survival

End point title	Progression Free and Disease Free Survival

End point description:

DFS was defined as the time from the first date of no disease (date of surgery) to the first documentation of PD or death. Participants without progression after surgery were considered Disease Free. Any evidence of contralateral disease in-situ was not considered as PD. PFS was defined as the time from the date of randomization to the first documentation of PD or death. Any evidence of contralateral disease in-situ was not considered as PD. DFS and PFS were determined using Kaplan-Meier estimates. 99999 (99999-99999) = Data not available. Median and corresponding 80% confidence interval were not achieved due to the low number of events in this patient population, as expected. Analysis was performed on ITT population according to initial randomization. Number of participants analyzed = participants evaluable for this outcome.

End point type	Secondary

End point timeframe:

Randomization up to a maximum of 329 weeks

End point values	Trastuzumab + Docetaxel	Trastuzumab+ Pertuzumab+D ocetaxel	Trastuzumab+ Pertuzumab	Pertuzumab+D ocetaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	107	107	107	96
Units: months				
median (confidence interval 95%)				
Progression Free	99999 (99999 to 99999)	71 (71 to 76)	99999 (99999 to 99999)	99999 (99999 to 99999)
Disease Free	99999 (99999 to 99999)	67.2 (67 to 72)	99999 (99999 to 99999)	99999 (99999 to 99999)

Statistical analyses

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

HR is based on Cox proportional hazard regression stratified by breast cancer type and hormone positivity. Comparison is for PFS.

Comparison groups	Trastuzumab + Docetaxel v Trastuzumab+Pertuzumab+Docetaxel

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2983
Method	Cox proportional Hazards
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.4

Statistical analysis title	Statistical Analysis 8
Statistical analysis description:	
HR is based on Cox proportional hazard regression stratified by breast cancer type and hormone positivity. Comparison is for PFS.	
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab+Pertuzumab
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4722
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.3

Statistical analysis title	Statistical Analysis 9
Statistical analysis description:	
HR is based on Cox proportional hazard regression stratified by breast cancer type and hormone positivity. Comparison is for PFS.	
Comparison groups	Trastuzumab+Pertuzumab+Docetaxel v Pertuzumab+Docetaxel
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0268
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	2.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	3.93

Statistical analysis title	Statistical Analysis 10
Statistical analysis description:	
HR is based on Cox proportional hazard regression stratified by breast cancer type and hormone positivity. Comparison is for DFS.	
Comparison groups	Trastuzumab + Docetaxel v Pertuzumab+Docetaxel
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1805
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.27

Statistical analysis title	Statistical Analysis 11
Statistical analysis description:	
HR is based on Cox proportional hazard regression stratified by breast cancer type and hormone positivity. Comparison is for DFS.	
Comparison groups	Trastuzumab + Docetaxel v Trastuzumab+Pertuzumab+Docetaxel
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5901
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.64

Statistical analysis title	Statistical Analysis 12

Statistical analysis description:

HR is based on Cox proportional hazard regression stratified by breast cancer type and hormone positivity. Comparison is for DFS.

Comparison groups	Trastuzumab+Pertuzumab+Docetaxel v Pertuzumab+Docetaxel
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025
Method	Cochran-Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	4.32

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the date of Screening until the clinical cutoff date 20th October 2014 up to 7 years.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Trastuzumab+Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg on Day 1 of Cycles 2-4 and docetaxel IV infusion at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab+Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 17.

Reporting group title	Trastuzumab+Pertuzumab

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received trastuzumab IV infusion at a loading dose of 8 mg/kg and pertuzumab IV infusion at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 6 mg/kg trastuzumab and 420 mg pertuzumab on Day 1 of Cycles 2-4.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by docetaxel 75 mg/m^2 IV on Day 1 of Cycle 5 followed by docetaxel 100 mg/m^2 for three cycles (Cycles 6−8) if no dose-limiting toxicity occurred. For Cycles 9 to 11, participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles. Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 12 until Cycle 17.

Reporting group title	Pertuzumab+Docetaxel

Reporting group description:

Neoadjuvant (Pre-Operative) Treatment: Participants received pertuzumab IV at a loading dose of 840 mg on Day 1 of Cycle 1 (21-day cycle) followed by a maintenance dose of 420 mg on Day 1 of Cycles 2-4. Docetaxel IV infusion was administered at a starting dose of 75 mg/m^2 on Day 1 of Cycle 1 followed by 100 mg/m^2 on Day 1 of Cycles 2-4, if no dose limiting toxicity occurred.
Adjuvant (2-Week Post-Operative) Treatment: Participants received trastuzumab 6 mg/kg IV followed by FEC on Day 1 and every 3 weeks thereafter for three cycles (Cycles 5−7). Trastuzumab 6 mg/kg IV was continued every 3 weeks from Cycle 8 to Cycle 21.

Serious adverse events	Trastuzumab+Docetaxel	Trastuzumab+Pertuzumab+Docetaxel	Trastuzumab+Pertuzumab
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 107 (19.63%)	22 / 107 (20.56%)	19 / 108 (17.59%)
number of deaths (all causes)	6	8	9
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous insufficiency			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	2 / 108 (1.85%)
occurrences causally related to treatment / all	1 / 1	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ovarian cyst ruptured			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian disorder			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular dysfunction			

subjects affected / exposed	0 / 107 (0.00%)	3 / 107 (2.80%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dural arteriovenous fistula			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	10 / 107 (9.35%)	8 / 107 (7.48%)	4 / 108 (3.70%)
occurrences causally related to treatment / all	10 / 10	8 / 8	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 107 (0.93%)	6 / 107 (5.61%)	3 / 108 (2.78%)
occurrences causally related to treatment / all	2 / 2	6 / 6	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 107 (1.87%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal strangulated hernia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis fulminant			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin mass			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Neutropenic infection			

subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 107 (0.00%)	2 / 107 (1.87%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	2 / 107 (1.87%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			

subjects affected / exposed	0 / 107 (0.00%)	1 / 107 (0.93%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	1 / 108 (0.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 107 (0.00%)	0 / 107 (0.00%)	0 / 108 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Pertuzumab+Docetaxel		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 94 (22.34%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous insufficiency			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Impaired healing			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst ruptured			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian disorder			

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine haemorrhage			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound dehiscence			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			

subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dural arteriovenous fistula				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	12 / 94 (12.77%)			
occurrences causally related to treatment / all	16 / 16			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	6 / 94 (6.38%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal strangulated hernia				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer haemorrhage				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis fulminant			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin mass			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Neutropenic infection			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			

subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast abscess				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
H1N1 influenza				
subjects affected / exposed	0 / 94 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				

subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Trastuzumab+Docetaxel	Trastuzumab+Pertuzumab+Docetaxel	Trastuzumab+Pertuzumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 107 (100.00%)	105 / 107 (98.13%)	101 / 108 (93.52%)
Vascular disorders			
Hot flush			
subjects affected / exposed	11 / 107 (10.28%)	12 / 107 (11.21%)	8 / 108 (7.41%)
occurrences (all)	13	12	8
Lymphoedema			

subjects affected / exposed	4 / 107 (3.74%)	6 / 107 (5.61%)	12 / 108 (11.11%)
occurrences (all)	4	6	13
Flushing			
subjects affected / exposed	6 / 107 (5.61%)	5 / 107 (4.67%)	5 / 108 (4.63%)
occurrences (all)	8	14	10
Hypertension			
subjects affected / exposed	5 / 107 (4.67%)	6 / 107 (5.61%)	4 / 108 (3.70%)
occurrences (all)	6	6	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	35 / 107 (32.71%)	35 / 107 (32.71%)	34 / 108 (31.48%)
occurrences (all)	93	68	66
Mucosal inflammation			
subjects affected / exposed	28 / 107 (26.17%)	33 / 107 (30.84%)	18 / 108 (16.67%)
occurrences (all)	45	60	28
Asthenia			
subjects affected / exposed	22 / 107 (20.56%)	29 / 107 (27.10%)	19 / 108 (17.59%)
occurrences (all)	62	66	52
Pyrexia			
subjects affected / exposed	16 / 107 (14.95%)	25 / 107 (23.36%)	21 / 108 (19.44%)
occurrences (all)	17	32	26
Oedema peripheral			
subjects affected / exposed	12 / 107 (11.21%)	7 / 107 (6.54%)	18 / 108 (16.67%)
occurrences (all)	18	7	19
Chills			
subjects affected / exposed	8 / 107 (7.48%)	4 / 107 (3.74%)	10 / 108 (9.26%)
occurrences (all)	9	5	12
Chest pain			
subjects affected / exposed	4 / 107 (3.74%)	2 / 107 (1.87%)	4 / 108 (3.70%)
occurrences (all)	5	2	4
Pain			
subjects affected / exposed	2 / 107 (1.87%)	3 / 107 (2.80%)	3 / 108 (2.78%)
occurrences (all)	3	3	3
Oedema			

subjects affected / exposed	1 / 107 (0.93%)	0 / 107 (0.00%)	6 / 108 (5.56%)
occurrences (all)	1	0	7
General disorders			
subjects affected / exposed	17 / 107 (15.89%)	16 / 107 (14.95%)	15 / 108 (13.89%)
occurrences (all)	43	29	39
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 107 (1.87%)	6 / 107 (5.61%)	12 / 108 (11.11%)
occurrences (all)	3	7	21
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	7 / 107 (6.54%)	4 / 107 (3.74%)	10 / 108 (9.26%)
occurrences (all)	7	4	10
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 107 (10.28%)	9 / 107 (8.41%)	19 / 108 (17.59%)
occurrences (all)	16	11	24
Epistaxis			
subjects affected / exposed	6 / 107 (5.61%)	11 / 107 (10.28%)	6 / 108 (5.56%)
occurrences (all)	9	19	9
Oropharyngeal pain			
subjects affected / exposed	7 / 107 (6.54%)	9 / 107 (8.41%)	2 / 108 (1.85%)
occurrences (all)	11	10	3
Dyspnoea			
subjects affected / exposed	5 / 107 (4.67%)	7 / 107 (6.54%)	7 / 108 (6.48%)
occurrences (all)	6	9	8
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 107 (13.08%)	13 / 107 (12.15%)	8 / 108 (7.41%)
occurrences (all)	18	17	13
Anxiety			
subjects affected / exposed	2 / 107 (1.87%)	3 / 107 (2.80%)	6 / 108 (5.56%)
occurrences (all)	2	3	9
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	9 / 107 (8.41%)	2 / 107 (1.87%)	2 / 108 (1.85%)
occurrences (all)	10	2	2
Weight increased			
subjects affected / exposed	4 / 107 (3.74%)	2 / 107 (1.87%)	9 / 108 (8.33%)
occurrences (all)	4	2	9
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 107 (8.41%)	0 / 107 (0.00%)	2 / 108 (1.85%)
occurrences (all)	10	0	2
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	21 / 107 (19.63%)	19 / 107 (17.76%)	22 / 108 (20.37%)
occurrences (all)	22	22	24
Infusion related reaction			
subjects affected / exposed	6 / 107 (5.61%)	7 / 107 (6.54%)	8 / 108 (7.41%)
occurrences (all)	7	8	18
Seroma			
subjects affected / exposed	6 / 107 (5.61%)	7 / 107 (6.54%)	4 / 108 (3.70%)
occurrences (all)	7	7	5
Procedural pain			
subjects affected / exposed	2 / 107 (1.87%)	3 / 107 (2.80%)	6 / 108 (5.56%)
occurrences (all)	2	4	7
Incision site pain			
subjects affected / exposed	1 / 107 (0.93%)	2 / 107 (1.87%)	3 / 108 (2.78%)
occurrences (all)	1	2	5
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 107 (1.87%)	5 / 107 (4.67%)	7 / 108 (6.48%)
occurrences (all)	2	8	9
Left ventricular dysfunction			
subjects affected / exposed	2 / 107 (1.87%)	6 / 107 (5.61%)	2 / 108 (1.85%)
occurrences (all)	2	6	2
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 107 (15.89%)	14 / 107 (13.08%)	25 / 108 (23.15%)
occurrences (all)	25	22	41
Dysgeusia			

subjects affected / exposed	16 / 107 (14.95%)	16 / 107 (14.95%)	14 / 108 (12.96%)
occurrences (all)	21	24	20
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 107 (13.08%)	10 / 107 (9.35%)	15 / 108 (13.89%)
occurrences (all)	17	11	18
Dizziness			
subjects affected / exposed	8 / 107 (7.48%)	6 / 107 (5.61%)	14 / 108 (12.96%)
occurrences (all)	9	6	25
Neuropathy peripheral			
subjects affected / exposed	10 / 107 (9.35%)	6 / 107 (5.61%)	4 / 108 (3.70%)
occurrences (all)	15	6	5
Paraesthesia			
subjects affected / exposed	7 / 107 (6.54%)	2 / 107 (1.87%)	3 / 108 (2.78%)
occurrences (all)	8	2	3
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	80 / 107 (74.77%)	64 / 107 (59.81%)	46 / 108 (42.59%)
occurrences (all)	236	168	134
Leukopenia			
subjects affected / exposed	24 / 107 (22.43%)	13 / 107 (12.15%)	13 / 108 (12.04%)
occurrences (all)	63	32	34
Anaemia			
subjects affected / exposed	9 / 107 (8.41%)	6 / 107 (5.61%)	11 / 108 (10.19%)
occurrences (all)	14	7	14
Eye disorders			
Lacrimation increased			
subjects affected / exposed	3 / 107 (2.80%)	8 / 107 (7.48%)	6 / 108 (5.56%)
occurrences (all)	3	8	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	70 / 107 (65.42%)	71 / 107 (66.36%)	52 / 108 (48.15%)
occurrences (all)	145	178	123
Diarrhoea			
subjects affected / exposed	40 / 107 (37.38%)	55 / 107 (51.40%)	46 / 108 (42.59%)
occurrences (all)	72	107	96
Vomiting			

subjects affected / exposed	31 / 107 (28.97%)	39 / 107 (36.45%)	31 / 108 (28.70%)
occurrences (all)	46	53	56
Stomatitis			
subjects affected / exposed	12 / 107 (11.21%)	22 / 107 (20.56%)	21 / 108 (19.44%)
occurrences (all)	16	38	34
Abdominal pain upper			
subjects affected / exposed	8 / 107 (7.48%)	9 / 107 (8.41%)	12 / 108 (11.11%)
occurrences (all)	10	9	13
Constipation			
subjects affected / exposed	12 / 107 (11.21%)	14 / 107 (13.08%)	9 / 108 (8.33%)
occurrences (all)	26	20	12
Abdominal pain			
subjects affected / exposed	9 / 107 (8.41%)	11 / 107 (10.28%)	8 / 108 (7.41%)
occurrences (all)	11	13	8
Haemorrhoids			
subjects affected / exposed	5 / 107 (4.67%)	8 / 107 (7.48%)	8 / 108 (7.41%)
occurrences (all)	5	8	8
Dyspepsia			
subjects affected / exposed	6 / 107 (5.61%)	6 / 107 (5.61%)	6 / 108 (5.56%)
occurrences (all)	12	11	13
Abdominal distension			
subjects affected / exposed	1 / 107 (0.93%)	1 / 107 (0.93%)	2 / 108 (1.85%)
occurrences (all)	1	1	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	75 / 107 (70.09%)	73 / 107 (68.22%)	59 / 108 (54.63%)
occurrences (all)	79	79	59
Rash			
subjects affected / exposed	26 / 107 (24.30%)	30 / 107 (28.04%)	22 / 108 (20.37%)
occurrences (all)	43	57	26
Nail disorder			
subjects affected / exposed	17 / 107 (15.89%)	13 / 107 (12.15%)	16 / 108 (14.81%)
occurrences (all)	17	14	18
Pruritus			
subjects affected / exposed	8 / 107 (7.48%)	5 / 107 (4.67%)	10 / 108 (9.26%)
occurrences (all)	9	7	10

Erythema			
subjects affected / exposed	5 / 107 (4.67%)	6 / 107 (5.61%)	7 / 108 (6.48%)
occurrences (all)	7	7	15
Skin hyperpigmentation			
subjects affected / exposed	5 / 107 (4.67%)	7 / 107 (6.54%)	2 / 108 (1.85%)
occurrences (all)	5	7	2
Urticaria			
subjects affected / exposed	1 / 107 (0.93%)	6 / 107 (5.61%)	4 / 108 (3.70%)
occurrences (all)	1	9	5
Acne			
subjects affected / exposed	3 / 107 (2.80%)	7 / 107 (6.54%)	2 / 108 (1.85%)
occurrences (all)	3	10	3
Dry skin			
subjects affected / exposed	7 / 107 (6.54%)	2 / 107 (1.87%)	3 / 108 (2.78%)
occurrences (all)	9	2	4
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	24 / 107 (22.43%)	25 / 107 (23.36%)	29 / 108 (26.85%)
occurrences (all)	43	43	61
Arthralgia			
subjects affected / exposed	16 / 107 (14.95%)	18 / 107 (16.82%)	13 / 108 (12.04%)
occurrences (all)	27	21	19
Musculoskeletal pain			
subjects affected / exposed	13 / 107 (12.15%)	13 / 107 (12.15%)	5 / 108 (4.63%)
occurrences (all)	21	19	6
Bone pain			
subjects affected / exposed	13 / 107 (12.15%)	11 / 107 (10.28%)	7 / 108 (6.48%)
occurrences (all)	20	21	11
Back pain			
subjects affected / exposed	7 / 107 (6.54%)	7 / 107 (6.54%)	8 / 108 (7.41%)
occurrences (all)	8	7	12
Pain in extremity			
subjects affected / exposed	9 / 107 (8.41%)	7 / 107 (6.54%)	7 / 108 (6.48%)
occurrences (all)	11	9	10
Infections and infestations			

Upper respiratory tract infection			
subjects affected / exposed	12 / 107 (11.21%)	9 / 107 (8.41%)	11 / 108 (10.19%)
occurrences (all)	14	12	15
Nasopharyngitis			
subjects affected / exposed	12 / 107 (11.21%)	8 / 107 (7.48%)	7 / 108 (6.48%)
occurrences (all)	13	13	8
Pharyngitis			
subjects affected / exposed	8 / 107 (7.48%)	4 / 107 (3.74%)	4 / 108 (3.70%)
occurrences (all)	8	5	4
Urinary tract infection			
subjects affected / exposed	7 / 107 (6.54%)	4 / 107 (3.74%)	3 / 108 (2.78%)
occurrences (all)	10	4	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 107 (17.76%)	18 / 107 (16.82%)	15 / 108 (13.89%)
occurrences (all)	32	39	22

Non-serious adverse events	Pertuzumab+Docetaxel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 94 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	7		
Lymphoedema			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Flushing			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	3 / 94 (3.19%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	37 / 94 (39.36%)		
occurrences (all)	70		
Mucosal inflammation			
subjects affected / exposed	28 / 94 (29.79%)		
occurrences (all)	43		
Asthenia			
subjects affected / exposed	23 / 94 (24.47%)		
occurrences (all)	54		
Pyrexia			
subjects affected / exposed	14 / 94 (14.89%)		
occurrences (all)	19		
Oedema peripheral			
subjects affected / exposed	9 / 94 (9.57%)		
occurrences (all)	10		
Chills			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	7		
Oedema			
subjects affected / exposed	4 / 94 (4.26%)		
occurrences (all)	4		
General disorders			
subjects affected / exposed	26 / 94 (27.66%)		
occurrences (all)	47		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	7		
Reproductive system and breast disorders			

Menstruation irregular subjects affected / exposed occurrences (all)	9 / 94 (9.57%) 9		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 12 / 94 (12.77%) 14 6 / 94 (6.38%) 9 10 / 94 (10.64%) 12 4 / 94 (4.26%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	 14 / 94 (14.89%) 23 0 / 94 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	 5 / 94 (5.32%) 5 1 / 94 (1.06%) 1 2 / 94 (2.13%) 2		
Injury, poisoning and procedural complications			

Radiation skin injury subjects affected / exposed occurrences (all)	24 / 94 (25.53%) 25		
Infusion related reaction subjects affected / exposed occurrences (all)	8 / 94 (8.51%) 13		
Seroma subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5		
Procedural pain subjects affected / exposed occurrences (all)	2 / 94 (2.13%) 2		
Incision site pain subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 5		
Left ventricular dysfunction subjects affected / exposed occurrences (all)	5 / 94 (5.32%) 6		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	22 / 94 (23.40%) 34		
Dysgeusia subjects affected / exposed occurrences (all)	10 / 94 (10.64%) 12		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	14 / 94 (14.89%) 14		
Dizziness subjects affected / exposed occurrences (all)	8 / 94 (8.51%) 10		
Neuropathy peripheral			

subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Paraesthesia			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	67 / 94 (71.28%)		
occurrences (all)	192		
Leukopenia			
subjects affected / exposed	15 / 94 (15.96%)		
occurrences (all)	32		
Anaemia			
subjects affected / exposed	12 / 94 (12.77%)		
occurrences (all)	14		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	6		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	61 / 94 (64.89%)		
occurrences (all)	139		
Diarrhoea			
subjects affected / exposed	52 / 94 (55.32%)		
occurrences (all)	96		
Vomiting			
subjects affected / exposed	37 / 94 (39.36%)		
occurrences (all)	60		
Stomatitis			
subjects affected / exposed	11 / 94 (11.70%)		
occurrences (all)	17		
Abdominal pain upper			
subjects affected / exposed	12 / 94 (12.77%)		
occurrences (all)	14		
Constipation			

subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	7		
Abdominal pain			
subjects affected / exposed	10 / 94 (10.64%)		
occurrences (all)	10		
Haemorrhoids			
subjects affected / exposed	4 / 94 (4.26%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Abdominal distension			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	65 / 94 (69.15%)		
occurrences (all)	66		
Rash			
subjects affected / exposed	30 / 94 (31.91%)		
occurrences (all)	43		
Nail disorder			
subjects affected / exposed	13 / 94 (13.83%)		
occurrences (all)	14		
Pruritus			
subjects affected / exposed	8 / 94 (8.51%)		
occurrences (all)	9		
Erythema			
subjects affected / exposed	11 / 94 (11.70%)		
occurrences (all)	13		
Skin hyperpigmentation			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	6		
Urticaria			
subjects affected / exposed	7 / 94 (7.45%)		
occurrences (all)	7		

Acne			
subjects affected / exposed	4 / 94 (4.26%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	22 / 94 (23.40%)		
occurrences (all)	37		
Arthralgia			
subjects affected / exposed	19 / 94 (20.21%)		
occurrences (all)	27		
Musculoskeletal pain			
subjects affected / exposed	11 / 94 (11.70%)		
occurrences (all)	13		
Bone pain			
subjects affected / exposed	8 / 94 (8.51%)		
occurrences (all)	10		
Back pain			
subjects affected / exposed	11 / 94 (11.70%)		
occurrences (all)	12		
Pain in extremity			
subjects affected / exposed	6 / 94 (6.38%)		
occurrences (all)	6		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	13 / 94 (13.83%)		
occurrences (all)	19		
Nasopharyngitis			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Pharyngitis			
subjects affected / exposed	5 / 94 (5.32%)		
occurrences (all)	6		
Urinary tract infection			

subjects affected / exposed occurrences (all)	6 / 94 (6.38%) 6		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 23 / 94 (24.47%) 29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2007	1. Addition of a fourth treatment arm (Arm D), in order to evaluate the efficacy of pertuzumab, in the absence of trastuzumab. 2. Increase in the number of subjects participating in the study from 180 to 400, and corresponding increase in the number of centers, from 45-55 to 100. 3. Amendment of efficacy endpoints, hypothesis testing and analyses to reflect addition of Arm D and increased participant numbers. Addition of an exclusion criterion.
11 December 2008	Correction of the tumor-node-metastasis (TNM) classes used to classify participants' disease for the stratification groups operable, locally advanced, or inflammatory cancer for this study.
27 June 2009	1. Updates to: the definition of post-menopausal women, the contraceptive requirements for women of child bearing potential as recommended by The Medicines and Healthcare Products Regulatory Agency (MHRA) in accordance with the ICH M3 guideline, and the pregnancy testing scheduling. 2. Clarification of clinical response definition.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported