Clinical trial results:
A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Rituximab Plus Lenalidomide (CC-5013) Versus Rituximab Plus Placebo in Subjects With Relapsed/Refractory Indolent Lymphoma

Summary

EudraCT number	2013-001245-14
Trial protocol	GB BE CZ IT PT ES PL
Global end of trial date	26 January 2022

Results information

Result version number	v1 (current)
This version publication date	11 February 2023
First version publication date	11 February 2023

Trial information

Trial identification

Sponsor protocol code	CC-5013-NHL-007

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	11 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the efficacy and safety of rituximab plus lenalidomide (R^2) versus rituximab plus placebo in subjects with relapsed/refractory indolent lymphoma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2013
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	Belgium: 22
Country: Number of subjects enrolled	Brazil: 42
Country: Number of subjects enrolled	China: 75
Country: Number of subjects enrolled	Czechia: 33
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	358
EEA total number of subjects	143

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)	203
From 65 to 84 years	149
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

358 randomized and 356 treated

Period 1

Period 1 title	Pre-Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab + Lenalidomide (R^2)

Arm description:

Participants received rituximab 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg on days 1 to 21 every 28 days.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

Arm title	Rituximab + Placebo

Arm description:

Participants received rituximab 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

Arm type	Control
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

Number of subjects in period 1	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo
Started	178	180
Completed	176	180
Not completed	2	0
Adverse event, serious fatal	1	-
Adverse Event unrelated to Study Drug	1	-

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab + Lenalidomide (R^2)

Arm description:

Participants received rituximab 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg on days 1 to 21 every 28 days.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

Arm title	Rituximab + Placebo

Arm description:

Participants received rituximab 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

Arm type	Control
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m^2 every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5

Number of subjects in period 2	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo
Started	176	180
Completed	124	110
Not completed	52	70
Adverse event, serious fatal	2	-
Consent withdrawn by subject	13	7
Adverse event, non-fatal	14	8
Progressive Disease	21	54
Other reasons	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab + Lenalidomide (R^2)
Reporting group description:	
Participants received rituximab 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.	
Reporting group title	Rituximab + Placebo
Reporting group description:	
Participants received rituximab 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.	

Reporting group values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo	Total
Number of subjects	178	180	358
Age categorical Units:			
Age Continuous Units: years			
arithmetic mean	62.30	61.48	
standard deviation	± 11.227	± 11.160	-
Sex: Female, Male Units: Participants			
Female	103	83	186
Male	75	97	172
Race/Ethnicity, Customized Units: Subjects			
White	118	115	233
Other Races	54	64	118
Not Collected or Reported	6	1	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	24	20	44
Not Hispanic or Latino	147	158	305
Unknown or Not Reported	7	2	9

End points

End points reporting groups

Reporting group title	Rituximab + Lenalidomide (R^2)

Reporting group description:

Participants received rituximab 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

Reporting group title	Rituximab + Placebo

Reporting group description:

Participants received rituximab 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

Reporting group title	Rituximab + Lenalidomide (R^2)

Reporting group description:

Participants received rituximab 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

Reporting group title	Rituximab + Placebo

Reporting group description:

Participants received rituximab 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

Primary: Kaplan Meier Estimate of Progression Free Survival Assessed by the Independent Review Committee (IRC) According to the 2007 International Working Group Response Criteria (IWGRC)

End point title	Kaplan Meier Estimate of Progression Free Survival Assessed by the Independent Review Committee (IRC) According to the 2007 International Working Group Response Criteria (IWGRC)

End point description:

Progression-free survival (PFS) was defined as the time from date of randomization into the study to the first observation of documented disease progression or death due to any cause, whichever occurred first. PFS was based on the data from the IRC review using the modified 2007 International Working Group Response Criteria (IWGRC) using FDA censoring rules.
99999=NA; not enough events had occurred at the time of the data cut-off date

End point type	Primary

End point timeframe:

From randomization of study drug up to disease progression or death, which occurred first; up to the data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months).

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: months				
median (confidence interval 95%)	39.4 (22.9 to 99999)	14.1 (11.4 to 16.7)		

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.62

Secondary: Durable Complete Response Rate (DCCR) as Assessed by the IRC According to the 2007 IWGRC

End point title	Durable Complete Response Rate (DCCR) as Assessed by the IRC According to the 2007 IWGRC

End point description:

DCCR was defined as the percentage of participants with a best response of complete response (CR) that lasted no less than one year (≥ 48 weeks) during the study prior to administration of new anti-lymphoma therapy. A CR is defined as a complete disappearance of any disease-related symptoms and normalization of biochemical abnormalities.

End point type	Secondary

End point timeframe:

From first dose of investigational product (IP) to data cut-off date of 22 June 2018; the median treatment duration was 11.19 months in the rituximab/lenalidomiade arm and 11.04 months in the rituximab/placebo arm

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (confidence interval 95%)	25.3 (19.1 to 32.3)	11.1 (6.9 to 16.6)		

Statistical analyses

Statistical analysis title	P-Value
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	Cochran-Mantel-Haenszel

Secondary: Kaplan-Meier Estimate of Overall Survival (OS)

End point title	Kaplan-Meier Estimate of Overall Survival (OS)

End point description:

Overall survival was defined as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented. 99999=NA; insufficient number of participants with events.

End point type	Secondary

End point timeframe:

From date of randomization to death due to any cause (Average of 55.71 months and a maximum up to 95.2 months)

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)

Statistical analysis description:

Stratified by 3 factors: previous rituximab treatment, time since last antilymphoma therapy (≤ 2, > 2

years), and disease histology (FL, MZL).

Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.95

Secondary: Percentage of Participants with an Objective Response as Assessed by the IRC According to the 2007 IWGRC

End point title	Percentage of Participants with an Objective Response as Assessed by the IRC According to the 2007 IWGRC

End point description:

Percentage of participants with an objective response is defined as having a response of at least a PR during the study without administration of new anti-lymphoma therapy. A complete response = a complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of any disease-related symptoms, and normalization of biochemical abnormalities; a partial response (PR) = 50% decrease in SPD of the 6 largest dominant nodes or nodal masses. No increase in the size of other nodes, liver, or spleen. Splenic and hepatic nodules must regress by at least 50% in the SPD.

End point type	Secondary

End point timeframe:

From date of first dose to data cut-off date of 22 June 2018; the median treatment duration was 11.19 months in the rituximab/lenalidomide arm and 11.04 months in the rituximab/placebo arm

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (confidence interval 95%)	77.5 (70.7 to 83.4)	53.3 (45.8 to 60.8)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo

Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of Participants with a Best Response of Complete Response as Assessed by the IRC According to the 2007 IWGRC

End point title	Percentage of Participants with a Best Response of Complete Response as Assessed by the IRC According to the 2007 IWGRC

End point description:

Percentage of participants with a best response of at CR during the study without administration of new anti-lymphoma therapy. A CR = Complete disappearance of all detectable clinical and radiographic evidence of disease, disappearance of any disease-related symptoms, and normalization of biochemical abnormalities.

End point type	Secondary

End point timeframe:

From date of first dose up to data cut-off date of 22 June 2018; the median treatment duration was 11.19 months in the rituximab/lenalidomide arm and 11.04 months in the rituximab/placebo arm

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (confidence interval 95%)	33.7 (26.8 to 41.2)	18.3 (13.0 to 24.8)		

Statistical analyses

Statistical analysis title	P-value
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Kaplan-Meier Estimate of Duration of Objective Response as Assessed by the IRC According to the 2007 IWGRC

End point title	Kaplan-Meier Estimate of Duration of Objective Response as Assessed by the IRC According to the 2007 IWGRC

End point description:

Duration of response (DOR) was defined as the time from initial response (at least PR) until documented progressive disease (PD) or death. Participants who had not progressed at the time of analysis were censored at the last assessment date that the participant was known to be progression free. Participants who received a new treatment without documented progression were censored at the last assessment date that the participants was known to be progression free.
99999=NA; Not estimable as not enough events had occurred at the time of the data cut-off date

End point type	Secondary

End point timeframe:

From randomization up to data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months).

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	96		
Units: months				
median (confidence interval 95%)	36.6 (22.9 to 99999)	21.7 (12.8 to 27.6)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0015
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.79

Secondary: Kaplan-Meier Estimate of Duration of Complete Response (DOCR) as Assessed by the IRC According to the 2007 IWGRC

End point title	Kaplan-Meier Estimate of Duration of Complete Response (DOCR) as Assessed by the IRC According to the 2007 IWGRC

End point description:

DOCR was defined as the time from initial CR until documented PD or death. Participants who had not progressed at the time of analysis were censored at the last assessment date that the participant was known to be progression free. Participants who received a new treatment without documented progression were censored at the last assessment date that the participants was known to be progression free.

99999=NA; Not enough events had occurred at the time of the data cut-off date

End point type	Secondary

End point timeframe:

From randomization up to data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months).

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	33		
Units: months				
median (confidence interval 95%)	99999 (25.3 to 99999)	99999 (13.8 to 99999)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2993
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.43

Secondary: Kaplan Meier Estimate of Event Free Survival as Assessed by the IRC According to the 2007 IWGRC

End point title	Kaplan Meier Estimate of Event Free Survival as Assessed by the IRC According to the 2007 IWGRC

End point description:

Event-free survival (EFS) was defined as the time from date of randomization to date of first documented progression, relapse, institution of new anti-lymphoma treatment (chemotherapy, radiotherapy or immunotherapy) or death from any cause. Responding participants and those who were lost to follow up were censored at their last tumor assessment date.
99999=NA; Not enough events had occurred at the time of the data cut-off date

End point type	Secondary

End point timeframe:

From date of randomization to data cut-off date of 22 June 2018; overall median follow-up time for all participants was 28.30 months (range: 0.1 to 51.3 months).

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: months				
median (confidence interval 95%)	27.6 (22.1 to 99999)	13.9 (11.4 to 16.7)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log-Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.67

Secondary: Kaplan Meier Estimate of Time to Next Anti-Lymphoma Treatment (TTNLT)

End point title	Kaplan Meier Estimate of Time to Next Anti-Lymphoma Treatment (TTNLT)

End point description:

Time to next anti-lymphoma treatment (TTNLT) was defined as the time from date of randomization to date of first documented administration of a new anti-lymphoma treatment (including chemotherapy, radiotherapy, radioimmunotherapy or immunotherapy). The time to the next anti-lymphoma treatment was of special interest to the study.
99999=NA; upper limit not available due to insufficient number of participants with events

End point type	Secondary

End point timeframe:

From date of randomization to date of first documented administration of a new anti-lymphoma treatment (Average of 55.71 months and a maximum up to 95.2 months)

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Months				
median (confidence interval 95%)	73.1 (43.0 to 99999)	31.8 (22.2 to 39.4)		

Statistical analyses

Statistical analysis title	Hazard Ratio (HR)
Comparison groups	Rituximab + Lenalidomide (R^2) v Rituximab + Placebo
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.71

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point description:

TEAEs include AEs that started or worsened between the date of the first dose and 28 days after the date of the last dose. A serious adverse event (SAE) is any: • Death; • Life-threatening event; • Any inpatient hospitalization or prolongation of existing hospitalization; • Persistent or significant disability or incapacity; • Congenital anomaly or birth defect; • Any other important medical event. The investigator determined the relationship of an AE to study drug based on the timing of the AE relative to drug administration and whether or not other drugs, therapeutic interventions, or underlying conditions could provide a sufficient explanation for the event. The severity of an AE was evaluated by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.03) where Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death

End point type	Secondary

End point timeframe:

From first dose to 28 days post last dose (Average of 55.71 months and a maximum up to 95.2 months)

End point values	Rituximab + Lenalidomide (R^2)	Rituximab + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	180		
Units: Participants				
Any TEAE	174	173		
Any TEAE Related to Lenalidomide/Placebo (LEN/PBO)	159	118		
Any TEAE Related to Rituximab (RIT)	134	105		
Any Serious TEAE	45	25		
Any Serious TEAE Related to LEN/PBO	23	8		
Any Serious TEAE Related to RIT	13	4		
Any CTCAE Grade (GR) 3/4 TEAE	121	58		
Any CTCAE GR 3/4 TEAE Related to LEN/PBO	101	38		
Any CTCAE GR 3/4 TEAE Related to RIT	57	20		
Any GR 5 TEAE	2	2		
Any TEAE Leading to Dose Reduction LEN/PBO	46	6		
Any TEAE Leading to Dose Interruption LEN/PBO	113	47		
Any TEAE Leading to Dose Interruption RIT	59	38		
Any TEAE Leading to Discontinuation of LEN/PBO	15	9		
Any TEAE Leading to Discontinuation of RIT	6	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs are collected from first dose to 28 days post last dose (Average of 55.71 months and a maximum of 95.2 months). Deaths (All-causes) was assessed from date of randomization to study completion (Up to approximately 100 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Rituximab + Placebo

Reporting group description:

Participants received rituximab 375 mg/m^2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from cycle 2 to 5 plus placebo (identically matched capsule) once daily on Days 1 to 21 of every 28-day cycle up to 12 cycles.

Reporting group title	Rituximab + Lenalidomide (R^2)

Reporting group description:

Participants received rituximab 375 mg/m^2 intravenously (IV) every week in Cycle 1 (Days 1, 8, 15 and 22) and on Day 1 of every 28-day cycle from Cycles 2 to 5 plus lenalidomide 20 mg by mouth (PO) once daily on Days 1 to 21 every 28 days up to 12 cycles (21-day treatment and 7-day rest period); if creatinine clearance (CrCl) was ≥ 30 mL/min but < 60 mL/min, participants received lenalidomide 10 mg capsules on days 1 to 21 every 28 days.

Serious adverse events	Rituximab + Placebo	Rituximab + Lenalidomide (R^2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 180 (13.89%)	45 / 176 (25.57%)	
number of deaths (all causes)	47	26	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			

subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 180 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell cancer of the renal pelvis and ureter localised			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour flare			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (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			
Asthenia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 180 (0.56%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Localised oedema			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 180 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 180 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related hypersensitivity reaction			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexal torsion			

subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 180 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 180 (1.67%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 180 (0.56%)	4 / 176 (2.27%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 180 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Fall			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (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 pectoris			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arrhythmia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrial fibrillation			
subjects affected / exposed	2 / 180 (1.11%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 180 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 180 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 180 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	2 / 180 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 180 (0.00%)	5 / 176 (2.84%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 180 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 180 (0.00%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 180 (0.00%)	2 / 176 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seronegative arthritis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 180 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosyphilis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 180 (3.33%)	6 / 176 (3.41%)	
occurrences causally related to treatment / all	2 / 7	5 / 8	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 180 (1.11%)	3 / 176 (1.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 180 (1.11%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 180 (0.56%)	1 / 176 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 180 (0.56%)	0 / 176 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rituximab + Placebo	Rituximab + Lenalidomide (R^2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 180 (87.78%)	170 / 176 (96.59%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare			
subjects affected / exposed	1 / 180 (0.56%)	18 / 176 (10.23%)	
occurrences (all)	1	18	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 180 (6.11%)	6 / 176 (3.41%)	
occurrences (all)	14	7	
Hypotension			
subjects affected / exposed	1 / 180 (0.56%)	9 / 176 (5.11%)	
occurrences (all)	4	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 180 (10.00%)	24 / 176 (13.64%)	
occurrences (all)	22	28	
Chills			
subjects affected / exposed	8 / 180 (4.44%)	14 / 176 (7.95%)	
occurrences (all)	8	19	
Fatigue			
subjects affected / exposed	33 / 180 (18.33%)	38 / 176 (21.59%)	
occurrences (all)	42	46	
Influenza like illness			
subjects affected / exposed	7 / 180 (3.89%)	9 / 176 (5.11%)	
occurrences (all)	7	10	
Malaise			

subjects affected / exposed	10 / 180 (5.56%)	13 / 176 (7.39%)	
occurrences (all)	10	14	
Oedema peripheral			
subjects affected / exposed	15 / 180 (8.33%)	24 / 176 (13.64%)	
occurrences (all)	20	28	
Pyrexia			
subjects affected / exposed	27 / 180 (15.00%)	35 / 176 (19.89%)	
occurrences (all)	35	46	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 180 (17.22%)	40 / 176 (22.73%)	
occurrences (all)	43	54	
Dyspnoea			
subjects affected / exposed	7 / 180 (3.89%)	18 / 176 (10.23%)	
occurrences (all)	7	24	
Oropharyngeal pain			
subjects affected / exposed	9 / 180 (5.00%)	10 / 176 (5.68%)	
occurrences (all)	11	14	
Productive cough			
subjects affected / exposed	8 / 180 (4.44%)	12 / 176 (6.82%)	
occurrences (all)	9	17	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 180 (6.11%)	14 / 176 (7.95%)	
occurrences (all)	11	22	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 180 (8.33%)	18 / 176 (10.23%)	
occurrences (all)	23	31	
Lymphocyte count decreased			
subjects affected / exposed	13 / 180 (7.22%)	12 / 176 (6.82%)	
occurrences (all)	25	29	
Blood bilirubin increased			
subjects affected / exposed	0 / 180 (0.00%)	11 / 176 (6.25%)	
occurrences (all)	0	25	
Aspartate aminotransferase increased			

subjects affected / exposed	9 / 180 (5.00%)	10 / 176 (5.68%)	
occurrences (all)	14	18	
White blood cell count decreased			
subjects affected / exposed	14 / 180 (7.78%)	17 / 176 (9.66%)	
occurrences (all)	34	52	
Weight decreased			
subjects affected / exposed	2 / 180 (1.11%)	14 / 176 (7.95%)	
occurrences (all)	2	15	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	24 / 180 (13.33%)	24 / 176 (13.64%)	
occurrences (all)	36	28	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 180 (9.44%)	26 / 176 (14.77%)	
occurrences (all)	29	38	
Dizziness			
subjects affected / exposed	9 / 180 (5.00%)	15 / 176 (8.52%)	
occurrences (all)	11	18	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 180 (4.44%)	28 / 176 (15.91%)	
occurrences (all)	12	48	
Lymphopenia			
subjects affected / exposed	14 / 180 (7.78%)	8 / 176 (4.55%)	
occurrences (all)	21	26	
Leukopenia			
subjects affected / exposed	18 / 180 (10.00%)	37 / 176 (21.02%)	
occurrences (all)	25	140	
Neutropenia			
subjects affected / exposed	40 / 180 (22.22%)	103 / 176 (58.52%)	
occurrences (all)	81	355	
Thrombocytopenia			
subjects affected / exposed	9 / 180 (5.00%)	26 / 176 (14.77%)	
occurrences (all)	23	75	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	25 / 180 (13.89%)	46 / 176 (26.14%)	
occurrences (all)	34	71	
Abdominal pain			
subjects affected / exposed	16 / 180 (8.89%)	22 / 176 (12.50%)	
occurrences (all)	19	28	
Abdominal pain upper			
subjects affected / exposed	7 / 180 (3.89%)	11 / 176 (6.25%)	
occurrences (all)	7	14	
Diarrhoea			
subjects affected / exposed	42 / 180 (23.33%)	55 / 176 (31.25%)	
occurrences (all)	52	111	
Dyspepsia			
subjects affected / exposed	5 / 180 (2.78%)	16 / 176 (9.09%)	
occurrences (all)	5	20	
Nausea			
subjects affected / exposed	23 / 180 (12.78%)	21 / 176 (11.93%)	
occurrences (all)	28	33	
Stomatitis			
subjects affected / exposed	7 / 180 (3.89%)	9 / 176 (5.11%)	
occurrences (all)	10	11	
Vomiting			
subjects affected / exposed	13 / 180 (7.22%)	18 / 176 (10.23%)	
occurrences (all)	16	20	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	6 / 180 (3.33%)	9 / 176 (5.11%)	
occurrences (all)	6	9	
Pruritus			
subjects affected / exposed	8 / 180 (4.44%)	33 / 176 (18.75%)	
occurrences (all)	12	44	
Rash			
subjects affected / exposed	9 / 180 (5.00%)	20 / 176 (11.36%)	
occurrences (all)	10	28	
Rash maculo-papular			

subjects affected / exposed	4 / 180 (2.22%)	14 / 176 (7.95%)	
occurrences (all)	4	15	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 180 (9.44%)	19 / 176 (10.80%)	
occurrences (all)	23	25	
Back pain			
subjects affected / exposed	18 / 180 (10.00%)	14 / 176 (7.95%)	
occurrences (all)	24	17	
Muscle spasms			
subjects affected / exposed	9 / 180 (5.00%)	23 / 176 (13.07%)	
occurrences (all)	15	28	
Myalgia			
subjects affected / exposed	12 / 180 (6.67%)	10 / 176 (5.68%)	
occurrences (all)	12	14	
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 180 (4.44%)	17 / 176 (9.66%)	
occurrences (all)	10	17	
Pneumonia			
subjects affected / exposed	7 / 180 (3.89%)	14 / 176 (7.95%)	
occurrences (all)	8	16	
Nasopharyngitis			
subjects affected / exposed	18 / 180 (10.00%)	13 / 176 (7.39%)	
occurrences (all)	24	22	
Sinusitis			
subjects affected / exposed	5 / 180 (2.78%)	13 / 176 (7.39%)	
occurrences (all)	5	13	
Urinary tract infection			
subjects affected / exposed	7 / 180 (3.89%)	12 / 176 (6.82%)	
occurrences (all)	9	16	
Upper respiratory tract infection			
subjects affected / exposed	23 / 180 (12.78%)	33 / 176 (18.75%)	
occurrences (all)	28	48	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	11 / 180 (6.11%)	23 / 176 (13.07%)	
occurrences (all)	12	27	
Hyperglycaemia			
subjects affected / exposed	11 / 180 (6.11%)	12 / 176 (6.82%)	
occurrences (all)	16	20	
Hyperuricaemia			
subjects affected / exposed	8 / 180 (4.44%)	10 / 176 (5.68%)	
occurrences (all)	15	13	
Hypokalaemia			
subjects affected / exposed	5 / 180 (2.78%)	15 / 176 (8.52%)	
occurrences (all)	5	27	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2013	Update inclusion criteria and exploratory endpoints
22 May 2014	Update exclusion and inclusion criteria. Clarify treatment continuation rules and other minor clarifications/corrections.
21 October 2015	Modified inclusion criteria and revised exclusion criteria.
13 December 2018	Updated contact information. Updated follow-up frequency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported