Clinical trial results:
A Phase 3, Randomised, Parallel-Group, Active-Controlled, Double-Blind Study to Compare Efficacy and Safety between CT-P10 and Rituxan in Patients with Low Tumour Burden Follicular Lymphoma

Summary

EudraCT number	2014-005324-10
Trial protocol	CZ LV ES PT IT
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	07 February 2021
First version publication date	07 February 2021

Trial information

Trial identification

Sponsor protocol code	CT-P10_3.4

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02260804
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CELLTRION, Inc.
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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	17 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2018
Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that CT-P10 is similar to Rituxan in terms of efficacy as determined by overal response rate [ORR] (complete response [CR] + unconfirmed complete response [CRu] + partial response [PR]) at 7 months (Prior to Cycle 3 of Maintenance Study Period) according to the Modified Response Criteria for Malignant Lymphoma.

Protection of trial subjects:

Hypersensitivity was assessed by vital sign monitoring (including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) on each dosing day and recorded on each dosing day at the following time points:
- Before the beginning of study drug infusion on Day 1 of each cycle (within 15 minutes before the beginning of study drug infusion)
- At the end of study drug infusion (within 15 minutes after the end of study drug infusion)
- At 60 minutes (±15 minutes) after the end of study drug infusion
In addition, hypersensitivity was monitored by routine continuous clinical monitoring including ECG (3-lead or 12-lead) monitoring at 60 minutes (±15 minutes) after the end of study drug infusion.
For patients who experienced or developed life-threatening IRR, rituximab treatment was stopped immediately and the patient was withdrawn from the study.

Background therapy:

- Induction Study Period (up to 4 weeks): Patients were to receive study drug at a dose of 375 mg/m2, administered by an intravenous (IV) infusion, weekly for 4 weeks.
- Maintenance Study Period (up to a maximum of 12 cycles over 2 years): Patients who experienced a CR, CRu, PR, or stable disease after Cycle 4 of the Induction Study Period (as assessed at the MC1) were eligible to start maintenance therapy with the study drug at a dose of 375 mg/m2 administered by an IV infusion, every 8 weeks. After the 1st year of the Maintenance Period (MP1), once the similarity between the study drugs had been confirmed, additional CT-P10 administration was offered to all patients who had completed MP1, at the discretion of the participating investigator.

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. This study is designed to demonstrate similarity in efficacy and safety of CT P10 compared with rituximab in patients with low tumour burden FL

Actual start date of recruitment	01 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	27 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Russian Federation: 26

Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Belarus: 12
Country: Number of subjects enrolled	Korea, Republic of: 38
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	India: 10
Country: Number of subjects enrolled	Ukraine: 10
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Latvia: 3
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Mexico: 1
Worldwide total number of subjects	258
EEA total number of subjects	82

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)	174
From 65 to 84 years	83
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

258 patients from 96 study centers were randomly assigned to study drug.

Pre-assignment

Screening details:

Key Inclusion Criteria
- 18 year or older
- Histologically confirmed CD20+ Follicular Lymphoma grades 1 to 3a
- At least 1 measurable tumour mass
- Ann Arbor stage II, III, or IV
- Low tumour burden by Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria

Period 1

Period 1 title	Induction 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) weekly for 4 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 normal saline administered as an IV infusion.

Arm title	Rituxan

Arm description:

Patient treated with US-licensed rituximab (375 mg/m2, IV) weekly for 4 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 normal saline administered as an IV infusion.

Number of subjects in period 1	CT-P10	Rituxan
Started	130	128
Completed	128	128
Not completed	2	0
Protocol deviation	2	-

Period 2

Period 2 title	1st year of the Maintenance 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:

Patient treated with CT-P10 (375 mg/m2, IV) 2-weekly for 6 cycles (up to 1 year).

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 normal saline administered as an IV infusion.

Arm title	Rituxan

Arm description:

Patient treated with US-licensed rituximab (375 mg/m2, IV) 2-weekly for 6 cycles (up to 1 year).

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 normal saline administered as an IV infusion.

Number of subjects in period 2[1]	CT-P10	Rituxan
Started	123	120
Completed	111	105
Not completed	12	15
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	-
Physician decision	1	3
Adverse event, non-fatal	3	1
Lost to follow-up	-	1
Lack of efficacy	6	9
Protocol deviation	1	-

Notes:

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

Justification: Five patients discontinued study treatment before the initiation of the 1st year of the Maintenance Period after completion of the Induction Period.

Period 3

Period 3 title	2nd year of the Maintenance 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	Maintained CT-P10

Arm description:

Patient treated with CT-P10 (375 mg/m2, IV) 2-weekly for 6 cycles after the 1st year of Maintenance Period (MP1). The total infusion of the maintenance treatment will not exceed 12 cycles over 2 years.

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 normal saline administered as an IV infusion.

Arm title	Switched to CT-P10

Arm description:

After the 1st year of Maintenance Period (MP1), once the similarity between study drugs is confirmed, additional CT-P10 (375 mg/m2, IV) 2-weekly for 6 cycles will be offered to all patients who have completed MP1 at discretion of participating investigator. The total infusion of the maintenance treatment will not exceed 12 cycles over 2 years.

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 normal saline administered as an IV infusion.

Number of subjects in period 3[2]	Maintained CT-P10	Switched to CT-P10
Started	110	103
Completed	101	97
Not completed	9	6
Consent withdrawn by subject	-	1
Adverse event, non-fatal	3	-
Lack of efficacy	6	5

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: Eight patients discontinued study treatment before the initiation of the 1st year of the Maintenance Period after completion of the Induction Period.

Baseline characteristics

Reporting groups	
Reporting group title	CT-P10
Reporting group description:	
Patient treated with CT-P10 (375 mg/m2, IV) weekly for 4 cycles.	
Reporting group title	Rituxan
Reporting group description:	
Patient treated with US-licensed rituximab (375 mg/m2, IV) weekly for 4 cycles.	

Reporting group values	CT-P10	Rituxan	Total
Number of subjects	130	128	258
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)	84	90	174
From 65-84 years	46	37	83
85 years and over	0	1	1
Age continuous Units: years			
median	57.7	57.7	
standard deviation	± 12.68	± 11.53	-
Gender categorical Units: Subjects			
Female	64	71	135
Male	66	57	123

End points

End points reporting groups

Reporting group title	CT-P10
Reporting group description:	
Patient treated with CT-P10 (375 mg/m2, IV) weekly for 4 cycles.	
Reporting group title	Rituxan
Reporting group description:	
Patient treated with US-licensed rituximab (375 mg/m2, IV) weekly for 4 cycles.	
Reporting group title	CT-P10
Reporting group description:	
Patient treated with CT-P10 (375 mg/m2, IV) 2-weekly for 6 cycles (up to 1 year).	
Reporting group title	Rituxan
Reporting group description:	
Patient treated with US-licensed rituximab (375 mg/m2, IV) 2-weekly for 6 cycles (up to 1 year).	
Reporting group title	Maintained CT-P10
Reporting group description:	
Patient treated with CT-P10 (375 mg/m2, IV) 2-weekly for 6 cycles after the 1st year of Maintenance Period (MP1). The total infusion of the maintenance treatment will not exceed 12 cycles over 2 years.	
Reporting group title	Switched to CT-P10
Reporting group description:	
After the 1st year of Maintenance Period (MP1), once the similarity between study drugs is confirmed, additional CT-P10 (375 mg/m2, IV) 2-weekly for 6 cycles will be offered to all patients who have completed MP1 at discretion of participating investigator. The total infusion of the maintenance treatment will not exceed 12 cycles over 2 years.	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population consisted of all patients enrolled and randomly assigned to receive a study drug, regardless of whether or not any study drug dosing was completed.	
Subject analysis set title	PP population
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population consisted of all patients who were randomly assigned to study drug, and had at least 1 response evaluation after receiving at least 1 dose (full) of study drug in the Induction Study Period, without any major protocol violation or deviation that may have affected the interpretation of efficacy results.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of all patients who received at least 1 dose (full or partial) of study drug. For the safety population, patients who received at least 1 dose (full or partial) of CT-P10 up to MP1 were analyzed under the CT-P10 group; all other patients were analyzed under the Rituxan group.	
Subject analysis set title	PK population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PK population consisted of all patients who received at least 1 dose (full) of study drug and had at least 1 posttreatment PK result. All PK analyses were conducted using the PK population.	
Subject analysis set title	PD population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The PD population consisted of all patients who received at least 1 dose (full) of study drug and had at least 1 posttreatment PD result. All PD analyses were conducted using the PD population.	

Primary: ORR (CR+CRu+PR) by 7 months

End point title	ORR (CR+CRu+PR) by 7 months

End point description:

The ORR was defined as the proportion of patients who had a BOR of CR, CRu, or PR (the "responders"). The BOR was derived from the overall responses according to the Modified Response Criteria for Malignant Lymphoma, across all time points up to the 7-month assessment (prior to maintenance cycle 3). Centrally reviewed data was used for the primary efficacy analysis.

End point type	Primary

End point timeframe:

ORR (CR+CRu+PR) by 7 months (prior to the maintenance cycle 3)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Number of Patients				
ORR	108	104		
CR	36	43		
CRu	6	2		
PR	66	59		
SD	17	18		
RD/PD	0	4		
unable to access	0	1		
missing	5	1		

Statistical analyses

Statistical analysis title	Primary Efficacy Endpoint - ORR
Comparison groups	CT-P10 v Rituxan
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Difference in proportion
Point estimate	1.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.43
upper limit	10.2

Notes:

[1] - Equivalence margin: ±17%

Secondary: ORR (CR+CRu+PR) over study period

End point title	ORR (CR+CRu+PR) over study period

End point description:

The ORR was defined as the proportion of patients who had a BOR of CR, CRu, or PR (the "responders"). The BOR was derived from the overall responses according to the Modified Response Criteria for Malignant Lymphoma. Locally reviewed data was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Overall study period (median follow-up of 29.2 months)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Number of Patients				
ORR	109	112		
CR	51	63		
CRu	7	2		
PR	51	47		
SD	15	12		
RD/PD	1	3		
missing	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary PK endpoints - Cmax

End point title	Secondary PK endpoints - Cmax

End point description:

End point type	Secondary

End point timeframe:

by the primary endpoint (7-months)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	128		
Units: µg/mL				
arithmetic mean (standard deviation)				
Induction Cycle 1	212.86 (± 50.64)	217.38 (± 56.33)		
Induction Cycle 2	283.35 (± 53.84)	285.98 (± 62.26)		
Induction Cycle 3	327.32 (± 71.05)	341.59 (± 77.95)		
Induction Cycle 4	373.46 (± 70.50)	383.05 (± 83.86)		
Maintenance Cycle 1	256.97 (± 65.61)	265.03 (± 53.73)		
Maintenance Cycle 2	239.70 (± 65.72)	249.86 (± 69.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary PK endpoints - Ctrough

End point title	Secondary PK endpoints - Ctrough

End point description:

End point type	Secondary

End point timeframe:

by the primary endpoint (7-months)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	128		
Units: µg/mL				
arithmetic mean (standard deviation)				
Induction Cycle 1	64.66 (± 24.88)	72.94 (± 40.39)		
Induction Cycle 2	113.23 (± 34.60)	120.92 (± 36.02)		
Induction Cycle 3	149.53 (± 43.65)	161.80 (± 43.91)		
Induction Cycle 4	34.78 (± 33.58)	31.38 (± 19.15)		
Maintenance Cycle 1	22.68 (± 37.22)	21.35 (± 20.90)		
Maintenance Cycle 2	16.96 (± 9.61)	18.37 (± 10.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary PD endpoints - B-cell kinetics

End point title	Secondary PD endpoints - B-cell kinetics

End point description:

Any values below the LLoQ were set as LLoQ which was 20 cells/µL.

End point type	Secondary

End point timeframe:

Pharmacodynamics (B-cell counts) of rituximab by the primary endpoint (7-months)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	128		
Units: cells/µL				
median (inter-quartile range (Q1-Q3))				
Baseline	95.0 (56.0 to 171.0)	120.0 (64.0 to 182.0)		
Induction Cycle 1 (1 hour after end of infusion)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Induction Cycle 2 (predose)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Induction Cycle 3 (predose)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Induction Cycle 4 (predose)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
End of Treatment 1 (anytime)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Maintenance Cycle 1 (predose)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Maintenance Cycle 1 (1 hour after end of infusion)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Maintenance Cycle 2 (predose)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Maintenance Cycle 2 (1 hour after end of infusion)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		
Maintenance Cycle 3 (predose)	20.0 (20.0 to 20.0)	20.0 (20.0 to 20.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Efficacy endpoints - PFS

End point title	Secondary Efficacy endpoints - PFS

End point description:

Progression-free survival was defined as the interval between randomization and disease progression/relapse or death from any cause, whichever occurred first.
Locally reviewed data was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Overall study period (median follow-up of 29.2 months)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Estimates of survival rates				
number (confidence interval 95%)				
12 months	0.93 (0.87 to 0.96)	0.89 (0.82 to 0.93)		
24 months	0.88 (0.81 to 0.92)	0.83 (0.75 to 0.89)		
36 months	0.80 (0.70 to 0.87)	0.68 (0.54 to 0.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Efficacy endpoints - OS

End point title	Secondary Efficacy endpoints - OS

End point description:

Overall survival was defined as the interval between randomization and death from any cause.
Locally reviewed data was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Overall study period (median follow-up of 29.2 months)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Estimates of survival rates				
number (confidence interval 95%)				
12 months	0.98 (0.93 to 0.99)	0.98 (0.94 to 1.00)		
24 months	0.98 (0.93 to 0.99)	0.98 (0.94 to 1.00)		
36 months	0.98 (0.93 to 0.99)	0.97 (0.89 to 0.99)		
42 months	0.98 (0.93 to 0.99)	0.97 (0.89 to 0.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Efficacy endpoints - TTP

End point title	Secondary Efficacy endpoints - TTP

End point description:

Time to progression was defined as the interval between randomization and disease progression/relapse or death as a result of lymphoma, whichever occurred first.
Locally reviewed data was used for the secondary efficacy analyses.

End point type	Secondary

End point timeframe:

Overall study period (median follow-up of 29.2 months)

End point values	CT-P10	Rituxan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Estimates of survival rates				
number (confidence interval 95%)				
12 months	0.94 (0.88 to 0.97)	0.89 (0.83 to 0.94)		
24 months	0.89 (0.82 to 0.94)	0.84 (0.76 to 0.89)		
36 months	0.82 (0.72 to 0.88)	0.68 (0.54 to 0.79)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall study period (median follow-up of 29.2 months)

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: -

Reporting group title	Rituxan

Reporting group description: -

Serious adverse events	CT-P10	Rituxan	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 130 (10.77%)	14 / 128 (10.94%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal neoplasm benign			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			

subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Surgical and medical procedures			
Gastrointestinal surgery			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			

subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peptic ulcer perforation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Genital prolapse			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 130 (0.77%)	0 / 128 (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 / 130 (0.77%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Localised infection			

subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 130 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 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-P10	Rituxan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 130 (71.54%)	86 / 128 (67.19%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 130 (5.38%)	3 / 128 (2.34%)	
occurrences (all)	7	4	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	42 / 130 (32.31%)	39 / 128 (30.47%)	
occurrences (all)	59	51	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 130 (7.69%)	6 / 128 (4.69%)	
occurrences (all)	13	6	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 130 (4.62%)	7 / 128 (5.47%)	
occurrences (all)	6	8	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	10 / 130 (7.69%)	7 / 128 (5.47%)	
occurrences (all)	12	11	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 130 (7.69%)	13 / 128 (10.16%)	
occurrences (all)	12	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 130 (4.62%)	7 / 128 (5.47%)	
occurrences (all)	6	10	
Diarrhoea			
subjects affected / exposed	9 / 130 (6.92%)	11 / 128 (8.59%)	
occurrences (all)	11	16	
Nausea			
subjects affected / exposed	7 / 130 (5.38%)	11 / 128 (8.59%)	
occurrences (all)	8	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 130 (6.92%)	12 / 128 (9.38%)	
occurrences (all)	10	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 130 (6.15%)	5 / 128 (3.91%)	
occurrences (all)	8	5	
Infections and infestations			
Herpes virus infection			
subjects affected / exposed	7 / 130 (5.38%)	5 / 128 (3.91%)	
occurrences (all)	7	5	
Influenza			
subjects affected / exposed	3 / 130 (2.31%)	8 / 128 (6.25%)	
occurrences (all)	3	8	
Lower respiratory tract infection			
subjects affected / exposed	6 / 130 (4.62%)	11 / 128 (8.59%)	
occurrences (all)	7	13	
Upper respiratory tract infection			

subjects affected / exposed	31 / 130 (23.85%)	29 / 128 (22.66%)	
occurrences (all)	42	41	
Urinary tract infection			
subjects affected / exposed	9 / 130 (6.92%)	13 / 128 (10.16%)	
occurrences (all)	10	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2015	Summary of significant change included the following: - Added a single transition from Rituxan to CT-P10 after 1 year maintenance therapy to assess the safety profiles. - Recalculated the sample size according to the updated statistical assumption.
06 September 2016	Summary of significant change included the following: - Inclusion criterion (#2) was revised to extend the FL tissue biopsy period based on literature references and discussion with KOLs. - Updated the efficacy assessment method for patients who developed an allergy to a contrast agent during the study period.

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.

In this study, TTE endpoints were secondary endpoints and were not powered. As medians of PFS, TTP, and OS were not reached in both treatment groups, longer follow-up is needed to ascertain the median time for TTE parameters of PFS, TTP, and OS.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30389036