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) International Conference on Malignant Lymphoma (ICML) 2017 (2.Buske (2017)_ICML 2017 abstract.pdf) European Hematology Association (EHA) 2017 (3.Ogura (2017)_EHA 2017 abstract.pdf) American Society of Clinical Oncology (ASCO) 2017 (4.Kim (2017)_ASCO 2017 abstract.pdf) European Society for Medical Oncology (ESMO) Asia 2017 (5.Kim (2017)_ESMO asia 2017 abstract.pdf) American Society of Hematology (ASH) 2017 (6.Kim (2017)_ASH 2017 abstract.pdf) American Society of Hematology (ASH) 2018 (7.Kim (2018)_ASH 2018 abstract.pdf) 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 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 Units: years			
median	57.0	58.5	
full range (min-max)	30 to 85	26 to 84	-
Gender categorical 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: -Acceptance of patients aged 18 years to enroll. -Clarification of nodal and extranodal lesions, and dimensions. -Acceptance of previous radiotherapy under specific circumstances. -Providing flexibility in the acceptable methods for diagnosis of active TB. -The reduced number of blood samples for PK and PD analyses. -Sample size recalculation after expansion of research into randomized controlled trials with R-CVP. -Changes of analysis method from exact binomial approach to descriptive analysis, and clarification of Cox's proportional hazard model not used in this study. -Reduced freqeuncy of folow-up visits upon the information available in the phase 3 PRIMA study. -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: -Reflection of changed covariates for PK analysis. -Deletion of sensitivity analysis in efficacy considered irrelevant. -Specification of how to maintain blinding. -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