# Clinical trial results:
# A Phase 1/3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Demonstrate Equivalence of Pharmacokinetics and Noninferiority of Efficacy for CT-P10 in Comparison With Rituxan, Each Administered in Combination With Cyclophosphamide, Vincristine, and Prednisone (CVP) in Patients With Advanced Follicular Lymphoma

## Summary

| | |
|---|---|
| EudraCT number | 2013-004493-96 |
| Trial protocol | NL ES GR IT PT BG |
| Global end of trial date | 29 December 2018 |
| **Results information** | |
| Result version number | v1 (current) |
| This version publication date | 27 December 2019 |
| First version publication date | 27 December 2019 |
| Summary attachment (see zip file) | American Society of Hematology (ASH) 2016 (1.Coiffier (2016)_ASH 2016 abstract.pdf)<br>International Conference on Malignant Lymphoma (ICML) 2017 (2.Buske (2017)_ICML 2017 abstract.pdf)<br>European Hematology Association (EHA) 2017 (3.Ogura (2017)_EHA 2017 abstract.pdf)<br>American Society of Clinical Oncology (ASCO) 2017 (4.Kim (2017)_ASCO 2017 abstract.pdf)<br>European Society for Medical Oncology (ESMO) Asia 2017 (5.Kim (2017)_ESMO asia 2017 abstract.pdf)<br>American Society of Hematology (ASH) 2017 (6.Kim (2017)_ASH 2017 abstract.pdf)<br>American Society of Hematology (ASH) 2018 (7.Kim (2018)_ASH 2018 abstract.pdf)<br>Lancet Hematology (8. Kim et al. (2018) Lancet Haematol 2017.pdf) |

## Trial information

| **Trial identification** | |
|---|---|
| Sponsor protocol code | CT-P10-3.3 |
| **Additional study identifiers** | |
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02162771 |
| WHO universal trial number (UTN) | - |

Notes:

| **Sponsors** | |
|---|---|
| Sponsor organisation name | CELLTRION, Inc |
| Sponsor organisation address | 23 Academy-ro, Yeonsu-gu , Incheon Metropolitan City , Korea, Republic of, |
| Public contact | Clinical Operation, CELLTRION, Inc, +82 328505776, sueun.song@celltrion.com |
| Scientific contact | Clinical Planning, CELLTRION, Inc, +82 328505778, sunghyun. |

| | |
|---|---|
| | kim@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 | 28 December 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 December 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This study will be divided into 2 parts, each of which will assess one of its 2 primary endpoints (pharmacokinetics and efficacy of CT-P10 compared to Rituxan).

The primary objective of Part 1 of this study is:
- To demonstrate that CT-P10 is similar to Rituxan in terms of pharmacokinetics as determined by AUCtau and CmaxSS at Cycle 4.

The primary objective of Part 2 of this study is:
- To demonstrate that CT-P10 is noninferior to Rituxan in terms of efficacy as determined by overall response rate (CR + CRu + PR) over Cycle 8 (Core Study Period) according to the 1999 International Working Group (IWG) criteria in previously untreated patients with advanced (stage III-IV) CD20+ FL.

Protection of trial subjects:

Hypersensitivity will be assessed by vital sign monitoring (including systolic and diastolic blood pressure (BP), heart rate, respiratory rate, and temperature) on each dosing day and recorded on each dosing day at the following time points:
- Before beginning the study drug infusion on Day 1 of each cycle (within 15 minutes before the beginning of the study drug infusion)
- At the end of the study drug infusion (within 15 minutes after the end of the study drug infusion)
- At 60 minutes (±15 minutes) after the end of the study drug infusion

In addition, hypersensitivity should be monitored by routine continuous clinical monitoring including ECG monitoring at 60 minutes (±15 minutes) after the end of the study drug infusion.

Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support (including inhalational therapy, oxygen, and artificial ventilator), must be available.

For patients who experience or develop life-threatening infusion-related anaphylactic reactions, rituximab treatment must be stopped immediately and the patient withdrawn from the study.

Background therapy:

CT-P10 or Rituxan will be administered with standard premedication during the Core Study Period, followed by CVP chemotherapy, constituting 1 cycle of therapy. The sequence of the study treatment will be as follows: prednisone, study drug, and CVP chemotherapy.

- Prednisone (40 mg/m2, oral)
- Cyclophosphamide (750 mg/m2, IV)
- Vincristine (1.4 mg/m2 - maximum 2 mg, IV)

Premedication consisting of an antipyretic, an antihistamine, and a glucocorticoid must be administered 30 minutes before each infusion of CT P10 or Rituxan during the Core Study Period (in all combination treatment cycles) and during the Maintenance Study Period. The following recommended premedications can be given:

- Paracetamol (500 mg, oral)
- H1 antihistamine (oral or IV)
- Prednisone (40 mg/m2, oral)

Evidence for comparator:

CT P10 is being developed as a proposed biosimilar product of Rituxan (rituximab), a compound with established efficacy in the treatment of NHL. The purpose of this study is to determine whether CT-P10 is similar to Rituxan with respect to pharmacokinetics and noninferior to Rituxan with respect to efficacy and to assess efficacy and safety in patients with advanced FL.

| | |
|---|---|
| Actual start date of recruitment | 14 July 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Belarus: 14 |
| Country: Number of subjects enrolled | Brazil: 12 |
| Country: Number of subjects enrolled | Chile: 2 |
| Country: Number of subjects enrolled | Georgia: 4 |
| Country: Number of subjects enrolled | India: 12 |
| Country: Number of subjects enrolled | Korea, Republic of: 8 |
| Country: Number of subjects enrolled | Mexico: 1 |
| Country: Number of subjects enrolled | Philippines: 3 |
| Country: Number of subjects enrolled | Russian Federation: 10 |
| Country: Number of subjects enrolled | South Africa: 4 |
| Country: Number of subjects enrolled | Turkey: 2 |
| Country: Number of subjects enrolled | Ukraine: 8 |
| Country: Number of subjects enrolled | Poland: 17 |
| Country: Number of subjects enrolled | Portugal: 2 |
| Country: Number of subjects enrolled | Romania: 6 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | Bulgaria: 1 |
| Country: Number of subjects enrolled | Greece: 4 |

| | |
|---|---|
| Country: Number of subjects enrolled | Italy: 4 |
| Worldwide total number of subjects | 140 |
| EEA total number of subjects | 60 |

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) | 100 |
| From 65 to 84 years | 39 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

First patient randomly assigned to treatment: 28 July 2014
A total of 64 study centers were initiated in Europe, Africa, Asia Pacific, and Latin America.

### Pre-assignment

Screening details:

Key Inclusion Criteria
1. Patient is male or female 18 years or older.
2. Patient has histologically confirmed CD20+ FL according to the WHO 2008 classification; grades 1 to 3a based on local laboratory review.
3. Patient has at least 1 measurable tumour mass that has not previously been irradiated.
4. Patient has Ann Arbor stage III or IV.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 184[1] |
| Intermediate milestone: Number of subjects | Enrolled: 140 |
| Number of subjects completed | 140 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Screening Failure: 44 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported to have started the pre-assignment period, 184, represents the number of subjects screened for this study. Of those, 44 failed screening and 140 patients were randomised.

### Period 1

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

Blinding implementation details:

This study was double-blinded. The study blind was not to be broken except in either a medical emergency (where knowledge of the study drug received was able to affect the treatment of the emergency) or a regulatory requirement, and the overall randomization code will be broken only for reporting purpose. Sponsor and CRO will predefine unblinded team and run them separately to maintain blinding throughout the study.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | CT-P10 |

Arm description:

Patient treated with CT-P10 (375 mg/m2, IV) in combination with cyclophosphamide (750 mg/m2 IV), vincristine (1.4 mg/m2 [up to a maximum of 2 mg] IV), and prednisolone (40 mg/m2 orally) up to 8 cycles.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CT-P10 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

CT-P10 375 mg/m2 diluted in 500 mL of normal saline administered as an IV infusion.

| **Arm title** | Rituxan |
|---|---|

Arm description:

US-licensed product. Patient treated with Rituxan (375 mg/m2, IV) in combination with cyclophosphamide (750 mg/m2 IV), vincristine (1.4 mg/m2 [up to a maximum of 2 mg] IV), and prednisolone (40 mg/m2 orally) up to 8 cycles.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Rituxan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Rituxan 375 mg/m2 diluted in 500 mL of normal saline administered as an IV infusion.

| **Number of subjects in period 1** | CT-P10 | Rituxan |
|---|---|---|
| Started | 70 | 70 |
| Completed | 62 | 62 |
| Not completed | 8 | 8 |
| Consent withdrawn by subject | 1 | 2 |
| Physician decision | - | 2 |
| Adverse event, non-fatal | 4 | 1 |
| Death | 1 | - |
| Progressive disease | 2 | 3 |

## Period 2

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

Blinding implementation details:

This study was double-blinded. The study blind was not to be broken except in either a medical emergency (where knowledge of the study drug received was able to affect the treatment of the emergency) or a regulatory requirement, and the overall randomization code will be broken only for reporting purpose. Sponsor and CRO will predefine unblinded team and run them separately to maintain blinding throughout the study.

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |

| **Arm title** | CT-P10 |
|---|---|

Arm description:

Patients having responses during Period 1 (Core Study Period) were treated with CT-P10 (375 mg/m2, IV) monotherapy up to 12 cycles.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CT-P10 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

CT-P10 375 mg/m2 diluted in 500 mL of normal saline administered as an IV infusion.

| **Arm title** | Rituxan |
|---|---|

Arm description:

US-licensed product. Patients having responses during Period 1 (Core Study Period) were treated with Rituxan (375 mg/m2, IV) monotherapy up to 12 cycles.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Rituxan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Rituxan 375 mg/m2 diluted in 500 mL of normal saline administered as an IV infusion.

| **Number of subjects in period 2[2]** | CT-P10 | Rituxan |
|---|---|---|
| Started | 62 | 60 |
| Completed | 46 | 38 |
| Not completed | 16 | 22 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | - | 3 |
| Adverse event, non-fatal | 2 | 3 |
| Death | 2 | 1 |
| Stable disease | - | 1 |
| Progressive disease | 11 | 13 |
| Protocol deviation | - | 1 |

Notes:

[2] - 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: Two subjects did not enter the Maintenance Study Period due to a withdrawal by subject and a non-responder, respectively. Patients having responses (CR, CRu or PR) during the Core Study Period were allowed to proceed with the Maintenance Study Period after completion of the Core Study Period as per protocol.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | CT-P10 |
| Reporting group description: | |
| Patient treated with CT-P10 (375 mg/m2, IV) in combination with cyclophosphamide (750 mg/m2 IV), vincristine (1.4 mg/m2 [up to a maximum of 2 mg] IV), and prednisolone (40 mg/m2 orally) up to 8 cycles. | |
| Reporting group title | Rituxan |
| Reporting group description: | |
| US-licensed product. Patient treated with Rituxan (375 mg/m2, IV) in combination with cyclophosphamide (750 mg/m2 IV), vincristine (1.4 mg/m2 [up to a maximum of 2 mg] IV), and prednisolone (40 mg/m2 orally) up to 8 cycles. | |

| Reporting group values | CT-P10 | Rituxan | Total |
|---|---|---|---|
| Number of subjects | 70 | 70 | 140 |
| 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) | 51 | 49 | 100 |
| From 65-84 years | 18 | 21 | 39 |
| 85 years and over | 1 | 0 | 1 |
| Age continuous<br>Units: years | | | |
| median | 57.0 | 58.5 | |
| full range (min-max) | 30 to 85 | 26 to 84 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 40 | 37 | 77 |
| Male | 30 | 33 | 63 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | CT-P10 |
| Reporting group description: | |
| Patient treated with CT-P10 (375 mg/m2, IV) in combination with cyclophosphamide (750 mg/m2 IV), vincristine (1.4 mg/m2 [up to a maximum of 2 mg] IV), and prednisolone (40 mg/m2 orally) up to 8 cycles. | |
| Reporting group title | Rituxan |
| Reporting group description: | |
| US-licensed product. Patient treated with Rituxan (375 mg/m2, IV) in combination with cyclophosphamide (750 mg/m2 IV), vincristine (1.4 mg/m2 [up to a maximum of 2 mg] IV), and prednisolone (40 mg/m2 orally) up to 8 cycles. | |
| Reporting group title | CT-P10 |
| Reporting group description: | |
| Patients having responses during Period 1 (Core Study Period) were treated with CT-P10 (375 mg/m2, IV) monotherapy up to 12 cycles. | |
| Reporting group title | Rituxan |
| Reporting group description: | |
| US-licensed product. Patients having responses during Period 1 (Core Study Period) were treated with Rituxan (375 mg/m2, IV) monotherapy up to 12 cycles. | |
| Subject analysis set title | Pharmacokinetic Population |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The PK population was defined as all patients who receive at least 1 dose (full) of study drug (CT-P10 or Rituxan) and who had at least 1 posttreatment PK concentration result. The PK population was the primary population for the summary of PK data. | |
| Subject analysis set title | Efficacy Population |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| The per-protocol (PP) population in this study was defined for the principle of efficacy population. The PP population was defined as all randomly assigned patients who had at least 1 response evaluation after receiving at least 1 treatment cycle (full) in the Core Study Period and who did not have any major protocol deviation that were relevant to the efficacy endpoint. | |
| Subject analysis set title | Pharmacodynamic Population |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The pharmacodynamic (PD) population was defined as all patients who received at least 1 dose (full) of study drug (CT-P10 or Rituxan) and who had at least 1 posttreatment PD result and who did not have any major protocol deviation that was relevant to the PD endpoint. The PD population was the primary population for the summary of PD data. | |

### Primary: AUCtau

| | |
|---|---|
| End point title | AUCtau |
| End point description: | |
| Area under the serum concentration-time curve at steady state. Measure type is geometric least squares mean. | |
| End point type | Primary |
| End point timeframe: | |
| Core Cycle 4 at Steady State | |

| End point values | CT-P10 | Rituxan | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50[1] | 56[2] | | |
| Units: h•µg/mL | | | | |
| geometric mean (standard error) | 41002.43 (± 1.136) | 40099.08 (± 1.143) | | |

Notes:

[1] - Patients who did not receive full dose of study drug up to Core Cycle 4 and outliers were excluded.

[2] - Patients who did not receive full dose of study drug up to Core Cycle 4 and outliers were excluded.

## Statistical analyses

| Statistical analysis title | Co-primary Pharmacokinetic Endpoints - AUCtau |
|---|---|

Statistical analysis description:

The primary PK endpoints of the AUCtau between patients treated with CT-P10 and Rituxan reference product at steady state were analyzed using an analysis of covariance with treatment as a fixed effect and country, gender, race, the value of ECOG status, and the FLIPI Score (0 to 2 vs. 3 to 5) at baseline fitted as covariates. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

| | |
|---|---|
| Comparison groups | CT-P10 v Rituxan |
| Number of subjects included in analysis | 106 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence[3] |
| Method | ANCOVA |
| Parameter estimate | Ratio of geometric least square means |
| Point estimate | 102.25 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 94.05 |
| upper limit | 111.17 |

Notes:

[3] - Equivalence margin: 80%-125%

## Primary: CmaxSS

| End point title | CmaxSS |
|---|---|

End point description:

Maximum serum concentration at steady state. Measure type is geometric least square means.

| End point type | Primary |
|---|---|

End point timeframe:

Core Cycle 4 at Steady State

| End point values | CT-P10 | Rituxan | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 53[4] | 56[5] | | |
| Units: µg/mL | | | | |
| geometric mean (standard error) | 256.19 (± 1.115) | 254.49 (± 1.120) | | |

Notes:

[4] - Patients who did not receive full dose of study drug up to Core Cycle 4 and outliers were excluded.

[5] - Patients who did not receive full dose of study drug up to Core Cycle 4 and outliers were excluded.

## Statistical analyses

| **Statistical analysis title** | Co-primary Pharmacokinetic Endpoints - CmaxSS |
|---|---|

Statistical analysis description:

The primary PK endpoints of the CmaxSS between patients treated with CT-P10 and Rituxan reference product at steady state were analyzed using an analysis of covariance with treatment as a fixed effect and country, gender, race, the value of ECOG status, and the FLIPI Score (0 to 2 vs. 3 to 5) at baseline fitted as covariates. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric least square means on the original scale.

| | |
|---|---|
| Comparison groups | CT-P10 v Rituxan |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence[6] |
| Method | ANCOVA |
| Parameter estimate | Ratio of geometric least square means |
| Point estimate | 100.67 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 93.84 |
| upper limit | 108 |

Notes:

[6] - Equivalence margin: 80%-125%

## Primary: ORR (CR + CRu + PR) during the Core Study Period

| End point title | ORR (CR + CRu + PR) during the Core Study Period |
|---|---|

End point description:

Overall response rate (CR + CRu + PR) according to the 1999 IWG criteria during the Core Study Period by central review.

| End point type | Primary |
|---|---|

End point timeframe:

During the Core Study Period (up to 8 cycles)

| **End point values** | CT-P10 | Rituxan | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 66[7] | 68[8] | | |
| Units: Number of Patients | | | | |
| ORR (CR+CRu+PR) | 64 | 63 | | |
| Complete Response (CR) | 20 | 15 | | |
| Unconfirmed CR (CRu) | 6 | 8 | | |
| Partial Response (PR) | 38 | 40 | | |

| | | | | |
|---|---|---|---|---|
| Stable disease | 1 | 2 | | |
| Relapse/Progressive disease | 1 | 2 | | |
| Unable to assess | 0 | 1 | | |

Notes:

[7] - Four patients with major protocol deviations or no posttreatment efficacy results were excluded.

[8] - Two patients with no posttreatment efficacy results were excluded.

### Statistical analyses

| **Statistical analysis title** | Co-primary Efficacy Endpoint - ORR |
|---|---|
| Statistical analysis description: | |
| The point estimate difference of the ORR between the CT-P10 and Rituxan. | |
| Comparison groups | CT-P10 v Rituxan |
| Number of subjects included in analysis | 134 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[9] |
| Parameter estimate | Point estimate difference |
| Point estimate | 4.3 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | -4.25 |

Notes:

[9] - Non-inferiority margin : -7%

### Secondary: B-cell kinetics (B-cell depletion and recovery) during the Core Study Period

| End point title | B-cell kinetics (B-cell depletion and recovery) during the Core Study Period |
|---|---|
| End point description: | |
| Pharmacodynamics (B-cell counts) of rituximab during the Core Study Period | |
| End point type | Secondary |
| End point timeframe: | |
| During the Core Study Period (up to 8 cycles) | |

| **End point values** | CT-P10 | Rituxan | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 70 | 70 | | |
| Units: cells/µL | | | | |
| median (full range (min-max)) | | | | |
| Core Cycle 1 (Predose) | 92.5 (20 to 2890) | 62.0 (20 to 2890) | | |
| Core Cycle 1 (1Hr after End of Infusion) | 20.0 (20 to 1108) | 20.0 (20 to 51) | | |
| Core Cycle 2 (Predose) | 20.0 (20 to 1750) | 20.0 (20 to 2890) | | |
| Core Cycle 3 (Predose) | 20.0 (20 to 231) | 20.0 (20 to 35) | | |
| Core Cycle 4 (Predose) | 20.0 (20 to 51) | 20.0 (20 to 20) | | |
| Core Cycle 5 (Predose) | 20.0 (20 to 20) | 20.0 (20 to 20) | | |

| | | | | |
|---|---|---|---|---|
| Core Cycle 6 (Predose) | 20.0 (20 to 33) | 20.0 (20 to 20) | | |
| Core Cycle 7 (Predose) | 20.0 (20 to 24) | 20.0 (20 to 20) | | |
| Core Cycle 8 (Predose) | 20.0 (20 to 20) | 20.0 (20 to 20) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Overall study period | |
| Adverse event reporting additional description: | |
| All TESAEs and non-serious AEs reported for more than 5% of the patients in either treatment group are summarized for the safety population. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

| Reporting groups | |
|---|---|
| Reporting group title | CT-P10 |
| Reporting group description: | |
| All randomly assigned patients who received at least 1 dose (full or partial) of CT-P10. | |
| Reporting group title | Rituxan |
| Reporting group description: | |
| All randomly assigned patients who received at least 1 dose (full or partial) of Rituxan. | |

| Serious adverse events | CT-P10 | Rituxan | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 70 (34.29%) | 13 / 70 (18.57%) | |
| number of deaths (all causes) | 8 | 4 | |
| number of deaths resulting from adverse events | 4 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatocellular carcinoma | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Invasive lobular breast carcinoma | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer metastatic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| 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 | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (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 | | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Post procedural fistula | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | 3 / 70 (4.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal infection | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes virus infection | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | 1 / 70 (1.43%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sialoadenitis | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 2 / 70 (2.86%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoalbuminaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 0 / 70 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |

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

| **Non-serious adverse events** | CT-P10 | Rituxan | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 58 / 70 (82.86%) | 57 / 70 (81.43%) | |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | 1 / 70 (1.43%) | |
| occurrences (all) | 5 | 1 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 16 / 70 (22.86%) | 19 / 70 (27.14%) | |
| occurrences (all) | 24 | 25 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 3 / 70 (4.29%) | |
| occurrences (all) | 6 | 3 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Dizziness | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | 5 / 70 (7.14%) | |
| occurrences (all) | 4 | 5 | |
| Headache | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | 6 / 70 (8.57%) | |
| occurrences (all) | 4 | 6 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 2 / 70 (2.86%) | |
| occurrences (all) | 6 | 3 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 10 / 70 (14.29%) | 12 / 70 (17.14%) | |
| occurrences (all) | 12 | 15 | |
| Paraesthesia | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | 8 / 70 (11.43%) | |
| occurrences (all) | 7 | 9 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 5 / 70 (7.14%) | |
| occurrences (all) | 6 | 6 | |
| Neutropenia | | | |
| subjects affected / exposed | 27 / 70 (38.57%) | 20 / 70 (28.57%) | |
| occurrences (all) | 60 | 37 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 70 (7.14%) | 8 / 70 (11.43%) | |
| occurrences (all) | 5 | 12 | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 8 / 70 (11.43%) | |
| occurrences (all) | 7 | 12 | |
| Oedema | | | |
| subjects affected / exposed | 5 / 70 (7.14%) | 3 / 70 (4.29%) | |
| occurrences (all) | 6 | 3 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 70 (4.29%) | 6 / 70 (8.57%) | |
| occurrences (all) | 5 | 10 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Abdominal pain | | | |
| subjects affected / exposed | 8 / 70 (11.43%) | 11 / 70 (15.71%) | |
| occurrences (all) | 8 | 12 | |
| Constipation | | | |
| subjects affected / exposed | 12 / 70 (17.14%) | 10 / 70 (14.29%) | |
| occurrences (all) | 13 | 12 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 7 / 70 (10.00%) | |
| occurrences (all) | 8 | 8 | |
| Nausea | | | |
| subjects affected / exposed | 9 / 70 (12.86%) | 7 / 70 (10.00%) | |
| occurrences (all) | 11 | 7 | |
| Stomatitis | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | 4 / 70 (5.71%) | |
| occurrences (all) | 2 | 6 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 5 / 70 (7.14%) | |
| occurrences (all) | 6 | 10 | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | 1 / 70 (1.43%) | |
| occurrences (all) | 4 | 1 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 70 (1.43%) | 4 / 70 (5.71%) | |
| occurrences (all) | 1 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 10 / 70 (14.29%) | 5 / 70 (7.14%) | |
| occurrences (all) | 10 | 5 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | 6 / 70 (8.57%) | |
| occurrences (all) | 2 | 9 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 7 / 70 (10.00%) | 4 / 70 (5.71%) | |
| occurrences (all) | 8 | 7 | |
| Back pain | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | 12 / 70 (17.14%) | |
| occurrences (all) | 2 | 15 | |
| Myalgia | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 2 / 70 (2.86%) | |
| occurrences (all) | 7 | 2 | |
| Infections and infestations | | | |
| Fungal infection | | | |
| subjects affected / exposed | 4 / 70 (5.71%) | 4 / 70 (5.71%) | |
| occurrences (all) | 4 | 4 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | 4 / 70 (5.71%) | |
| occurrences (all) | 2 | 4 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 7 / 70 (10.00%) | 1 / 70 (1.43%) | |
| occurrences (all) | 12 | 1 | |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 70 (7.14%) | 2 / 70 (2.86%) | |
| occurrences (all) | 5 | 6 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 14 / 70 (20.00%) | 18 / 70 (25.71%) | |
| occurrences (all) | 21 | 31 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 6 / 70 (8.57%) | 6 / 70 (8.57%) | |
| occurrences (all) | 9 | 15 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 70 (0.00%) | 6 / 70 (8.57%) | |
| occurrences (all) | 0 | 7 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 70 (2.86%) | 5 / 70 (7.14%) | |
| occurrences (all) | 2 | 5 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 July 2014 | Summary of significant change included the following:<br>-Acceptance of patients aged 18 years to enroll.<br>-Clarification of nodal and extranodal lesions, and dimensions.<br>-Acceptance of previous radiotherapy under specific circumstances.<br>-Providing flexibility in the acceptable methods for diagnosis of active TB.<br>-The reduced number of blood samples for PK and PD analyses.<br>-Sample size recalculation after expansion of research into randomized controlled trials with R-CVP.<br>-Changes of analysis method from exact binomial approach to descriptive analysis, and clarification of Cox's proportional hazard model not used in this study.<br>-Reduced freqeuncy of folow-up visits upon the information available in the phase 3 PRIMA study.<br>-Revised definitions of some efficacy analyses based on the 2007 IWG criteria and the 1999 IWG criteria. |
| 16 March 2016 | Summary of significant changes included the following:<br>-Reflection of changed covariates for PK analysis.<br>-Deletion of sensitivity analysis in efficacy considered irrelevant.<br>-Specification of how to maintain blinding.<br>-Addition of evaluation variables other than pharmacokinetics for the first CSR. |

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.

| |
|---|
| None |

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/28712940