Clinical trial results:
A Phase 3, Double-Blind, Randomized, Parallel-Group, Active-Controlled Study to Compare the Efficacy and Safety of CT-P6 and Herceptin as Neoadjuvant and Adjuvant Treatment in Patients with HER2-Positive Early Breast Cancer

Summary

EudraCT number	2013-004525-84
Trial protocol	LV GR HU ES IT PT RO PL HR
Global end of trial date	23 October 2018

Results information

Result version number	v1 (current)
This version publication date	06 October 2019
First version publication date	06 October 2019

Trial information

Trial identification

Sponsor protocol code	CT-P6 3.2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02162667
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CELLTRION, Inc.
Sponsor organisation address	23, Academy-ro, Yeonsu-gu, Incheon, Korea, Republic of, 22014
Public contact	CELLTRION, Inc., CELLTRION, Inc., +82 850 5000, contact@celltrion.com
Scientific contact	CELLTRION, Inc., CELLTRION, Inc., +82 850 5000, contact@celltrion.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	23 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate equivalence of CT-P6 and Herceptin, both given in combination with docetaxel (75 mg/m2, Cycles 1 to 4) followed by FEC (5-fluorouracil 500 mg/m2, epirubicin 75 mg/m2, and cyclophosphamide 500 mg/m2, Cycles 5 to 8), in terms of efficacy as determined by pathological complete response (pCR), in patients with HER2-positive operable early breast cancer.

Protection of trial subjects:

The study was conducted according to the principles of the International Council for Harmonisation (ICH) harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) (ICH 1996) and the ethical principles that have their origin in the World Medical Association Declaration of Helsinki. The investigators agreed to conduct all aspects of this study in accordance with national, state, and local laws or regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Belarus: 54
Country: Number of subjects enrolled	Bosnia and Herzegovina: 1
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Georgia: 59
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	India: 24
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 30
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Philippines: 35
Country: Number of subjects enrolled	Poland: 30

Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Romania: 31
Country: Number of subjects enrolled	Russian Federation: 159
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Ukraine: 61
Worldwide total number of subjects	549
EEA total number of subjects	80

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)	478
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 112 study centers were included in Europe, the Middle East, and Africa (EMEA), Asia Pacific, and Latin America and 99 study centers randomized subjects.

Pre-assignment

Screening details:

This study will include females 18 years of age or older with pathologically confirmed, newly diagnosed, operable early breast cancer (Stage I, II, or IIIa).

Period 1

Period 1 title	Neoadjuvant Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P6

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Trastuzumab (CT-P6, Herzuma)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg body weight on Day 1 of Neoadjuvant Period Cycle 1, followed by 6 mg/kg body weight repeated every 3 weeks for 8 cycles

Arm title	Herceptin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab (Herceptin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg body weight on Day 1 of Neoadjuvant Period Cycle 1, followed by 6 mg/kg body weight repeated every 3 weeks for 8 cycles

Number of subjects in period 1	CT-P6	Herceptin
Started	271	278
Completed	258	261
Not completed	13	17
Adverse event, serious fatal	2	1
Consent withdrawn by subject	2	3
Physician decision	-	1
Adverse event, non-fatal	5	8
Missing primary endpoint	1	1
Protocol deviation	1	3
Lack of efficacy	2	-

Period 2

Period 2 title	Adjuvant Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P6

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Trastuzumab (CT-P6, Herzuma)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg body weight repeated every 3 weeks up to 1 year from the first day of study drug administered in the Neoadjuvant Period

Arm title	Herceptin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab (Herceptin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg body weight repeated every 3 weeks up to 1 year from the first day of study drug administered in the Neoadjuvant Period

Number of subjects in period 2[1]	CT-P6	Herceptin
Started	254	262
Completed	243	249
Not completed	11	13
Adverse event, serious fatal	-	1
Consent withdrawn by subject	4	2
Adverse event, non-fatal	2	3
Other	-	2
Lack of efficacy	5	4
Protocol deviation	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: There were two patients (one in Arm CT-P6 and another in Arm Herceptin) who entered the Adjuvant Period after completing the Neoadjuvant Period without assessing the primary endpoint. After period 1 (Neoadjuvant Period with primary endpoint assessment), four patients in Arm CT-P6 withdrew and did not enter the Adjuvant Period.

Baseline characteristics

Reporting groups	
Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin
Reporting group description: -	

Reporting group values	CT-P6	Herceptin	Total
Number of subjects	271	278	549
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	240	238	478
From 65-84 years	31	40	71
85 years and over	0	0	0
Age continuous Units: years			
median	53	53	
full range (min-max)	24 to 78	22 to 74	-
Gender categorical Units: Subjects			
Female	271	278	549
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients in the ITT set, except for those patients excluded because of major protocol deviations. A major protocol deviation was one that may have affected the interpretation of study results; major protocol deviations were defined in the statistical analysis plan.

Reporting group values	Per protocol set (PPS)		
Number of subjects	504		
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)	441		
From 65-84 years	63		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)			
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups	
Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin
Reporting group description: -	
Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin
Reporting group description: -	
Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

All patients in the ITT set, except for those patients excluded because of major protocol deviations. A major protocol deviation was one that may have affected the interpretation of study results; major protocol deviations were defined in the statistical analysis plan.

Primary: Pathological complete response (pCR)	
End point title	Pathological complete response (pCR)

End point description:

The pCR which is defined as the absence of invasive tumor cells in the breast and in axillary lymph nodes, regardless of the ductal carcinoma in situ (DCIS) was the primary efficacy endpoint.

End point type	Primary

End point timeframe:

at the time of surgery after 8 cycles of treatment (4 cycles of CT-P6 or Herceptin with docetaxel followed by 4 cycles of CT-P6 or Herceptin with FEC)

End point values	CT-P6	Herceptin	Per protocol set (PPS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	248	256	504	
Units: pCR Rate				
Number of Responders	116	129	245	
Number of Non-Responders	132	127	259	

Statistical analyses

Statistical analysis title	pCR (Per protocol set)
Comparison groups	CT-P6 v Herceptin
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Risk difference (RD)
Point estimate	-0.0362

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1238
upper limit	0.0516

Notes:

[1] - Equivalence margin: (-0.15 - 0.15)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	CT-P6
Reporting group description: -	
Reporting group title	Herceptin
Reporting group description: -	

Serious adverse events	CT-P6	Herceptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 271 (7.75%)	35 / 278 (12.59%)	
number of deaths (all causes)	18	18	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 271 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			

subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Implant site extravasation			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Complications of transplant surgery			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scar			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			

subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Adams-Stokes syndrome			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 271 (0.37%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 271 (2.21%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	4 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 271 (0.74%)	3 / 278 (1.08%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Dacryostenosis acquired			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis acute			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Neurodermatitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 271 (0.37%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 271 (0.00%)	2 / 278 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 271 (0.74%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic embolus			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 271 (0.37%)	0 / 278 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 271 (0.00%)	1 / 278 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CT-P6	Herceptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	263 / 271 (97.05%)	263 / 278 (94.60%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 271 (7.01%)	11 / 278 (3.96%)	
occurrences (all)	19	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	47 / 271 (17.34%)	38 / 278 (13.67%)	
occurrences (all)	117	99	
Fatigue			
subjects affected / exposed	53 / 271 (19.56%)	62 / 278 (22.30%)	
occurrences (all)	134	179	
Oedema peripheral			
subjects affected / exposed	8 / 271 (2.95%)	18 / 278 (6.47%)	
occurrences (all)	11	26	
Pyrexia			
subjects affected / exposed	31 / 271 (11.44%)	30 / 278 (10.79%)	
occurrences (all)	42	40	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 271 (5.17%)	14 / 278 (5.04%)	
occurrences (all)	16	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 271 (5.90%)	7 / 278 (2.52%)	
occurrences (all)	16	8	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	18 / 271 (6.64%)	30 / 278 (10.79%)	
occurrences (all)	24	43	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 271 (5.17%)	25 / 278 (8.99%)	
occurrences (all)	17	40	
Ejection fraction decreased			
subjects affected / exposed	20 / 271 (7.38%)	9 / 278 (3.24%)	
occurrences (all)	24	11	
Neutrophil count decreased			
subjects affected / exposed	14 / 271 (5.17%)	13 / 278 (4.68%)	
occurrences (all)	34	42	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	31 / 271 (11.44%)	28 / 278 (10.07%)	
occurrences (all)	47	37	
Radiation skin injury			
subjects affected / exposed	33 / 271 (12.18%)	34 / 278 (12.23%)	
occurrences (all)	34	35	
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 271 (5.17%)	8 / 278 (2.88%)	
occurrences (all)	15	14	
Headache			
subjects affected / exposed	25 / 271 (9.23%)	21 / 278 (7.55%)	
occurrences (all)	35	28	
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 271 (5.17%)	20 / 278 (7.19%)	
occurrences (all)	19	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	59 / 271 (21.77%)	66 / 278 (23.74%)	
occurrences (all)	98	125	
Febrile neutropenia			
subjects affected / exposed	11 / 271 (4.06%)	16 / 278 (5.76%)	
occurrences (all)	11	18	

Leukopenia			
subjects affected / exposed	28 / 271 (10.33%)	40 / 278 (14.39%)	
occurrences (all)	45	92	
Neutropenia			
subjects affected / exposed	95 / 271 (35.06%)	115 / 278 (41.37%)	
occurrences (all)	216	255	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	16 / 271 (5.90%)	15 / 278 (5.40%)	
occurrences (all)	34	35	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	24 / 271 (8.86%)	18 / 278 (6.47%)	
occurrences (all)	43	26	
Diarrhoea			
subjects affected / exposed	52 / 271 (19.19%)	50 / 278 (17.99%)	
occurrences (all)	75	75	
Nausea			
subjects affected / exposed	99 / 271 (36.53%)	94 / 278 (33.81%)	
occurrences (all)	281	284	
Stomatitis			
subjects affected / exposed	46 / 271 (16.97%)	33 / 278 (11.87%)	
occurrences (all)	72	45	
Vomiting			
subjects affected / exposed	27 / 271 (9.96%)	26 / 278 (9.35%)	
occurrences (all)	40	46	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	196 / 271 (72.32%)	213 / 278 (76.62%)	
occurrences (all)	269	293	
Rash			
subjects affected / exposed	18 / 271 (6.64%)	10 / 278 (3.60%)	
occurrences (all)	20	14	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	34 / 271 (12.55%)	40 / 278 (14.39%)	
occurrences (all)	53	65	
Bone pain			
subjects affected / exposed	11 / 271 (4.06%)	20 / 278 (7.19%)	
occurrences (all)	13	34	
Myalgia			
subjects affected / exposed	27 / 271 (9.96%)	28 / 278 (10.07%)	
occurrences (all)	50	47	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	17 / 271 (6.27%)	8 / 278 (2.88%)	
occurrences (all)	23	11	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 271 (7.75%)	20 / 278 (7.19%)	
occurrences (all)	49	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 December 2014	-Clinical response rate and radiological response rate were combined as tumor response rate additional since CT assessment was added after Neoadjuvant Period Cycle 4. The relevant text was updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

N/A

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28592386