# 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<br>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<br>Units: years | | | |
| median | 53 | 53 | |
| full range (min-max) | 24 to 78 | 22 to 74 | - |
| Gender categorical<br>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<br>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