Clinical trial results:
A Multicenter, Open-Label, Single-Arm Safety Study of Herceptin SC In Combination With Perjeta and Docetaxel in Treatment of Patients With HER2-Positive Advanced Breast Cancer (Metastatic or Locally Recurrent).

Summary

EudraCT number	2014-001458-40
Trial protocol	PT GB IT ES HU BE DE FR BG PL
Global end of trial date	22 February 2019

Results information

Result version number	v1 (current)
This version publication date	05 March 2020
First version publication date	05 March 2020

Trial information

Trial identification

Sponsor protocol code	BO29159

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02402712
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2019
Global end of trial reached?	Yes
Global end of trial date	22 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

An open-label, single-arm, multicenter, Phase IIIb study to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in female patients with HER2-positive metastatic or locally recurrent breast cancer.

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. All study subjects were required to read and sign and informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	Hungary: 43
Country: Number of subjects enrolled	Italy: 81
Country: Number of subjects enrolled	Mexico: 44
Country: Number of subjects enrolled	Poland: 82
Country: Number of subjects enrolled	Portugal: 21
Worldwide total number of subjects	418
EEA total number of subjects	373

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)	315
From 65 to 84 years	103
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer (metastatic or locally recurrent) who had not previously received systemic non-hormonal anti-cancer therapy in the metastatic setting.

Period 1

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

Arms

Arm title	Herceptin SC + Perjeta IV + Docetaxel IV

Arm description:

Single arm

Arm type	Experimental
Investigational medicinal product name	Herceptin SC
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Fixed dose of 600 mg/5 mL administered as a subcutaneous (SC) injection into the thigh on Day 1 of each cycle every 3 weeks (Q3W) throughout the treatment phase.

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

Dosage and administration details:

Administered as an intravenous (IV) infusion on Day 1 of the first treatment cycle as a loading dose of 840 mg, followed by 420 mg on Day 1 of each subsequent cycle Q3W throughout the treatment phase. Perjeta IV was administered 60 minutes after the end of Herceptin SC administration.

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

Dosage and administration details:

Administered after Herceptin SC and Perjeta IV on Day 1 at a recommended initial dose of 75 mg/m2, of each cycle Q3W throughout the treatment phase. After Cycle 6, continuation of docetaxel treatment was at the discretion of the treating physician in agreement with the patient. The dose of docetaxel could be escalated to 100 mg/m2 at the investigator’s discretion on subsequent cycles if the initial dose is well tolerated.

Number of subjects in period 1	Herceptin SC + Perjeta IV + Docetaxel IV
Started	418
Received Study Drug	412
Completed	276
Not completed	142
Withdrawal By Subject	43
Other	3
Death	87
Lost to follow-up	9

Baseline characteristics

Reporting groups	
Reporting group title	Herceptin SC + Perjeta IV + Docetaxel IV
Reporting group description:	
Single arm	

Reporting group values	Herceptin SC + Perjeta IV + Docetaxel IV	Total	
Number of subjects	418	418	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	315	315	
From 65-84 years	103	103	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	55.6		
standard deviation	± 11.7	-	
Gender categorical			
Units: Subjects			
Female	418	418	
Male	0	0	
Race			
Units: Subjects			
American Indian or Alaska Native	26	26	
Asian	3	3	
Black or African American	8	8	
White	352	352	
Multiple	2	2	
Unknown	27	27	
Ethnicity			
Units: Subjects			
Hispanic or Latino	69	69	
Not Hispanic or Latino	309	309	
Not Stated	28	28	
Unknown	12	12	

Subject analysis sets

Subject analysis set title	Herceptin SC + Perjeta IV + Docetaxel IV
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety-Evaluable Subjects

Reporting group values	Herceptin SC + Perjeta IV + Docetaxel IV		
Number of subjects	412		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	310		
From 65-84 years	102		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	55.6		
standard deviation	± 11.7		
Gender categorical Units: Subjects			
Female	412		
Male	0		
Race Units: Subjects			
American Indian or Alaska Native	26		
Asian	2		
Black or African American	8		
White	347		
Multiple	2		
Unknown	27		
Ethnicity Units: Subjects			
Hispanic or Latino	69		
Not Hispanic or Latino	305		
Not Stated	27		
Unknown	11		

End points

End points reporting groups

Reporting group title	Herceptin SC + Perjeta IV + Docetaxel IV
Reporting group description: Single arm	
Subject analysis set title	Herceptin SC + Perjeta IV + Docetaxel IV
Subject analysis set type	Safety analysis
Subject analysis set description: Safety-Evaluable Subjects	

Primary: Number of Subjects with at Least one Adverse Event (AEs)

End point title	Number of Subjects with at Least one Adverse Event (AEs)[1]
End point description: According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution.	
End point type	Primary
End point timeframe: Up to 24 months after the last subject has been enrolled, approximately 3.5 years	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary objective for this study is to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2−positive advanced (metastatic or locally recurrent) breast cancer. As there is only one treatment group in this study, no comparisons were done, and thus descriptive statistics (numbers of patients and percentages) were used to summarize results.

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	412			
Units: Subjects	406			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with at Least one Adverse Events Grade ≥3, According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0

End point title	Number of Subjects with at Least one Adverse Events Grade ≥3, According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0[2]
End point description: Adverse events Grade ≥ 3 for the treatment of Herceptin SC in combination with Perjeta IV, and Docetaxel IV	
End point type	Primary

End point timeframe:

Up to 24 months after the last subject has been enrolled, approximately 3.5 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary objective for this study is to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2−positive advanced (metastatic or locally recurrent) breast cancer. As there is only one treatment group in this study, no comparisons were done, and thus descriptive statistics (numbers of patients and percentages) were used to summarize results.

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	412			
Units: Subjects	221			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Cardiac Adverse Events, Congestive Heart Failure (CHF), and Cardiac Death

End point title	Number of Subjects with Cardiac Adverse Events, Congestive Heart Failure (CHF), and Cardiac Death[3]

End point description:

Cardiac adverse events, defined as one of the following: All-grade adverse events within the System Organ Class (SOC) of Cardiac Disorders, Grade ≥3 cardiac adverse events according to NCI CTCAE v4.0 within the SOC of Cardiac Disorders, serious cardiac adverse events within the SOC of Cardiac Disorders, serious adverse events suggestive of CHF defined by any adverse events within the standardized MedDRA query (SMQ) of cardiac failure (wide), CHF assessed by the investigator using NCI CTCAE grades and New York Heart Association class (MedDRA preferred term), Cardiac deaths defined as deaths caused by an event within the SOC of Cardiac Disorders

End point type	Primary

End point timeframe:

Up to 24 months after the last patient has been enrolled, approximately 3.5 years

Notes:

[3] - 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: The primary objective for this study is to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2−positive advanced (metastatic or locally recurrent) breast cancer. As there is only one treatment group in this study, no comparisons were done, and thus descriptive statistics (numbers of patients and percentages) were used to summarize results.

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	412			
Units: Subjects				
All-grade AEs within the SOC Cardiac Disorders	33			
Grade ≥3 AEs within the SOC Cardiac Disorders	3			

Serious AEs within the SOC Cardiac Disorders	4			
Serious AE suggesting CHF	1			
Cardiac Death	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Significant Decrease in LVEF (≥10 Percentage Points from Baseline to LVEF <50%)

End point title	Number of Subjects with Significant Decrease in LVEF (≥10 Percentage Points from Baseline to LVEF <50%)[4]

End point description:

Significant Decrease in LVEF ≥10% Percentage Points from Baseline to LVEF <50%

End point type	Primary

End point timeframe:

Up to 24 months after last subject enrolled, approximately 3.5 years

Notes:

[4] - 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: The primary objective for this study is to evaluate the safety and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2−positive advanced (metastatic or locally recurrent) breast cancer. As there is only one treatment group in this study, no comparisons were done, and thus descriptive statistics (numbers of patients and percentages) were used to summarize results.

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	396			
Units: Subjects	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival, Tumor Assessments According to RECIST v1.1

End point title	Progression-Free Survival, Tumor Assessments According to RECIST v1.1

End point description:

Kaplan-Meier Event-Free Rates for Progression-Free Survival Over Time

End point type	Secondary

End point timeframe:

6 months, 12 months, 18 months, 24 months

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	412			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
6 Months	86.47 (83.11 to 89.83)			
12 Months	64.13 (59.34 to 68.92)			
18 Months	51.47 (46.44 to 56.50)			
24 Months	42.47 (37.42 to 47.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
Kaplan-Meier Event-Free Rates for Overall Survival Over Time	
End point type	Secondary
End point timeframe:	
6 months, 12 months, 18 months, 24 months	

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	412			
Units: Percentage				
arithmetic mean (confidence interval 95%)				
6 Months	97.29 (95.70 to 98.87)			
12 Months	92.89 (90.35 to 95.43)			
18 months	86.79 (83.41 to 90.17)			
24 months	81.13 (77.19 to 85.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR), Defined as a Complete Response (CR) or a Partial Response (PR)

End point title	Objective Response Rate (ORR), Defined as a Complete Response (CR) or a Partial Response (PR)

End point description:

ORR is defined as a complete response or partial response determined by the investigator using RECIST v1.1 on two consecutive occasions ≥4 weeks apart. Subjects with disease localized only to the bone will not be included in the analysis of objective response. Only subjects with measurable disease at baseline will be included in the analysis of objective response. An estimate of the ORR and its two-sided 95% CI according to Pearson Clopper is calculated.

End point type	Secondary

End point timeframe:

Up to 3.5 years

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	336			
Units: Percentage				
arithmetic mean (confidence interval 95%)	75.6 (70.64 to 80.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Anti-Herceptin Antibodies at Baseline

End point title	Percentage of Subjects with Anti-Herceptin Antibodies at Baseline

End point description:

Percentage of subjects anti-drug antibody (ADA)-positive at baseline

End point type	Secondary

End point timeframe:

Up to 3.5 years

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	398			
Units: Percentage				
number (not applicable)	14.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-Emergent Anti-Herceptin Antibodies

End point title	Percentage of Subjects with Treatment-Emergent Anti-Herceptin Antibodies
End point description:	
Percentage of subjects ADA-positive post-baseline	
End point type	Secondary
End point timeframe:	
Up to 3.5 years	

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	396			
Units: Percentage				
number (not applicable)	24			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Anti-rHuPH20 Antibodies at Baseline

End point title	Percentage of Subjects with Anti-rHuPH20 Antibodies at Baseline
End point description:	
Percentage of subjects ADA-positive at baseline	
End point type	Secondary
End point timeframe:	
Up to 3.5 years	

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	399			
Units: Percentage				
number (not applicable)	6.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-Emergent Anti-rHuPH20 Antibodies

End point title	Percentage of Subjects with Treatment-Emergent Anti-rHuPH20 Antibodies
End point description:	
Percentage of subjects ADA-positive post-baseline	
End point type	Secondary
End point timeframe:	
Up to 3.5 years	

End point values	Herceptin SC + Perjeta IV + Docetaxel IV			
Subject group type	Subject analysis set			
Number of subjects analysed	396			
Units: Percentage				
number (not applicable)	2.8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 24 months after the last patient has been enrolled, approximately 3.5 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Herceptin SC + Perjeta IV + Docetaxel IV

Reporting group description: -

Serious adverse events	Herceptin SC + Perjeta IV + Docetaxel IV		
Total subjects affected by serious adverse events			
subjects affected / exposed	107 / 412 (25.97%)		
number of deaths (all causes)	87		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphocytic leukaemia			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tumour haemorrhage			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Hypertension				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	2 / 412 (0.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lymphoedema				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	2 / 412 (0.49%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	4 / 412 (0.97%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 4			
Pyrexia				
subjects affected / exposed	3 / 412 (0.73%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	4 / 412 (0.97%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			

subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood electrolytes decreased			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incisional hernia, obstructive			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Rib fracture				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congenital, familial and genetic disorders				
Atrial septal defect				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disease				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular hypokinesia				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Epilepsy				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				

subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	3 / 412 (0.73%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	25 / 412 (6.07%)		
occurrences causally related to treatment / all	26 / 26		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	4 / 412 (0.97%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	9 / 412 (2.18%)			
occurrences causally related to treatment / all	8 / 10			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal inflammation				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				

subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Bone pain				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Breast abscess				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter infection				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				

subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 412 (0.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 412 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mastitis			

subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	6 / 412 (1.46%)			
occurrences causally related to treatment / all	3 / 6			
deaths causally related to treatment / all	0 / 1			
Post procedural infection				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	2 / 412 (0.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				

subjects affected / exposed	2 / 412 (0.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lactic acidosis				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Tumour lysis syndrome				
subjects affected / exposed	1 / 412 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Herceptin SC + Perjeta IV + Docetaxel IV		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	399 / 412 (96.84%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	23 / 412 (5.58%)		
occurrences (all)	25		
Hypertension			
subjects affected / exposed	36 / 412 (8.74%)		
occurrences (all)	42		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	136 / 412 (33.01%)		
occurrences (all)	243		
Fatigue			
subjects affected / exposed	94 / 412 (22.82%)		
occurrences (all)	128		
Mucosal inflammation			
subjects affected / exposed	68 / 412 (16.50%)		
occurrences (all)	95		
Oedema peripheral			
subjects affected / exposed	51 / 412 (12.38%)		
occurrences (all)	62		
Pyrexia			
subjects affected / exposed	64 / 412 (15.53%)		
occurrences (all)	84		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	48 / 412 (11.65%)		
occurrences (all)	65		
Epistaxis			
subjects affected / exposed	58 / 412 (14.08%)		
occurrences (all)	77		

Oropharyngeal pain subjects affected / exposed occurrences (all)	26 / 412 (6.31%) 31		
Rhinorrhoea subjects affected / exposed occurrences (all)	30 / 412 (7.28%) 34		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	35 / 412 (8.50%) 40		
Investigations Ejection fraction decreased subjects affected / exposed occurrences (all)	48 / 412 (11.65%) 60		
Weight decreased subjects affected / exposed occurrences (all)	23 / 412 (5.58%) 25		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	65 / 412 (15.78%) 90		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	34 / 412 (8.25%) 38		
Headache subjects affected / exposed occurrences (all)	44 / 412 (10.68%) 53		
Neuropathy peripheral subjects affected / exposed occurrences (all)	42 / 412 (10.19%) 43		
Paraesthesia subjects affected / exposed occurrences (all)	37 / 412 (8.98%) 45		
Taste disorder			

subjects affected / exposed	26 / 412 (6.31%)		
occurrences (all)	28		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	75 / 412 (18.20%)		
occurrences (all)	83		
Leukopenia			
subjects affected / exposed	29 / 412 (7.04%)		
occurrences (all)	36		
Neutropenia			
subjects affected / exposed	71 / 412 (17.23%)		
occurrences (all)	104		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	64 / 412 (15.53%)		
occurrences (all)	76		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	26 / 412 (6.31%)		
occurrences (all)	33		
Abdominal pain upper			
subjects affected / exposed	31 / 412 (7.52%)		
occurrences (all)	36		
Constipation			
subjects affected / exposed	39 / 412 (9.47%)		
occurrences (all)	51		
Diarrhoea			
subjects affected / exposed	259 / 412 (62.86%)		
occurrences (all)	575		
Dyspepsia			
subjects affected / exposed	32 / 412 (7.77%)		
occurrences (all)	34		
Nausea			
subjects affected / exposed	115 / 412 (27.91%)		
occurrences (all)	181		
Stomatitis			

subjects affected / exposed	56 / 412 (13.59%)		
occurrences (all)	80		
Vomiting			
subjects affected / exposed	56 / 412 (13.59%)		
occurrences (all)	90		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	193 / 412 (46.84%)		
occurrences (all)	197		
Dry skin			
subjects affected / exposed	23 / 412 (5.58%)		
occurrences (all)	26		
Erythema			
subjects affected / exposed	23 / 412 (5.58%)		
occurrences (all)	30		
Nail disorder			
subjects affected / exposed	23 / 412 (5.58%)		
occurrences (all)	25		
Pruritus			
subjects affected / exposed	47 / 412 (11.41%)		
occurrences (all)	56		
Rash			
subjects affected / exposed	68 / 412 (16.50%)		
occurrences (all)	89		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	21 / 412 (5.10%)		
occurrences (all)	25		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	82 / 412 (19.90%)		
occurrences (all)	116		
Back pain			
subjects affected / exposed	34 / 412 (8.25%)		
occurrences (all)	50		
Bone pain			

subjects affected / exposed	33 / 412 (8.01%)		
occurrences (all)	37		
Muscle spasms			
subjects affected / exposed	32 / 412 (7.77%)		
occurrences (all)	38		
Musculoskeletal pain			
subjects affected / exposed	21 / 412 (5.10%)		
occurrences (all)	29		
Myalgia			
subjects affected / exposed	49 / 412 (11.89%)		
occurrences (all)	68		
Pain in extremity			
subjects affected / exposed	42 / 412 (10.19%)		
occurrences (all)	54		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	42 / 412 (10.19%)		
occurrences (all)	45		
Influenza			
subjects affected / exposed	23 / 412 (5.58%)		
occurrences (all)	25		
Nasopharyngitis			
subjects affected / exposed	36 / 412 (8.74%)		
occurrences (all)	48		
Rhinitis			
subjects affected / exposed	21 / 412 (5.10%)		
occurrences (all)	25		
Upper respiratory tract infection			
subjects affected / exposed	29 / 412 (7.04%)		
occurrences (all)	45		
Urinary tract infection			
subjects affected / exposed	23 / 412 (5.58%)		
occurrences (all)	29		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	61 / 412 (14.81%)		
occurrences (all)	85		
Hypokalaemia			
subjects affected / exposed	24 / 412 (5.83%)		
occurrences (all)	29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2015	Protocol BO29159 has been amended to correct a typographical error in one of exclusion criteria from "at least" to "less than."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported