



Clinical trial results:

A Double-blind Randomised, Parallel Phase I/IIb Study to Evaluate Initial Safety and Efficacy, Comparative Pharmacokinetics and Immunogenicity for CT-P6 and Herceptin in Metastatic Breast Cancer

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2009-014463-39 |
| Trial protocol | LV BG GB |
| Global end of trial date | 29 December 2023 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 24 August 2024 |
| First version publication date | 24 August 2024 |

Trial information

Trial identification

| | |
|-----------------------|-----|
| Sponsor protocol code | 1.1 |
|-----------------------|-----|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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, Incheon, Korea, Republic of, |
| Public contact | Celltrion, Inc., Celltrion, Inc., 82 850 5000, contact@celltrion.com, Celltrion, Inc., 82 8505000, |
| Scientific contact | Celltrion, Inc., Celltrion, Inc., 82 850 5000, contact@celltrion.com, Celltrion, Inc., 82 8505000, |

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 | 18 March 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 June 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 December 2023 |
| 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 equivalent PK in terms of area under the curve at steady state (AUCSS) between CT-P6 and the comparator Herceptin in patients with metastatic breast cancer.

Protection of trial subjects:

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 02 February 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 14 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Bulgaria: 10 |
| Country: Number of subjects enrolled | Latvia: 15 |
| Country: Number of subjects enrolled | Serbia: 11 |
| Country: Number of subjects enrolled | Ukraine: 29 |
| Country: Number of subjects enrolled | Korea, Republic of: 63 |
| Country: Number of subjects enrolled | Russian Federation: 45 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Worldwide total number of subjects | 174 |
| EEA total number of subjects | 25 |

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) | 150 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled at 7 sites across Bulgaria, Korea, Republic of, Latvia, Russian Federation, Serbia, Taiwan, and Ukraine.

Pre-assignment

Screening details:

This study included females 18 years of age or older with HER-2 positive metastatic breast cancer who had not been treated in the first line metastatic setting.

Pre-assignment period milestones

| | |
|----------------------------|-----|
| Number of subjects started | 174 |
|----------------------------|-----|

| | |
|------------------------------|-----|
| Number of subjects completed | 143 |
|------------------------------|-----|

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | excluded from Full Analysis Set (FAS): 31 |
|----------------------------|---|

Period 1

| | |
|----------------|-----------------------------|
| Period 1 title | Main Study Treatment Period |
|----------------|-----------------------------|

| | |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

| | |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

| | |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

| | |
|---------------|---|
| Roles blinded | Subject, Investigator, Monitor, Data analyst, 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, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

| | |
|------------------|-----------|
| 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, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

| Number of subjects in period 1^[1] | CT-P6 | Herceptin |
|---|-------|-----------|
| Started | 76 | 67 |
| Completed | 60 | 56 |
| Not completed | 16 | 11 |
| Disease progression | 11 | 7 |
| Adverse Event | 5 | 3 |
| Other reason | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Overall, 31 enrolled patients who did not met definition of FAS was excluded.

Period 2

| | |
|------------------------------|---|
| Period 2 title | Treatment Period Beyond Cycle 8 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, 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, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

| | |
|--|-------------------------|
| 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, Cycle 1, followed by 6 mg/kg body weight repeated at every 3 weeks until disease progression, death, or discontinuation.

| Number of subjects in period 2 | CT-P6 | Herceptin |
|---------------------------------------|-------|-----------|
| Started | 60 | 56 |
| Discontinued treatment after Cycle 8 | 60 | 56 |
| Completed | 0 | 0 |
| Not completed | 60 | 56 |
| Consent withdrawn by subject | 4 | 4 |
| Physician decision | 2 | 4 |
| Disease progression | 51 | 45 |
| Adverse Event | 1 | - |
| Unknown | - | 1 |
| Other reason | 2 | 2 |

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 | 76 | 67 | 143 |
| 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) | 63 | 59 | 122 |
| From 65-84 years | 13 | 8 | 21 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| median | 56.0 | 56.0 | |
| full range (min-max) | 33 to 75 | 28 to 76 | - |
| Gender categorical Units: Subjects | | | |
| Female | 76 | 67 | 143 |
| Male | 0 | 0 | 0 |

Subject analysis sets

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All randomized patients who received any study drug and had at least one post-baseline assessment, with the exception of the patients who violated against Herceptin indication. Patients were analyzed according to the treatment to which they were randomized and not according to what they actually received, in the event there will be a discrepancy between the actual treatment received and the randomized treatment. All summaries of study population data, including disposition of patients, major protocol deviations, and analysis sets, as well as demographic and baseline characteristics were performed using the FAS. Also, all efficacy analysis were performed using the FAS.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | PK Analysis Set – Global (PKASg) |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All FAS patients who had achieved steady state by the 8th cycle, which required 3 consecutive similar trough concentrations. Patients were analyzed according to the study drug they actually received. All summaries of PK parameter were performed using the PKASg.

| Reporting group values | Full Analysis Set (FAS) | PK Analysis Set – Global (PKASg) | |
|--|-------------------------|----------------------------------|--|
| Number of subjects | 143 | 100 | |
| 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) | 122 | 83 | |
| From 65-84 years | 21 | 17 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 56.0 | 56.0 | |
| full range (min-max) | 28 to 76 | 28 to 76 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 143 | 100 | |
| Male | 0 | 0 | |

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 | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All randomized patients who received any study drug and had at least one post-baseline assessment, with the exception of the patients who violated against Herceptin indication. Patients were analyzed according to the treatment to which they were randomized and not according to what they actually received, in the event there will be a discrepancy between the actual treatment received and the randomized treatment. All summaries of study population data, including disposition of patients, major protocol deviations, and analysis sets, as well as demographic and baseline characteristics were performed using the FAS. Also, all efficacy analysis were performed using the FAS. | |
| Subject analysis set title | PK Analysis Set – Global (PKASg) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All FAS patients who had achieved steady state by the 8th cycle, which required 3 consecutive similar trough concentrations. Patients were analyzed according to the study drug they actually received. All summaries of PK parameter were performed using the PKASg. | |

Primary: AUCss at 6 months (8 treatment cycles).

| | |
|---|---|
| End point title | AUCss at 6 months (8 treatment cycles). |
| End point description: | |
| The primary endpoint was to demonstrate PK equivalence in terms of area under the concentration time curve at steady state (AUCss) between CT-P6 and the comparator. The primary endpoint was reached at 6 months (8 treatment cycle; Main Study Treatment Period). | |
| End point type | Primary |
| End point timeframe: | |
| 6 months | |

| End point values | CT-P6 | Herceptin | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 49 | | |
| Units: ug*h/mL | | | | |
| arithmetic mean (standard deviation) | 34400 (± 15000) | 31800 (± 9820) | | |

Statistical analyses

| | |
|---|----------------------|
| Statistical analysis title | Geometric Mean Ratio |
| Comparison groups | Herceptin v CT-P6 |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric Mean Ratio |
| Point estimate | 104.57 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 93.64 |
| upper limit | 116.78 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 14 years.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

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 | 12 / 76 (15.79%) | 19 / 67 (28.36%) | |
| number of deaths (all causes) | 2 | 3 | |
| number of deaths resulting from adverse events | 0 | 1 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Biliary drainage | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 5 / 67 (7.46%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Infusion related reaction | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Endoscopic retrograde cholangiopancreatography | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Nervous system disorders | | | |
| Brain oedema | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 3 / 67 (4.48%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 3 / 67 (4.48%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis cholestatic | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 2 / 76 (2.63%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Sepsis | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 76 (1.32%) | 0 / 67 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 76 (0.00%) | 1 / 67 (1.49%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| 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 | 75 / 76 (98.68%) | 65 / 67 (97.01%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 8 / 67 (11.94%) | |
| occurrences (all) | 12 | 19 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 7 / 67 (10.45%) | |
| occurrences (all) | 8 | 16 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 4 / 67 (5.97%) | |
| occurrences (all) | 6 | 9 | |
| Nervous system disorders | | | |

| | | | |
|---|------------------------|------------------------|--|
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 21 / 76 (27.63%) 79 | 27 / 67 (40.30%) 50 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 23 / 76 (30.26%) 46 | 21 / 67 (31.34%) 54 | |
| Headache subjects affected / exposed occurrences (all) | 11 / 76 (14.47%) 16 | 13 / 67 (19.40%) 18 | |
| Dizziness subjects affected / exposed occurrences (all) | 6 / 76 (7.89%) 11 | 13 / 67 (19.40%) 23 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 32 / 76 (42.11%) 59 | 33 / 67 (49.25%) 85 | |
| Leukopenia subjects affected / exposed occurrences (all) | 8 / 76 (10.53%) 10 | 12 / 67 (17.91%) 28 | |
| Anaemia subjects affected / exposed occurrences (all) | 9 / 76 (11.84%) 19 | 5 / 67 (7.46%) 9 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 24 / 76 (31.58%) 52 | 10 / 67 (14.93%) 14 | |
| Fatigue subjects affected / exposed occurrences (all) | 10 / 76 (13.16%) 27 | 10 / 67 (14.93%) 31 | |
| Pyrexia subjects affected / exposed occurrences (all) | 10 / 76 (13.16%) 18 | 10 / 67 (14.93%) 18 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 8 / 76 (10.53%) 10 | 8 / 67 (11.94%) 12 | |
| Chills | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 6 / 76 (7.89%) 11 | 7 / 67 (10.45%) 8 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 4 / 76 (5.26%) 5 | 5 / 67 (7.46%) 6 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 13 / 76 (17.11%) 23 | 18 / 67 (26.87%) 38 | |
| Stomatitis subjects affected / exposed occurrences (all) | 6 / 76 (7.89%) 13 | 11 / 67 (16.42%) 14 | |
| Constipation subjects affected / exposed occurrences (all) | 4 / 76 (5.26%) 6 | 10 / 67 (14.93%) 14 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 4 / 76 (5.26%) 4 | 8 / 67 (11.94%) 13 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 5 / 76 (6.58%) 6 | 3 / 67 (4.48%) 3 | |
| Nausea subjects affected / exposed occurrences (all) | 19 / 76 (25.00%) 51 | 17 / 67 (25.37%) 41 | |
| Vomiting subjects affected / exposed occurrences (all) | 5 / 76 (6.58%) 10 | 9 / 67 (13.43%) 14 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 11 / 76 (14.47%) 13 | 8 / 67 (11.94%) 11 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 8 / 76 (10.53%) 11 | 5 / 67 (7.46%) 7 | |
| Oropharyngeal pain | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 76 (3.95%) 4 | 5 / 67 (7.46%) 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 47 / 76 (61.84%) | 44 / 67 (65.67%) | |
| occurrences (all) | 59 | 50 | |
| Rash | | | |
| subjects affected / exposed | 10 / 76 (13.16%) | 12 / 67 (17.91%) | |
| occurrences (all) | 16 | 29 | |
| Pruritus | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 12 / 67 (17.91%) | |
| occurrences (all) | 11 | 18 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 7 / 76 (9.21%) | 13 / 67 (19.40%) | |
| occurrences (all) | 14 | 16 | |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 31 / 76 (40.79%) | 31 / 67 (46.27%) | |
| occurrences (all) | 134 | 127 | |
| Arthralgia | | | |
| subjects affected / exposed | 10 / 76 (13.16%) | 15 / 67 (22.39%) | |
| occurrences (all) | 33 | 29 | |
| Pain in extremity | | | |
| subjects affected / exposed | 10 / 76 (13.16%) | 17 / 67 (25.37%) | |
| occurrences (all) | 14 | 32 | |
| Bone pain | | | |
| subjects affected / exposed | 13 / 76 (17.11%) | 6 / 67 (8.96%) | |
| occurrences (all) | 22 | 10 | |
| Back pain | | | |
| subjects affected / exposed | 5 / 76 (6.58%) | 11 / 67 (16.42%) | |
| occurrences (all) | 7 | 19 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 6 / 76 (7.89%) | 7 / 67 (10.45%) | |
| occurrences (all) | 7 | 9 | |
| Infections and infestations | | | |

| | | | |
|--|----------------------|-----------------------|--|
| Nasopharyngitis subjects affected / exposed occurrences (all) | 7 / 76 (9.21%) 11 | 3 / 67 (4.48%) 9 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 76 (3.95%) 3 | 6 / 67 (8.96%) 10 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 7 / 76 (9.21%) 12 | 8 / 67 (11.94%) 22 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 19 May 2010 | Amendments in the eligibility criteria and procedures |
| 02 December 2010 | Amendments in the sample size calculation |
| 23 February 2012 | Clarification in determination of disease progression related to follow-up of patient was moved to the Investigator from ITRC |
| 03 July 2013 | Amendments in study duration and updated study protocol to open-label study |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported