Clinical trial results:
Phase 3 Randomized, Double-Blind, Placebo Controlled, Multicenter Study to Compare the Efficacy and Safety of Lenalidomide (Cc-5013) Plus R-Chop Chemotherapy (R2-Chop) Versus Placebo Plus R-Chop Chemotherapy in Subjects with Previously Untreated Activated B-Cell Type Diffuse Large

Summary

EudraCT number	2013-004054-21
Trial protocol	ES IE CZ IT PT BE NL
Global end of trial date	25 July 2022

Results information

Result version number	v1 (current)
This version publication date	07 June 2023
First version publication date	07 June 2023

Trial information

Trial identification

Sponsor protocol code	CC-5013-DLC-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02285062
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee 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	26 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the efficacy of R2-CHOP versus placebo-RCHOP.

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 January 2015
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	Italy: 134
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 23
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Spain: 40
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Turkey: 25
Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	China: 105
Country: Number of subjects enrolled	Czechia: 23
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Israel: 12

Worldwide total number of subjects	570
EEA total number of subjects	272

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)	275
From 65 to 84 years	295
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

570 participants were randomized (Intent to Treat (ITT) population) and 567 participants were treated (Safety population).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide Plus R-CHOP (R2-CHOP)

Arm description:

Participants received lenalidomide 15 mg capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 cycles. Treatment continued until completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, whichever occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

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:

15 mg capsule (oral administration) PO once daily for 14 days in each 21-day cycle

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

100 mg PO (oral administration) or intravenously (IV) on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2 IV on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m2 (max of 2.0 mg total) IV on day 1 of each 21-day cycle for up to 6 cycles.

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

Dosage and administration details:

375 mg/m2 IV on Day -1 or Day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg/m2 IV on Day 1 of each 21-day treatment cycle for up to 6 cycles.

Arm title	Placebo Plus R-CHOP

Arm description:

Participants received identically matching placebo capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 to 8 cycles. Treatment continued until 6-8 cycles were completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

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

Dosage and administration details:

15 mg capsule (oral administration) PO once daily for 14 days in each 21-day cycle

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

Dosage and administration details:

375 mg/m2 IV on Day -1 or Day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

100 mg PO (oral administration) or intravenously (IV) on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m2 (max of 2.0 mg total) IV on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2 IV on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg/m2 IV on Day 1 of each 21-day treatment cycle for up to 6 cycles.

Number of subjects in period 1	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP
Started	285	285
Completed	284	283
Not completed	1	2
Consent withdrawn by subject	1	-
Protocol deviation	-	2

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide Plus R-CHOP (R2-CHOP)

Arm description:

Participants received lenalidomide 15 mg capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 cycles. Treatment continued until completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, whichever occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

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:

15 mg capsule (oral administration) PO once daily for 14 days in each 21-day cycle

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

Dosage and administration details:

375 mg/m2 IV on Day -1 or Day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

100 mg PO (oral administration) or intravenously (IV) on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2 IV on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m2 (max of 2.0 mg total) IV on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg/m2 IV on Day 1 of each 21-day treatment cycle for up to 6 cycles.

Arm title	Placebo Plus R-CHOP

Arm description:

Participants received identically matching placebo capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 to 8 cycles. Treatment continued until 6-8 cycles were completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

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

Dosage and administration details:

15 mg capsule (oral administration) PO once daily for 14 days in each 21-day cycle

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

Dosage and administration details:

375 mg/m2 IV on Day -1 or Day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

100 mg PO (oral administration) or intravenously (IV) on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m2 (max of 2.0 mg total) IV on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2 IV on day 1 of each 21-day cycle for up to 6 cycles.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

750 mg/m2 IV on Day 1 of each 21-day treatment cycle for up to 6 cycles.

Number of subjects in period 2	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP
Started	283	284
Completed	211	240
Not completed	72	44
Combined reasons for not completing 6-full cycles.	72	44

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide Plus R-CHOP (R2-CHOP)
Reporting group description:	
Participants received lenalidomide 15 mg capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 cycles. Treatment continued until completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, whichever occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.	
Reporting group title	Placebo Plus R-CHOP
Reporting group description:	
Participants received identically matching placebo capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 to 8 cycles. Treatment continued until 6-8 cycles were completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.	

Reporting group values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP	Total
Number of subjects	285	285	570
Age Categorical Units: Participants			
< 65	138	137	275
≥ 65	147	148	295
Age Continuous Units: Years			
arithmetic mean	62.5	63.9	
standard deviation	± 11.72	± 9.35	-
Sex: Female, Male Units: Participants			
Female	121	142	263
Male	164	143	307
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	17	31
Not Hispanic or Latino	270	267	537
Unknown or Not Reported	1	1	2
Race/Ethnicity, Customized Units: Subjects			
White	173	183	356
Asian	101	89	190
Black or African American	2	3	5
Other	3	2	5
Not Collected or Reported	6	8	14
Eastern Cooperative Oncology Group (ECOG) Performance Status			
The ECOG performance status is used to describe a patient’s level of functioning in terms of their ability			

to care for themselves, daily activity, and physical ability (walking, working, etc.). The scale ranges from 0 to 5: 0 = Fully active, no restrictions; 1 = Restricted activity but ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out work activities; 3 = Limited self-care, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled, no self-care, confined to bed or chair; 5 = Dead			
Units: Subjects			
0 = Fully Active	129	111	240
1 = Restrictive but ambulatory	104	118	222
2 = Ambulatory but unable to work	52	56	108
International Prognostic Index (IPI) Score			
The IPI score is a clinical tool developed to aid in predicting the prognosis of patients with aggressive non-Hodgkin's lymphoma, including DLBCL. One point is assigned for each of the following risk factors: Age greater than 60 years, Stage III or IV disease, elevated serum lactate dehydrogenase (LDH), ECOG performance status of 2, 3, or 4, more than 1 extranodal site. The sum of the points allotted correlates with the following risk groups: Low risk (0-1 points) Low-intermediate risk (2 points) High-intermediate risk (3 points) High risk (4-5 points)			
Units: Subjects			
= 2	121	120	241
≥ 3	164	165	329
Presence of Bulky Disease Units: Subjects			
< 7.0 cm (Non-Bulky Disease)	188	186	374
≥ 7.0 cm (Bulky Disease)	97	99	196
Disease Stage of Diffuse Large B-Cell Lymphoma at Diagnosis			
The criteria for clinical stage (Ann Arbor staging) are as below: I: involvement of a single nodal region. II: involvement of 2 or more lymph node regions on the same side of the diaphragm. III: involvement of lymph node regions on both sides of the diaphragm. IV: disseminated involvement of 1 or more extra-lymphatic sites with or without associated lymph node involvement.			
Units: Subjects			
Stage I	0	1	1
Stage II	37	32	69
Stage III	80	98	178
Stage IV	168	154	322
Creatinine Clearance			
Creatinine is a waste product from the normal breakdown of muscle tissue. As creatinine is produced, it's filtered through the kidneys and excreted in urine. Doctors measure the blood creatinine level as a test of kidney function.			
Units: mL/min			
arithmetic mean	92.08	90.19	
standard deviation	± 35.576	± 31.040	-
Body Surface Area (BSA)			
Body surface area is the calculated surface of a human body. BSA is often considered a more accurate measure of metabolic mass than body weight, since it's less affected by irregular amounts of fat tissue.			
Units: m^2			
arithmetic mean	1.780	1.775	
standard deviation	± 0.2167	± 0.2101	-

End points

End points reporting groups

Reporting group title	Lenalidomide Plus R-CHOP (R2-CHOP)

Reporting group description:

Participants received lenalidomide 15 mg capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 cycles. Treatment continued until completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, whichever occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

Reporting group title	Placebo Plus R-CHOP

Reporting group description:

Participants received identically matching placebo capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 to 8 cycles. Treatment continued until 6-8 cycles were completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

Reporting group title	Lenalidomide Plus R-CHOP (R2-CHOP)

Reporting group description:

Participants received lenalidomide 15 mg capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 cycles. Treatment continued until completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, whichever occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

Reporting group title	Placebo Plus R-CHOP

Reporting group description:

Participants received identically matching placebo capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 to 8 cycles. Treatment continued until 6-8 cycles were completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

Primary: Kaplan-Meier Estimate of Progression Free Survival (PFS)

End point title	Kaplan-Meier Estimate of Progression Free Survival (PFS)

End point description:

Progression free survival was defined as the time (months) from the date of randomization to the date of disease progression or death (any cause), whichever occurred earlier and was assessed by the Independent Response Adjudication Committee (IRAC). Relapse from complete response (CR) was considered as disease progression throughout the study. Disease progression was determined based on the Revised Response Criteria for Malignant Lymphoma. The PFS analysis was based on the censoring rules using the Food and Drug Administration (FDA) Guidance. Participants who did not experience disease progression and who did not die before the clinical data cutoff date were censored at the date of last adequate response assessment. "99999" = Not Applicable/Not Available.

End point type	Primary

End point timeframe:

From the date of randomization up to the data cut off date of 15 March 2019; median follow-up of 24.5

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (35.5 to 99999)		

Statistical analyses

Statistical analysis title	PFS Hazard Ratio
Comparison groups	Lenalidomide Plus R-CHOP (R2-CHOP) v Placebo Plus R-CHOP
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2864
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.849
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.632
upper limit	1.14

Secondary: Percentage of Participants who Achieved a Complete Response (CR)

End point title	Percentage of Participants who Achieved a Complete Response (CR)

End point description:

The percentage of participants who achieved a CR after initiation of the study treatment and prior to initiation of subsequent systemic antilymphoma therapy as assessed by the IRAC. A CR = complete metabolic response; target nodes/nodal masses regressed on computed tomography to (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy. Regressed to normal size by imaging, and absence of nodules related to lymphoma. If bone marrow was involved prior to therapy, no evidence of fluorodeoxyglucose avid disease in marrow per International Working Group (IWG) 2014 for Non-Hodgkin's Lymphoma (NHL). Participants who did not have any adequate response assessments during this period were not considered as responders.

End point type	Secondary

End point timeframe:

From randomization date up to the data cut off date of 15 March 2019; median follow-up was 24.5 months

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Percentage of Participants				
number (confidence interval 95%)	69.1 (63.4 to 74.4)	64.9 (59.1 to 70.4)		

Statistical analyses

Statistical analysis title	Complete Response
Comparison groups	Lenalidomide Plus R-CHOP (R2-CHOP) v Placebo Plus R-CHOP
Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2933 [1]
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Obtained from CMH test adjusting for stratification factors: IPI score (2 or ≥ 3), presence of bulky disease (bulky or nonbulky), and age (< 65 or ≥ 65)

Secondary: K-M Estimate of Overall Survival (OS)

End point title	K-M Estimate of Overall Survival (OS)

End point description:

Overall survival was assessed by the IRAC (Independent Response Adjudication Committee) and defined as time from randomization until death due to any cause. Participants who withdrew consent were censored at the time of withdrawal. Participants who were still alive before the clinical data cutoff date and participants who were lost to follow-up were censored at date last known alive. "99999" = Not Applicable/Not Available

End point type	Secondary

End point timeframe:

From randomization until death due to any cause (up to approximately 86 months)

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	OS Hazard Ratio
Comparison groups	Lenalidomide Plus R-CHOP (R2-CHOP) v Placebo Plus R-CHOP

Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.876
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.965
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.716
upper limit	1.3

Secondary: Kaplan-Meier (K-M) Estimate of Event Free Survival (EFS)

End point title	Kaplan-Meier (K-M) Estimate of Event Free Survival (EFS)

End point description:

EFS was defined as the time (months) from randomization until occurrence of one of the following events, whichever occurred first: • Disease progression • Initiation of subsequent systemic anti-lymphoma therapy • Death due to any cause The assessment of EFS was conducted by the IRAC using the International Working Group (IWG) criteria for NHL. Pre-specified optional therapies such as the extra 2 doses of single agent rituximab after Cycle 6 or consolidation radiotherapy did not count as an EFS event (initiation of subsequent systemic anti-lymphoma therapy) if the decision to treat and the location to be treated was determined prior to randomization. Participants who did not experience any of the events defined in the categories above before the clinical data cutoff date were censored at date last known alive. "99999" = Not Applicable/Not Available

End point type	Secondary

End point timeframe:

From the date of randomization up to the data cut off date of 15 March 2019; median follow-up was 24.5 months

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (31.3 to 99999)		

Statistical analyses

Statistical analysis title	EFS Hazard Ratio
Comparison groups	Lenalidomide Plus R-CHOP (R2-CHOP) v Placebo Plus R-CHOP

Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7294
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.802
upper limit	1.344

Secondary: K-M Estimate of Time to Next Lymphoma Therapy (TTNLT)

End point title	K-M Estimate of Time to Next Lymphoma Therapy (TTNLT)

End point description:

Time to next lymphoma therapy was defined as the time from randomization to the time of treatment change for the next lymphoma treatment. Participants without treatment change were censored at date last known alive. Pre-specified optional therapies such as the extra 2 doses of single agent rituximab after Cycle 6 or consolidation radiotherapy did not count as treatment change for the next lymphoma therapy if the decision to treat and the location to be treated were determined prior to randomization. "99999" = Not Applicable/Not Available

End point type	Secondary

End point timeframe:

From randomization date up to the data cut off date of 15 March 2019; median follow-up was 24.5 months

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	TTNLT
Comparison groups	Lenalidomide Plus R-CHOP (R2-CHOP) v Placebo Plus R-CHOP

Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.315
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.167
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.856
upper limit	1.59

Secondary: K-M Estimate of Duration of Complete Response

End point title	K-M Estimate of Duration of Complete Response

End point description:

Duration of complete response was calculated for complete responders only and was defined as the time from documented initial complete response prior to initiation of subsequent systemic antilymphoma therapy until documented disease progression or death, whichever occurred earlier. Participants who had not progressed or died at the time of the analysis were censored at the date of last response assessment demonstrating no disease progression. Participants who changed treatment without evidence of disease progression were censored at the last assessment showing no progression prior to treatment change. "99999" = Not Applicable/Not Available

End point type	Secondary

End point timeframe:

From randomization date up to the data cut off date of 15 March 2019; median follow-up was 24.5 months.

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	185		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	DOCR
Comparison groups	Lenalidomide Plus R-CHOP (R2-CHOP) v Placebo Plus R-CHOP

Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2143
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.521
upper limit	1.157

Secondary: Percentage of Participants who Achieved an Objective Response

End point title	Percentage of Participants who Achieved an Objective Response

End point description:

An objective response = percentage of participants who achieved a complete response or partial response after initiation of the treatment and prior to initiation of subsequent systemic anti-lymphoma therapy. A CR = complete metabolic response; Target nodes/nodal masses regressed on computed tomography to (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy. Regressed to normal size by imaging, and absence of nodules related to lymphoma. If bone marrow was involved prior to therapy, no evidence of fluorodeoxyglucose avid disease in marrow. PR = ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. No increase in other nodes, liver, or spleen. Splenic nodules regressed by ≥ 50% in their SPD or for single nodules, in the greatest transverse diameter; no new lesions. Participants who did not have any adequate response assessments during this period were not considered as responders.

End point type	Secondary

End point timeframe:

From randomization date up to the data cut off date of 15 March 2019; median total treatment duration was 18.10 weeks for both treatment arms; range = 1.6 to 29.0 weeks for R2-CHOP arm and 0.3 to 22.9 weeks for placebo-R-CHOP arm

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Percentage of Participants				
number (confidence interval 95%)	90.9 (86.9 to 94.0)	90.9 (86.9 to 94.0)		

Statistical analyses

Statistical analysis title	Objective Response
Comparison groups	Lenalidomide Plus R-CHOP (R2-CHOP) v Placebo Plus R-CHOP

Number of subjects included in analysis	570
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9964 [2]
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Obtained from CMH test adjusting for stratification factors: IPI score (2 or ≥ 3), presence of bulky disease (bulky or nonbulky), and age (< 65 or ≥ 65)

Secondary: Percentage of Participants who Completed the Euroqol 5-Dimension 3-Level (EQ-5D-3L) Health Related Quality of Life (HR-QoL) Questionnaire

End point title	Percentage of Participants who Completed the Euroqol 5-Dimension 3-Level (EQ-5D-3L) Health Related Quality of Life (HR-QoL) Questionnaire

End point description:

The completion rate for EQ-5D assessments was judged by looking at the number of completed assessments at each time point. Completion rates were calculated as the number and percentage of participants out of the total number of patients in the ITT population and summarized by visit/cycle and treatment group. The EQ-5D-3L is a generic, self-reported preference-based measure of health across five dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has three levels of 'severity' corresponding to "no problems", "some problems" and "extreme problems". The instrument is scored using the United Kingdom (UK) index ranges from -0.594 – 1, where 0 equates to death and 1 equates to full health -0.594 is considered 'worse than death'.

End point type	Secondary

End point timeframe:

Screening, Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Percentage of Participants				
number (not applicable)				
Screening	98.9	97.9		
Midcycle	87.0	86.3		
End of Treatment (EoT)	76.5	79.6		
Follow-Up Period: Week 34	68.1	69.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Completed the Functional Assessment of Cancer Therapy Lymphoma (FACT-Lym) Questionnaire

End point title	Percentage of Participants who Completed the Functional Assessment of Cancer Therapy Lymphoma (FACT-Lym) Questionnaire

End point description:

The completion rate for FACT-Lym assessments was judged by looking at the number of completed

FACT-Lym assessments at each time point. The FACT-Lym was considered completed if at least 1 calculable score was present. Completion rates were calculated as the number and percentage of participants out of the total number of patients in the ITT population and summarized by visit/cycle and treatment group. The FACT-Lym is a health related quality of life (HRQoL) questionnaire targeted to the management of chronic illness, predominantly within oncology and is considered an extension of the FACT-General questionnaire.

End point type	Secondary

End point timeframe:

Screening, Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Percentage of Participants				
number (not applicable)				
Screening	98.6	98.2		
Midcycle = After Cycle 3, but before Cycle 4	87.0	86.3		
End of Treatment (EoT) = 3-4 weeks after C6	76.1	79.6		
Follow-Up Period: Week 34	67.7	69.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the FACT-Lym Physical Well-Being Subscale

End point title	Mean Change from Baseline in the FACT-Lym Physical Well-Being Subscale

End point description:

The FACT-Lym questionnaire is a validated instrument for assessing the impact of lymphoma on HRQL and contains 42 questions covering HRQL and common lymphoma symptoms and treatment side-effects. It begins with the Functional Assessment of Cancer Therapy - General (FACT-G), which contains 27 questions covering four core subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 questions) used to assess NHL-related symptoms and concerns. All questions are answered on a 5-point scale ranging from "not at all" (0) to "very much" (4). The physical well-being subscale ranges from 0 to 28, where higher scores reflect better HRQoL.

End point type	Secondary

End point timeframe:

Baseline and Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	257		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Midcycle	-0.7 (± 5.91)	0.2 (± 5.40)		
C6 D1	-0.0 (± 6.35)	0.9 (± 6.02)		
EoT = 3-4 weeks after C6	1.5 (± 5.53)	0.7 (± 5.72)		
Follow-Up Period: Week 34	2.8 (± 5.24)	2.6 (± 5.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the FACT-Lym Functional Well-Being Subscale

End point title	Mean Change from Baseline in the FACT-Lym Functional Well-Being Subscale

End point description:

The FACT-Lym questionnaire is a validated instrument for assessing the impact of lymphoma on HRQL and contains 42 questions covering HRQL and common lymphoma symptoms and treatment side-effects. It begins with the Functional Assessment of Cancer Therapy - General (FACT-G), which contains 27 questions covering four core subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 questions) used to assess NHL-related symptoms and concerns. All questions are answered on a 5-point scale ranging from "not at all" (0) to "very much" (4). The functional well-being subscale ranges from 0 to 28, where higher scores reflect better HRQoL.

End point type	Secondary

End point timeframe:

Baseline and Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	256		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Midcycle	-0.5 (± 6.12)	0.5 (± 5.84)		
C6 D1	0.0 (± 6.24)	1.4 (± 5.63)		
EoT = 3-4 weeks after C6	1.0 (± 6.53)	0.7 (± 6.71)		
Follow-Up Period: Week 34	2.3 (± 6.65)	3.1 (± 6.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the FACT-Lym Additional Concerns Subscale

End point title	Mean Change from Baseline in the FACT-Lym Additional Concerns Subscale

End point description:

The FACT-Lym questionnaire is a validated instrument for assessing the impact of lymphoma on HRQL and contains 42 questions covering HRQL and common lymphoma symptoms and treatment side-effects. It begins with the Functional Assessment of Cancer Therapy - General (FACT-G), which contains 27 questions covering four core subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 questions) used to assess NHL-related symptoms such as pain, itching, night sweats,trouble sleeping, fatigue and trouble concentrating and concerns regarding lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. All questions are answered on a 5-point scale ranging from "not at all" (0) to "very much" (4). The Additional Concerns subscale ranges from 0 to 60, where higher scores reflect better HRQoL.

End point type	Secondary

End point timeframe:

Baseline and Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	255		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Midcycle	3.8 (± 10.33)	4.1 (± 8.88)		
C6 D1	5.8 (± 11.11)	5.2 (± 9.40)		
EoT = 3-4 weeks after C6	6.6 (± 10.11)	4.5 (± 9.62)		
Follow-Up Period: Week 34	8.3 (± 10.61)	6.5 (± 9.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the FACT-Lym Trial Outcome Index (TOI)

End point title	Mean Change from Baseline in the FACT-Lym Trial Outcome Index (TOI)

End point description:

The FACT-Lym questionnaire is a validated instrument for assessing the impact of lymphoma on HRQL and contains 42 questions covering HRQL and common lymphoma symptoms and treatment side-effects. It begins with the Functional Assessment of Cancer Therapy - General (FACT-G), which contains 27 questions covering four core subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 questions) used to assess NHL-related symptoms and concerns. All questions are answered on a 5-point scale ranging from "not at all" (0) to "very much" (4). The FACT-Lym TOI is calculated by summing the Physical Well-being, Functional Well-being and Additional Concerns scores and has a range of 0 to 116. Higher scores reflect better HRQoL or fewer symptoms.

End point type	Secondary

End point timeframe:

Baseline and Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	254		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Midcycle	2.6 (± 18.26)	4.6 (± 16.49)		
C6 D1	5.9 (± 19.85)	7.5 (± 17.40)		
EoT = 3-4 weeks after C6	9.1 (± 18.51)	5.8 (± 18.64)		
Follow-Up Period: Week 34	13.5 (± 18.74)	12.2 (± 17.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the Euroqol 5-Dimension 3-Level (EQ-5D-3L) Index Score

End point title	Mean Change from Baseline in the Euroqol 5-Dimension 3-Level (EQ-5D-3L) Index Score

End point description:

The EQ-5D-3L is a generic, self-reported preference-based measure of health across five dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has three levels of 'severity' corresponding to "no problems", "some problems" and "extreme problems". The instrument is scored as a single summary index using one of the available EQ-5D-3L value sets; in this study the UK scoring weights 9 were used. The UK index ranges from -0.594 to 1, where 0 equates to death and 1 equates to full health (-0.594 is considered 'worse than death').

End point type	Secondary

End point timeframe:

Baseline and Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	257	255		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Midcycle	0.08 (± 0.308)	0.08 (± 0.281)		
C6 D1	0.10 (± 0.325)	0.14 (± 0.330)		
EoT = 3-4 weeks after C6	0.10 (± 0.309)	0.06 (± 0.319)		
Follow-Up Period: Week 34	0.15 (± 0.293)	0.09 (± 0.311)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in the EQ-5D-3L Visual Analogue Scale (VAS)

End point title	Mean Change from Baseline in the EQ-5D-3L Visual Analogue Scale (VAS)

End point description:

The EQ-5D-3L questionnaire includes a visual analogue scale which records the respondent's self-rated health on a vertical, 0–100 scale where 100 = "Best imaginable health state" and 0 = "Worst imaginable health state". Higher scores again indicate better HRQoL and positive change scores indicate that post screening values were higher than those observed at screening. The EQ-5D-3L is a generic, self-reported preference-based measure of health across five dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has three levels of 'severity' corresponding to "no problems", "some problems" and "extreme problems".

End point type	Secondary

End point timeframe:

Baseline and Midcycle = after Cycle 3 but before Cycle 4, Cycle 6 Day 1 (C6D1), End of Treatment (C6,D21), and Follow-Up Period up to Week 34

End point values	Lenalidomide Plus R-CHOP (R2-CHOP)	Placebo Plus R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	255		
Units: Units on a Scale				
arithmetic mean (standard deviation)				
Midcycle	4.0 (± 20.5)	3.0 (± 18.2)		
C6 D1	6.0 (± 23.5)	9.0 (± 24.5)		
EoT = 3-4 weeks after C6	8.0 (± 18.7)	6.0 (± 21.5)		
Follow-Up Period: Week 34	12.0 (± 20.2)	9 (± 21.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs were monitored from the participant's first dose of study treatment up to 28 days after their last dose; measured up to approximately 33 weeks.

Adverse event reporting additional description:

Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication (Safety Population).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo Plus R-CHOP

Reporting group description:

Participants received identically matching placebo capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 to 8 cycles. Treatment continued until 6-8 cycles were completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

Reporting group title	Lenalidomide Plus R-CHOP (R2-CHOP)

Reporting group description:

Participants received lenalidomide 15 mg capsules on days 1 to 14 of each 21 day treatment cycle followed by R-CHOP: rituximab 375 mg/m^2 by intravenous (IV) administration on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV on Day 1 (maximum dose of 2.0 mg total), cyclophosphamide 750 mg/m^2 IV on Day 1 and oral or IV prednisone/prednisolone 100 mg on Day 1 to Day 5 of each 21 day treatment cycle for 6 cycles. Treatment continued until completed, unless unacceptable toxicity, treatment change, disease progression, or withdrawal of consent, whichever occurred first. An additional two doses (1 dose per 21-day cycle) of single agent rituximab after the 6 cycles of treatment were completed if considered standard of care per local practice.

Serious adverse events	Placebo Plus R-CHOP	Lenalidomide Plus R-CHOP (R2-CHOP)	
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 284 (30.99%)	104 / 283 (36.75%)	
number of deaths (all causes)	87	85	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 284 (0.00%)	3 / 283 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 284 (0.35%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 284 (0.35%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Extravasation			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pyrexia			
subjects affected / exposed	9 / 284 (3.17%)	7 / 283 (2.47%)	
occurrences causally related to treatment / all	4 / 9	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Interstitial lung disease			
subjects affected / exposed	4 / 284 (1.41%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 284 (1.06%)	5 / 283 (1.77%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 284 (0.70%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 284 (1.06%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 284 (0.70%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			

Confusional state			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tic			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 284 (0.70%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniofacial fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infusion related reaction			
subjects affected / exposed	3 / 284 (1.06%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural headache			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural nausea			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural vomiting			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
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	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			

subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 284 (0.00%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 284 (1.41%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 284 (1.06%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 284 (0.70%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	2 / 284 (0.70%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 284 (0.70%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
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			
Thrombocytopenia			
subjects affected / exposed	1 / 284 (0.35%)	16 / 283 (5.65%)	
occurrences causally related to treatment / all	1 / 1	20 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic necrosis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	13 / 284 (4.58%)	19 / 283 (6.71%)	
occurrences causally related to treatment / all	14 / 14	23 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (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	14 / 284 (4.93%)	31 / 283 (10.95%)	
occurrences causally related to treatment / all	15 / 15	41 / 42	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytopenia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	6 / 284 (2.11%)	6 / 283 (2.12%)	
occurrences causally related to treatment / all	6 / 7	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agranulocytosis			
subjects affected / exposed	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 284 (0.00%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			

subjects affected / exposed	4 / 284 (1.41%)	6 / 283 (2.12%)	
occurrences causally related to treatment / all	3 / 4	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 284 (0.00%)	4 / 283 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal haemorrhage			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 284 (0.35%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 284 (0.70%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 284 (0.00%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 284 (0.35%)	3 / 283 (1.06%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			

subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
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	1 / 284 (0.35%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 284 (0.70%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 284 (0.00%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Escherichia urinary tract infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 284 (0.00%)	3 / 283 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 284 (3.17%)	15 / 283 (5.30%)	
occurrences causally related to treatment / all	9 / 9	13 / 17	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pulmonary sepsis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 284 (0.70%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock			
subjects affected / exposed	1 / 284 (0.35%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 284 (1.41%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
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	1 / 284 (0.35%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			

subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 284 (0.70%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 283 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 284 (0.35%)	1 / 283 (0.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypercalcaemia			
subjects affected / exposed	0 / 284 (0.00%)	2 / 283 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo Plus R-CHOP	Lenalidomide Plus R-CHOP (R2-CHOP)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	270 / 284 (95.07%)	272 / 283 (96.11%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 284 (9.51%)	32 / 283 (11.31%)	
occurrences (all)	40	46	
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 284 (7.04%)	22 / 283 (7.77%)	
occurrences (all)	34	33	
Lymphocyte count decreased			
subjects affected / exposed	12 / 284 (4.23%)	16 / 283 (5.65%)	
occurrences (all)	22	36	
Platelet count decreased			
subjects affected / exposed	10 / 284 (3.52%)	21 / 283 (7.42%)	
occurrences (all)	14	37	
Weight decreased			
subjects affected / exposed	10 / 284 (3.52%)	21 / 283 (7.42%)	
occurrences (all)	10	23	
White blood cell count decreased			
subjects affected / exposed	19 / 284 (6.69%)	35 / 283 (12.37%)	
occurrences (all)	63	79	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	30 / 284 (10.56%)	27 / 283 (9.54%)	
occurrences (all)	30	28	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	51 / 284 (17.96%)	51 / 283 (18.02%)	
occurrences (all)	52	53	
Paraesthesia			
subjects affected / exposed	27 / 284 (9.51%)	26 / 283 (9.19%)	
occurrences (all)	28	27	

Neuropathy peripheral			
subjects affected / exposed	12 / 284 (4.23%)	19 / 283 (6.71%)	
occurrences (all)	12	22	
Headache			
subjects affected / exposed	28 / 284 (9.86%)	26 / 283 (9.19%)	
occurrences (all)	29	29	
Dizziness			
subjects affected / exposed	16 / 284 (5.63%)	16 / 283 (5.65%)	
occurrences (all)	20	18	
Dysgeusia			
subjects affected / exposed	15 / 284 (5.28%)	10 / 283 (3.53%)	
occurrences (all)	15	10	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	55 / 284 (19.37%)	68 / 283 (24.03%)	
occurrences (all)	130	167	
Neutropenia			
subjects affected / exposed	150 / 284 (52.82%)	183 / 283 (64.66%)	
occurrences (all)	366	505	
Lymphopenia			
subjects affected / exposed	31 / 284 (10.92%)	35 / 283 (12.37%)	
occurrences (all)	86	104	
Anaemia			
subjects affected / exposed	95 / 284 (33.45%)	127 / 283 (44.88%)	
occurrences (all)	161	222	
Leukopenia			
subjects affected / exposed	50 / 284 (17.61%)	50 / 283 (17.67%)	
occurrences (all)	151	196	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	40 / 284 (14.08%)	52 / 283 (18.37%)	
occurrences (all)	57	83	
Oedema peripheral			
subjects affected / exposed	32 / 284 (11.27%)	33 / 283 (11.66%)	
occurrences (all)	32	49	
Fatigue			

subjects affected / exposed	50 / 284 (17.61%)	40 / 283 (14.13%)	
occurrences (all)	61	43	
Asthenia			
subjects affected / exposed	28 / 284 (9.86%)	39 / 283 (13.78%)	
occurrences (all)	32	44	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	18 / 284 (6.34%)	11 / 283 (3.89%)	
occurrences (all)	24	15	
Abdominal pain			
subjects affected / exposed	16 / 284 (5.63%)	18 / 283 (6.36%)	
occurrences (all)	18	21	
Vomiting			
subjects affected / exposed	26 / 284 (9.15%)	32 / 283 (11.31%)	
occurrences (all)	30	46	
Constipation			
subjects affected / exposed	81 / 284 (28.52%)	92 / 283 (32.51%)	
occurrences (all)	109	115	
Diarrhoea			
subjects affected / exposed	40 / 284 (14.08%)	49 / 283 (17.31%)	
occurrences (all)	51	61	
Nausea			
subjects affected / exposed	66 / 284 (23.24%)	64 / 283 (22.61%)	
occurrences (all)	97	92	
Stomatitis			
subjects affected / exposed	37 / 284 (13.03%)	33 / 283 (11.66%)	
occurrences (all)	41	41	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	10 / 284 (3.52%)	16 / 283 (5.65%)	
occurrences (all)	11	17	
Dyspnoea			
subjects affected / exposed	15 / 284 (5.28%)	11 / 283 (3.89%)	
occurrences (all)	18	13	
Cough			

subjects affected / exposed	20 / 284 (7.04%)	31 / 283 (10.95%)	
occurrences (all)	23	38	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	43 / 284 (15.14%)	48 / 283 (16.96%)	
occurrences (all)	43	48	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	32 / 284 (11.27%)	23 / 283 (8.13%)	
occurrences (all)	47	24	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 284 (4.58%)	18 / 283 (6.36%)	
occurrences (all)	13	18	
Back pain			
subjects affected / exposed	22 / 284 (7.75%)	15 / 283 (5.30%)	
occurrences (all)	26	15	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	18 / 284 (6.34%)	23 / 283 (8.13%)	
occurrences (all)	21	29	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	32 / 284 (11.27%)	29 / 283 (10.25%)	
occurrences (all)	41	38	
Hyperglycaemia			
subjects affected / exposed	19 / 284 (6.69%)	18 / 283 (6.36%)	
occurrences (all)	24	24	
Hypokalaemia			
subjects affected / exposed	28 / 284 (9.86%)	41 / 283 (14.49%)	
occurrences (all)	42	74	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2017	Revised lenalidomide / placebo dose modification rules for neutropenia and thrombocytopenia toxicities.
12 June 2019	Protocol Amendment 4 removes the requirement of follow-up assessments for subjects continuing in the study except for overall survival (OS) and second primary malignancy (SPM) follow-up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported