Clinical trial results:
A Phase 2, Multicenter, Randomized Open-Label Study to Determine the Efficacy of Lenalidomide (Revlimid®) Versus Investigators Choice in Patients With Relapsed or Refractory Mantle Cell Lymphoma

Summary

EudraCT number	2008-003389-25
Trial protocol	BE GB CZ DE ES FR IT DK SE GR
Global end of trial date	09 October 2018

Results information

Result version number	v1 (current)
This version publication date	18 October 2019
First version publication date	18 October 2019

Trial information

Trial identification

Sponsor protocol code	CC-5013-MCL-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00875667
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Jeffrey Jones, MD, Celgene Corporation, 01 908-673-9686, JeJones@celgene.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	18 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression free survival (PFS) of lenalidomide monotherapy versus investigators choice single agent in patients with mantle cell lymphoma (MCL) who are refractory to their regimen or have relapsed once, twice or three times.

Protection of trial subjects:

Archiving of Essential Documents, Personal Data Protection, Informed Consent

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Poland: 45
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Czech Republic: 32
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	254
EEA total number of subjects	198

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)	82
From 65 to 84 years	169
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 67 sites including 3 sites in Belgium, 3 in Czech Republic, 14 in France, 7 in Germany, 2 in Israel, 10 in Italy, 1 in the Netherlands, 5 in Poland, 11 in Russia, 4 in Spain, 2 in Sweden, and 5 in the United Kingdom (UK).

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to receive lenalidomide monotherapy or investigators choice. Participants were stratified according to the time since diagnosis (< 3 years or ≥ 3 years), time since last treatment (< 6 months [refractory] or ≥ 6 months) and if they had undergone a prior stem cell transplant or not.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lenalidomide

Arm description:

Participants received lenalidomide (LEN) 25 mg capsules orally every day for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity. Participants with moderate renal insufficiency (creatinine clearance is ≥ 30 mL/min but < 60mL/min received 10 mg lenalidomide for 21 days of each 28-day cycle (Cycles 1 and 2). After Cycle 2, if the participant remained free of Grade 3 or Grade 4 toxicity, the dose was increased to 15 mg lenalidomide for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	CC-5013
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 25 mg capsules PO QD for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity.

Arm title	Investigators Choice

Arm description:

Participants received a single agent investigators choice (IC) of chlorambucil 40 mg/m^2 PO every 28 days until progressive disease (PD) or toxicity, OR rituximab 375 mg/m^2 by intravenous (IV) infusion on days 1, 8, 15 and 22 of each 56-day treatment cycle until PD or toxicity, OR cytarabine 1-2 g/m^2 by IV infusion on days 1 and 2 of each 28 day treatment cycle; up to 6 cycles, OR gemcitabine 1000 mg/m^2 by IV infusion on days 1, 8 and 15 of each 28 day treatment cycle; up to 6 cycles OR oral fludarabine 40 mg/m^2 or IV fludarabine 25 mg/m^2 on days 1 through 5 of each 28-day cycle; up to 6 cycles. Participants were given the option to enter into the lenalidomide crossover phase if PD occurred and received lenalidomide 25 mg capsules daily on days 1 to 21 of each 28 day treatment cycle until PD or toxicity.

Arm type	Active comparator
Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	Leukeran
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:	
Chlorambucil 40 mg/m^2 PO every 28 days until progressive disease (PD) or toxicity.	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan, MabThera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Rituximab 375 mg/m^2 by intravenous (IV) infusion on days 1, 8, 15 and 22 of each 56-day treatment cycle until PD or toxicity	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Cytosar-U®; Ara-C, Arabinosylcytosine
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Cytarabine 1-2 g/m^2 by IV infusion on days 1 and 2 of each 28 day treatment cycle; up to 6 cycles.	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Gemcitabine 1000 mg/m^2 by IV infusion on days 1, 8 and 15 of each 28 day treatment cycle; up to 6 cycles.	
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	Fludara®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Fludarabine 25 mg/m^2 by IV infusion on days 1 through 5 of each 28-day cycle; up to 6 cycles.	
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	Fludarabine phosphate
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Fludarabine 40 mg/m^2 by mouth on days 1 through 5 of each 28-day cycle; up to 6 cycles.	

Number of subjects in period 1	Lenalidomide	Investigators Choice
Started	170	84
Crossover from IC to Lenalidomide	0	40
Participants Treated	167	83
Completed	0	11
Not completed	170	73
Adverse event, serious fatal	7	2

Consent withdrawn by subject	17	5
Adverse event, non-fatal	29	10
Miscellaneous	12	6
Disease Progression	100	49
Randomized but no Study Drug Given	3	1
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide (LEN) 25 mg capsules orally every day for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity. Participants with moderate renal insufficiency (creatinine clearance is ≥ 30 mL/min but < 60mL/min received 10 mg lenalidomide for 21 days of each 28-day cycle (Cycles 1 and 2). After Cycle 2, if the participant remained free of Grade 3 or Grade 4 toxicity, the dose was increased to 15 mg lenalidomide for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity.

Reporting group title	Investigators Choice

Reporting group description:

Participants received a single agent investigators choice (IC) of chlorambucil 40 mg/m^2 PO every 28 days until progressive disease (PD) or toxicity, OR rituximab 375 mg/m^2 by intravenous (IV) infusion on days 1, 8, 15 and 22 of each 56-day treatment cycle until PD or toxicity, OR cytarabine 1-2 g/m^2 by IV infusion on days 1 and 2 of each 28 day treatment cycle; up to 6 cycles, OR gemcitabine 1000 mg/m^2 by IV infusion on days 1, 8 and 15 of each 28 day treatment cycle; up to 6 cycles OR oral fludarabine 40 mg/m^2 or IV fludarabine 25 mg/m^2 on days 1 through 5 of each 28-day cycle; up to 6 cycles. Participants were given the option to enter into the lenalidomide crossover phase if PD occurred and received lenalidomide 25 mg capsules daily on days 1 to 21 of each 28 day treatment cycle until PD or toxicity.

Reporting group values	Lenalidomide	Investigators Choice	Total
Number of subjects	170	84	254
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	55	27	82
From 65-84 years	113	56	169
85 years and over	2	1	3
Age Continuous Units: Years			
arithmetic mean	68.0	67.5	
standard deviation	± 9.38	± 8.20	-
Sex: Female, Male Units: Subjects			
Female	47	21	68
Male	123	63	186
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0

White	161	80	241
More than one race	0	0	0
Unknown or Not Reported	9	4	13
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status is used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living activities of the subject and determine appropriate treatment and prognosis. 0 = Fully Active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out light work; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities; 3 = Capable of only limited self-care; 4 = Completely Disabled, No self-care			
Units: Subjects			
0 = Fully Active	65	36	101
1 = Restrictive but Ambulatory	77	37	114
2 = Ambulatory but Unable to Work	27	11	38
3 = Limited Self-Care	0	0	0
Missing	1	0	1
Stage of Mantle Cell Lymphoma (MCL) at Diagnosis			
Ann Arbor staging is the staging system for lymphomas, both in Hodgkin's lymphoma (previously called Hodgkin's disease) and Non-Hodgkin lymphoma (abbreviated NHL). Stage I = Involvement of 1 Lymph Node (LN) or extralymphatic region Stage II = ≥ 2 LN sites on the same side of the diaphragm Stage III = LN regions on both sides of the diaphragm; may include spleen and 1 extralymphatic organ Stage IV = involvement of ≥ 1 extralymphatic organs with or without associated LN involvement (diffuse or disseminated)			
Units: Subjects			
Stage I	3	2	5
Stage II	10	1	11
Stage III	30	20	50
Stage IV	123	59	182
Missing	4	2	6
MCL International Prognostic Index (MIPI) Score at Baseline			
A prognostic index predictive of the outcome in advanced mantle cell lymphoma			
Units: Subjects			
Low Risk	42	21	63
Intermediate Risk	66	37	103
High Risk	60	25	85
Missing	2	1	3
Bone Marrow Involvment as Baseline			
Bone marrow involvement (biopsy score) was categorized according to the following observations (Cheson, 1999): (i) positive, if unequivocal cytologic or architectural evidence of malignancy, (ii) negative, if no aggregates or only a few well-circumscribed lymphoid aggregates, or (iii) indeterminate, if increased number or size of aggregates without cytologic or architectural atypia			
Units: Subjects			
Negative	27	11	38
Intermediate	4	3	7
Positive	21	13	34
Missing	118	57	175

End points

End points reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide (LEN) 25 mg capsules orally every day for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity. Participants with moderate renal insufficiency (creatinine clearance is ≥ 30 mL/min but < 60mL/min received 10 mg lenalidomide for 21 days of each 28-day cycle (Cycles 1 and 2). After Cycle 2, if the participant remained free of Grade 3 or Grade 4 toxicity, the dose was increased to 15 mg lenalidomide for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity.

Reporting group title	Investigators Choice

Reporting group description:

Participants received a single agent investigators choice (IC) of chlorambucil 40 mg/m^2 PO every 28 days until progressive disease (PD) or toxicity, OR rituximab 375 mg/m^2 by intravenous (IV) infusion on days 1, 8, 15 and 22 of each 56-day treatment cycle until PD or toxicity, OR cytarabine 1-2 g/m^2 by IV infusion on days 1 and 2 of each 28 day treatment cycle; up to 6 cycles, OR gemcitabine 1000 mg/m^2 by IV infusion on days 1, 8 and 15 of each 28 day treatment cycle; up to 6 cycles OR oral fludarabine 40 mg/m^2 or IV fludarabine 25 mg/m^2 on days 1 through 5 of each 28-day cycle; up to 6 cycles. Participants were given the option to enter into the lenalidomide crossover phase if PD occurred and received lenalidomide 25 mg capsules daily on days 1 to 21 of each 28 day treatment cycle until PD or toxicity.

Primary: Kaplan Meier Estimate for Progression Free Survival (PFS) by Independent Review Committee (IRC) Central Review

End point title	Kaplan Meier Estimate for Progression Free Survival (PFS) by Independent Review Committee (IRC) Central Review

End point description:

PFS was defined as time of randomization to the first observation of disease progression or death due to any cause, whichever was first. If a participant had not progressed or died, PFS was censored at the time of last assessment when the participant was known not to have progressed. For participants who received other anti-lymphoma therapy with no evidence of progression, PFS was censored at time of last tumor assessment with no evidence of progression prior to the start of new anti-lymphoma treatment. Intent to Treat (ITT) population included all randomized participants.

End point type	Primary

End point timeframe:

From randomization to progression of disease or death; up to data cut off date of 07 March 2014; overall median follow-up time was 93.9 weeks

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: weeks				
median (confidence interval 95%)	37.6 (24.0 to 52.6)	22.7 (15.9 to 30.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [1]
Method	Stratified Log Rank Test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.9

Notes:

[1] - Stratification factors were: time from diagnosis to first dose, time from last prior anti-lymphoma therapy to first dose, prior stem cell transplant, and MIPI at baseline

Primary: Kaplan Meier Estimate for Progression Free Survival by Investigators Assessment at the Final Analysis

End point title	Kaplan Meier Estimate for Progression Free Survival by Investigators Assessment at the Final Analysis

End point description:

Kaplan Meier estimates of PFS were defined as the time from randomization to the first observation of disease progression or death due to any cause, whichever was first. If a participant had not progressed or died, PFS was censored at the time of last completed assessment when the participant was known not to have progressed. For participants who received other anti-lymphoma therapy with no evidence of progression, PFS was censored at time of last tumor assessment with no evidence of progression prior to the start of new anti-lymphoma treatment. ITT population included all randomized participants.

End point type	Primary

End point timeframe:

From randomization to progression of disease or death; up to study discontinuation of 09 October 2018; overall median follow-up time was 285 weeks

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: weeks				
median (confidence interval 95%)	37.3 (24.1 to 52.6)	23.6 (15.9 to 33.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [2]
Method	Stratified Log Rank Test
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.85

Notes:

[2] - Stratification factors were: time from diagnosis to first dose, time from last prior anti-lymphoma therapy to first dose, prior stem cell transplant, and MIPI at baseline

Secondary: Percentage of Participants Who Achieved an Overall Response According to the IRC Central Review

End point title	Percentage of Participants Who Achieved an Overall Response According to the IRC Central Review

End point description:

Overall Response Rate (ORR) was defined as the percentage of participants whose best response was Complete Response (CR), Complete Response unconfirmed (CRu) or Partial Response (PR). Participants who discontinued before any response had been observed or changed to other anti-lymphoma treatments before response had been observed, were considered as non-responders. Tumor Response was assessed by a modification of the International Lymphoma Workshop Response Criteria, IWRC, Cheson, 1999; CR is defined as the disappearance of all clinical and radiographic evidence of disease; CRu is defined as a CR, with a 1) residual lymph node mass >1.5 cm that has decreased by 75% in the sum of the product of the diameters (SPD). Individual nodes previously confluent decreased by more than 75% in the SPD compared with original mass; 2) indeterminate bone marrow; PR = is defined ≥50% decrease in 6 largest nodes or nodal masses. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the data cut-off date of 07 March 2014; median treatment duration was 24.3 weeks for the lenalidomide arm and 13.1 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Percentage of Participants				
number (confidence interval 95%)	40.0 (32.58 to 47.78)	10.7 (5.02 to 19.37)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Secondary: Percentage of Participants Who Achieved an Overall Response as Assessed by the Investigator at the Final Analysis

End point title	Percentage of Participants Who Achieved an Overall Response as Assessed by the Investigator at the Final Analysis

End point description:

Overall Response Rate (ORR) was defined as the percentage of participants whose best response was Complete Response, Complete Response unconfirmed or Partial Response. Participants who had discontinued before any response has been observed or changed to other anti-lymphoma treatments before response had been observed, were considered as non-responders. Tumor Response was assessed by a modification of the International Lymphoma Workshop Response Criteria, IWRC, Cheson, 1999; CR is defined as the disappearance of all clinical and radiographic evidence of disease; CRu is defined as a CR, with a 1) residual lymph node mass >1.5 cm that has decreased by 75% in the sum of the product of the diameters (SPD). Individual nodes previously confluent decreased by more than 75% in the SPD compared with original mass; 2) indeterminate bone marrow; PR = is defined ≥50% decrease in 6 largest nodes or nodal masses. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the study discontinuation date of 09 October 2018; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Percentage of Participants				
number (confidence interval 95%)	45.9 (38.23 to 53.68)	22.6 (14.20 to 33.05)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared

Secondary: Kaplan Meier Estimate for Duration of Response (DOR) According to the

IRC Central Review	
End point title	Kaplan Meier Estimate for Duration of Response (DOR) According to the IRC Central Review

End point description:

Duration of response was defined as the time from when the first response of CR, CRu, or PR was first achieved until documented tumor progression, or until the participant died from any cause, whichever occurred first. Participants who did not progress or die 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 participant was known to be progression-free. The analysis population included participants with an overall response.

End point type	Secondary

End point timeframe:

From date of randomization to the data cut-off date of 07 March 2014; median study duration was 70.7 weeks for the lenalidomide arm and 69.3 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	9		
Units: Weeks				
median (confidence interval 95%)	69.6 (41.1 to 86.7)	45.1 (36.3 to 80.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.421
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.68

Secondary: Kaplan Meier Estimate for Duration of Response as Assessed by the Investigator at the Final Analysis	
End point title	Kaplan Meier Estimate for Duration of Response as Assessed by the Investigator at the Final Analysis

End point description:

Duration of response was defined as the time from when the first response of CR, CRu, or PR was first

achieved until documented tumor progression, or until the participant died from any cause, whichever occurred first. Participants who did not progress or die 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 participant was known to be progression-free. The analysis population included participants with an overall response.

End point type	Secondary

End point timeframe:

From date of randomization to the study discontinuation date of 09 October 2018; median study duration was 103.9 weeks for lenalidomide and 87.0 weeks for the investigator choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	19		
Units: Weeks				
median (confidence interval 95%)	70.1 (47.0 to 98.0)	91.7 (28.3 to 130.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.875
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.74

Secondary: Percentage of Participants with a Complete Response, Unconfirmed Complete Response, Partial Response and Stable Disease According to the IRC Central Review

End point title	Percentage of Participants with a Complete Response, Unconfirmed Complete Response, Partial Response and Stable Disease According to the IRC Central Review

End point description:

Tumor control rate was defined as the percentage of participants with a complete response (CR), unconfirmed complete response (CRu), partial response (PR) and stable disease (SD). Tumor Response was assessed by a modification of the International Lymphoma Workshop Response Criteria, IWRC, Cheson, 1999); CR is defined as the disappearance of all clinical and radiographic evidence of disease; CRu is defined as a CR, with a 1) residual lymph node mass >1.5 cm that has decreased by 75% in the sum of the product of the diameters (SPD). Individual nodes previously confluent decreased by more

than 75% in the SPD compared with original mass; 2) indeterminate bone marrow; PR = is defined ≥50% decrease in 6 largest nodes or nodal masses. Stable disease (SD) is defined as less than a PR (see above) but is not progressive disease or relapsed disease. ITT population includes all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the data cut-off date of 07 March 2014; median treatment duration was 24.3 weeks for the lenalidomide arm and 13.1 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Percentage of Participants				
number (confidence interval 95%)	69.4 (61.89 to 76.24)	63.1 (51.87 to 73.37)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313
Method	Chi-squared

Secondary: Percentage of Participants with a Complete Response, Unconfirmed Complete Response, Partial Response and Stable Disease at the Final Analysis

End point title	Percentage of Participants with a Complete Response, Unconfirmed Complete Response, Partial Response and Stable Disease at the Final Analysis

End point description:

Tumor control rate was defined as the percentage of participants with a complete response (CR), unconfirmed complete response (CRu), partial response (PR) and stable disease (SD). Tumor Response was assessed by a modification of the International Lymphoma Workshop Response Criteria, IWRC, Cheson, 1999); CR is defined as the disappearance of all clinical and radiographic evidence of disease; CRu is defined as a CR, with a 1) residual lymph node mass >1.5 cm that has decreased by 75% in the sum of the product of the diameters (SPD). Individual nodes previously confluent decreased by more than 75% in the SPD compared with original mass; 2) indeterminate bone marrow; PR = is defined ≥50% decrease in 6 largest nodes or nodal masses. Stable disease (SD) is defined as less than a PR (see above) but is not progressive disease or relapsed disease. ITT population includes all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the discontinuation date of 09 October 2018; median treatment duration was 24.3 weeks for the lenalidomide arm and 13.1 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Percentage of participants				
number (confidence interval 95%)	70.0 (62.51 to 76.78)	65.5 (54.31 to 75.52)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465
Method	Chi-squared

Secondary: Kaplan Meier Estimate of Time to Progression According to the IRC Central Review

End point title	Kaplan Meier Estimate of Time to Progression According to the IRC Central Review

End point description:

Time to progression (TTP) was defined as the time from randomization until objective tumor progression. Time to progression did not include deaths. Participants without progression 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 anti-lymphoma treatment without documented progression were censored at the last assessment date that the participant was known to be progression-free. ITT population includes all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the data cut-off date of 07 March 2014; median study duration was 70.7 weeks for the lenalidomide arm and 69.3 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Weeks				
median (confidence interval 95%)	39.3 (24.3 to 52.9)	24.7 (15.9 to 30.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.87

Secondary: Kaplan Meier Estimate of Time to Progression as Assessed by the Investigator at the Final Analysis

End point title	Kaplan Meier Estimate of Time to Progression as Assessed by the Investigator at the Final Analysis

End point description:

Time to progression (TTP) was defined as the time from randomization until objective tumor progression. Time to progression did not include deaths. Participants without progression 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 anti-lymphoma treatment without documented progression were censored at the last assessment date that the participant was known to be progression-free. ITT population includes all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the study discontinuation date of 09 October 2018; median study duration was 103.9 weeks for lenalidomide and 87.0 weeks for the investigator choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: Weeks				
median (confidence interval 95%)	39.3 (25.1 to 61.0)	24.7 (15.9 to 36.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.86

Secondary: Kaplan Meier Estimate of Time to Treatment Failure (TTF) as Assessed by the Investigator

End point title	Kaplan Meier Estimate of Time to Treatment Failure (TTF) as Assessed by the Investigator

End point description:

Time to treatment failure was defined as the time from the first dose of study drug to discontinuation of treatment for any reason, including disease progression assessed by the investigator, treatment toxicity, or death. Participants who were on-treatment or completed the treatment according to the protocol were censored at the last date of drug intake. Includes all treated participants.

End point type	Secondary

End point timeframe:

From the date of the first treatment to the data cut-off date of 07 March 2014; median treatment duration was 24.3 weeks for the lenalidomide arm and 13.1 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	83		
Units: weeks				
median (confidence interval 95%)	24.4 (17.1 to 37.6)	17.9 (14.1 to 24.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1

Secondary: Kaplan Meier Estimate of Time to Treatment Failure as Assessed by the Investigator at the Final Analysis

End point title	Kaplan Meier Estimate of Time to Treatment Failure as Assessed by the Investigator at the Final Analysis

End point description:

Time to treatment failure was defined as the time from the first dose of study drug to discontinuation of treatment for any reason, including disease progression assessed by the investigator, treatment toxicity, or death. Participants who were on-treatment or completed the treatment according to the protocol were censored at the last date of drug intake. Includes all treated participants.

End point type	Secondary

End point timeframe:

From date of first dose of treatment to the study discontinuation date of 09 October 2018; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	83		
Units: weeks				
median (confidence interval 95%)	24.4 (17.1 to 37.6)	17.9 (14.1 to 24.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice

Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.05

Secondary: Kaplan Meier Estimate of Time to First Response (TTFR) According to the IRC Central Review

End point title	Kaplan Meier Estimate of Time to First Response (TTFR) According to the IRC Central Review

End point description:

Time to Response was defined as the time from first dose of study drug to the date of the first response (having at least a PR) and was calculated only for responding participants). Participants with progression at the time of analysis were censored at the first assessment date that the participant was known to have progressed. Participants with SD at the time of analysis were censored at the last assessment date that the participant was known to be progression-free. ITT population includes all randomized participants.

End point type	Secondary

End point timeframe:

From randomization of study drug to time of first documented PR or better response; up to data cut-off date of 07 March 2014; median treatment duration was 24.3 weeks for the lenalidomide arm and 13.1 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84[3]		
Units: Weeks				
median (confidence interval 95%)	18.7 (16.7 to 49.7)	99999 (63.9 to 99999)		

Notes:

[3] - 99999 = Not estimable due to the low number of participants with a response.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	3.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.95
upper limit	7.85

Secondary: Kaplan Meier Estimate of Time to First Response as Assessed by the Investigator at the Final Analysis

End point title	Kaplan Meier Estimate of Time to First Response as Assessed by the Investigator at the Final Analysis

End point description:

Time to first response was defined as the time from first dose of study drug to the date of the first response (having at least a PR). Participants with progression at the time of analysis were censored at the first assessment date that the participant was known to have progressed. Participants with SD at the time of analysis were censored at the last assessment date that the subject was known to be progression-free. ITT population includes all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the study discontinuation date of 09 October 2018; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84[4]		
Units: Weeks				
median (confidence interval 95%)	23.9 (16.7 to 25.6)	40.0 (25.6 to 99999)		

Notes:

[4] - 99999 = Not estimable due to the low number of participants with a response.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.004
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.24
upper limit	3.42

Secondary: Kaplan Meier Estimate for Overall Survival (OS) According to the IRC Central Review

End point title	Kaplan Meier Estimate for Overall Survival (OS) According to the IRC Central Review

End point description:

Overall survival was defined as the time from randomization until death from any cause. Participants alive or lost to follow-up at the time of analysis were censored at the last date they were known to be alive. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

From date of randomization to the data cut-off date of 07 March 2014; overall median follow-up was 93.9 weeks

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: weeks				
median (confidence interval 95%)	121.0 (86.7 to 160.4)	91.7 (69.4 to 125.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.519
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.28

Secondary: Kaplan Meier Estimate for Overall Survival as Assessed by the Investigator at the Final Analysis

End point title	Kaplan Meier Estimate for Overall Survival as Assessed by the Investigator at the Final Analysis

End point description:

Overall survival was defined as the time from randomization until death from any cause. Participants alive or lost to follow-up at the time of analysis were censored at the last date they were known to be alive. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

From randomization to progression of disease or death; up to the study discontinuation date of 09 October 2018; overall median follow-up time was 285 weeks

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	84		
Units: weeks				
median (confidence interval 95%)	120.6 (98.1 to 153.0)	91.7 (69.4 to 137.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigators Choice
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.558
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.25

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

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

End point description:

Adverse events were assessed using National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3: according to the following scale: Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe and Undesirable, Grade 4 = Life-threatening or Disabling, and Grade 5 = Death; Serious AEs (SAEs) are those that resulted in death, were life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, congenital anomaly, or resulted in an important medical event that may have jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed above. after the first dose of study drug and within 28 days after the last dose. A TEAE = any AE occurring or worsening on or after the first dose of study drug and within 28 days after the last dose. The safety population included those who received at least one dose of study drug (either LEN or investigator's choice).

End point type	Secondary

End point timeframe:

From the date of the first dose of study drug to 28 days after the last dose, up to the study discontinuation date of 09 October 2018; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigators choice arm

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	83		
Units: Participants				
Any TEAE	159	69		
Any TEAE Grade 3 AE	126	49		
Any TEAE Grade 4 AE	56	29		
Any TEAE Grade 5 AE	15	2		
Any TEAE Related to the IP	141	51		
Any Grade 3 AE Related to IP	106	36		
Any Grade 4 AE Related to IP	46	19		
Any Grade 5 AE Related to IP	0	0		
Any Serious Adverse Event (SAE)	75	22		
Any SAE Related to IP	38	12		
Any TEAE Leading to Stopping of IP	31	14		
Any Treatment Related AE Leading to Stopping IP	18	7		
TEAE Leading to Dose Reduction/Interruption	114	33		
Related AE Leading to Dose Reduct/Interruption	103	29		
TEAE Leading to Dose Reduction	72	13		
Related AE Leading to Dose Reduction	69	10		
TEAE Leading to Dose Interruption	110	28		
Related AE Leading to Dose Interruption	98	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Physical Functioning Scale ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline (BL) known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation (D/C); median IP duration = 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline	71.8 (± 22.35)	78.9 (± 17.38)		
Change from BL to Cycle 3 Day 1; N = 104, 43	-0.5 (± 15.47)	-3.7 (± 16.22)		
Change from BL to Cycle 5 Day 1; N = 70, 26	1.6 (± 15.18)	-2.1 (± 19.02)		
Change from BL to Cycle 7 Day 1; N = 56, 8	2.4 (± 16.74)	4.2 (± 16.69)		
Change from BL to Cycle 9 Day 1; N = 46, 6	2.8 (± 18.08)	11.1 (± 11.67)		
Change from BL to IP Discontinuation; N = 62, 43	-5.6 (± 19.46)	-5.1 (± 17.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Physical Functioning Scale ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had

evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	57		
Units: units on a scale				
arithmetic mean (standard deviation)	3.4 (± 18.70)	-1.8 (± 17.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Role Functioning Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Role Functioning Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Role Functioning Scale ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	71.5 (± 31.10)	73.9 (± 25.60)		
Change from BL to Cycle 3 Day 1; N = 105, 43	-4.8 (± 26.12)	3.5 (± 21.69)		
Change from BL to Cycle 5 Day 1; N = 71, 26	1.4 (± 26.09)	-6.4 (± 30.21)		

Change from BL to Cycle 7 Day 1; N = 57, 8	0.3 (± 26.44)	0.0 (± 38.83)		
Change from BL to Cycle 9 Day 1; N = 47, 6	1.8 (± 26.75)	13.9 (± 19.48)		
Change from BL to IP Discontinuation; N =62, 43	-9.1 (± 29.05)	-4.3 (± 31.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Role Functioning Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Role Functioning Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Role Functioning Scale ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	3.1 (± 28.43)	5.0 (± 27.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Cognitive Functioning Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Cognitive Functioning Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-

C30 Cognitive Functioning Domain ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Hide Analysis Population Description
Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	84.6 (± 19.86)	83.6 (± 20.18)		
Change from BL to Cycle 3 Day 1; N = 105, 43	0.0 (± 16.34)	-2.3 (± 13.89)		
Change from BL to Cycle 5 Day 1; N = 71, 26	-1.9 (± 17.72)	1.3 (± 14.85)		
Change from BL to Cycle 7 Day 1; N = 57, 8	-3.2 (± 19.27)	4.2 (± 14.77)		
Change from BL to Cycle 9 Day 1; N = 47, 6	-2.5 (± 18.05)	5.6 (± 13.61)		
Change from BL to IP Discontinuation; N=62, 43	-5.1 (± 19.46)	-2.3 (± 15.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Cognitive Functioning Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Cognitive Functioning Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Cognitive Functioning Scale ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Hide Analysis Population Description
Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	3.2 (± 17.92)	2.9 (± 14.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Social Functioning Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Social Functioning Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Social Functioning Domain ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	74.9 (± 28.39)	78.4 (± 26.85)		
Change from BL to Cycle 3 Day 1; N = 105, 43	-1.0 (± 20.39)	-1.2 (± 22.54)		
Change from BL to Cycle 5 Day 1; N = 71, 26	1.6 (± 19.75)	-4.5 (± 29.27)		
Change from Baseline to Cycle 7 Day 1; N = 57, 8	-1.5 (± 25.06)	2.1 (± 28.78)		
Change from BL to Cycle 9 Day 1; N = 47, 6	4.3 (± 22.11)	0.0 (± 23.57)		
Change from BL to IP Discontinuation; N=62, 43	-5.1 (± 24.63)	-2.7 (± 20.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Social Functioning Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Social Functioning Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Social Functioning Scale ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)	5.1 (± 20.87)	3.8 (± 19.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Fatigue Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Fatigue Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Fatigue Domain was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	40.2 (± 26.67)	39.2 (± 23.50)		
Change from BL to Cycle 3 Day 1; N = 105, 43	0.1 (± 21.72)	2.1 (± 22.12)		
Change from BL to Cycle 5 Day 1; N = 71, 26	-3.2 (± 20.84)	3.4 (± 25.68)		
Change from BL to Cycle 7 Day 1; N = 57, 8	-1.0 (± 21.03)	-6.9 (± 25.85)		
Change from BL to Cycle 9 Day 1; N = 47, 6	-3.9 (± 26.64)	-7.4 (± 25.01)		
Change from BL to IP Discontinuation; N =62,43	5.2 (± 21.48)	2.6 (± 24.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Fatigue Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Fatigue Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Fatigue Scale was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-4.9 (± 22.76)	-2.9 (± 23.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Pain Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Pain Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Pain Domain was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	22.6 (± 25.86)	13.7 (± 20.15)		
Change from BL to Cycle 3 Day 1; N = 104, 43	-2.2 (± 19.99)	-1.2 (± 25.30)		
Change from BL to Cycle 5 Day 1; N = 70, 26	-0.2 (± 24.82)	-2.6 (± 20.38)		
Change from BL to Cycle 7 Day 1; N = 57, 8	3.2 (± 26.99)	0.0 (± 19.92)		
Change from BL to Cycle 9 Day 1; N = 47, 6	-3.2 (± 25.92)	-2.8 (± 6.80)		
Change from BL to IP Discontinuation; N=61,43	4.6 (± 26.38)	3.5 (± 22.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Pain Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Pain Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Pain Scale was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and time of discontinuation from treatment visit.Up to final data cut-0ff date of 07 March 2014

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-5.8 (± 24.61)	-3.5 (± 21.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Nausea / Vomiting Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Nausea / Vomiting Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Nausea and Vomiting Domain was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	4.9 (± 10.31)	3.8 (± 11.22)		
Change from BL to Cycle 3 Day 1; N = 105, 43	2.5 (± 14.39)	0.4 (± 10.60)		
Change from BL to Cycle 5 Day 1; N = 71, 26	2.6 (± 11.83)	5.8 (± 21.57)		
Change from BL to Cycle 7 Day 1; N = 57, 8	5.3 (± 17.30)	2.1 (± 22.60)		
Change from BL to Cycle 9 Day 1; N = 47, 6	-0.7 (± 10.40)	2.8 (± 6.80)		
Change from BL to IP Discontinuation; N =62, 43	0.5 (± 9.99)	6.6 (± 18.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Nausea and Vomiting Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Nausea and Vomiting Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Nausea and Vomiting Scale was scored between 0 and 100, with a high score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-2.3 (± 8.82)	-0.6 (± 8.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Constipation

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Constipation

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Constipation Domain was scored between 0 and 100, with a high score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	12.5 (± 23.27)	8.6 (± 19.16)		
Change from BL to Cycle 3 Day 1; N = 105, 43	6.3 (± 27.38)	-0.8 (± 18.53)		
Change from BL to Cycle 5 Day 1; N = 71, 26	4.2 (± 25.78)	1.3 (± 17.59)		
Change from BL to Cycle 7 Day 1; N = 57, 8	3.5 (± 27.95)	0.0 (± 30.86)		
Change from BL to Cycle 9 Day 1; 47, 6	-0.7 (± 20.25)	0.0 (± 21.08)		
Change from BL to IP Discontinuation; N=62, 43	10.2 (± 32.27)	0.8 (± 21.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Constipation Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Constipation Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Constipation Scale was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.3 (± 27.60)	-3.5 (± 16.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Diarhoea

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Diarhoea

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Diarhoea Domain was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	15.7 (± 27.15)	12.6 (± 20.42)		
Change from BL to Cycle 3 Day 1; N = 105, 43	-3.5 (± 25.71)	-3.1 (± 21.60)		
Change from BL to Cycle 5 Day 1; N = 71, 26	-4.2 (± 29.78)	1.3 (± 22.07)		
Change from BL to Cycle 7 Day 1; N = 55, 8	2.4 (± 32.62)	-4.2 (± 33.03)		
Change from BL to Cycle 9 Day 1; 47, 6	-2.1 (± 22.42)	0.0 (± 36.51)		

Change from BL to IP Discontinuation; N=62, 43	1.6 (± 30.44)	0.0 (± 25.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Diarhoea Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Diarhoea Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Diarhoea Scale was scored between 0 and 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and time of discontinuation from treatment visit.Up to final data cut-0ff date of 07 March 2014

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
least squares mean (standard deviation)	-7.2 (± 25.25)	-5.8 (± 21.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Insomnia Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Insomnia Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Insomnia Domain was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	29.4 (± 30.69)	25.7 (± 27.34)		
Change from BL to Cycle 3 Day 1; N = 105, 43	-7.6 (± 27.06)	-4.7 (± 31.36)		
Change from BL to Cycle 5 Day 1; N = 71, 26	-5.2 (± 24.97)	-6.4 (± 32.69)		
Change from BL to Cycle 7 Day 1; N = 57, 8	-1.8 (± 29.83)	-16.7 (± 39.84)		
Change from BL to Cycle 9 Day 1; N = 47, 6	-7.1 (± 30.25)	-16.7 (± 40.82)		
Change from BL to IP Discontinuation; N=62, 43	-3.2 (± 28.76)	0.8 (± 22.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Insomnia Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Insomnia Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Dyspnoea Domain was scored between 0 and 100, with a high score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-12.8 (± 28.64)	-7.6 (± 30.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Dyspnoea Domain to Treatment Discontinuation Visit

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Dyspnoea Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Dyspnoea Domain was scored between 0 and 100, with a high score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	26.5 (± 28.98)	21.2 (± 28.97)		
Change from BL to Cycle 3 Day 1; N = 103, 43	-1.6 (± 27.76)	-0.8 (± 29.54)		
Change from BL to Cycle 5 Day 1; N = 70, 26	-1.4 (± 26.88)	0.0 (± 33.99)		
Change from BL to Cycle 7 Day 1; N = 57, 8	-2.9 (± 25.42)	4.2 (± 48.59)		
Change from BL to Cycle 9 Day 1; N = 47, 6	1.4 (± 31.05)	5.6 (± 25.09)		
Change from BL to IP Discontinuation; N=61, 43	6.0 (± 28.22)	0.8 (± 23.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Dyspnoea Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Dyspnoea Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Dyspnoea Domain to Treatment Scale was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-7.3 (± 25.70)	-5.8 (± 27.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Appetite Loss Domain to Treatment Discontinuation Visit

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Appetite Loss Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Appetite Loss Domain was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	18.1 (± 27.69)	16.2 (± 26.02)		
Change from BL to Cycle 3 Day 1; N = 105, 43	2.5 (± 31.25)	-0.8 (± 34.49)		
Change from BL to Cycle 5 Day 1; N = 71, 26	1.9 (± 28.67)	5.1 (± 43.91)		
Change from BL to Cycle 7 Day 1; N = 57, 8	-2.3 (± 23.45)	-12.5 (± 46.93)		
Change from BL to Cycle 9 Day 1; N = 47, 6	-4.3 (± 27.47)	-11.1 (± 27.22)		
Change from BL to IP Discontinuation; N =62, 43	4.8 (± 32.42)	5.4 (± 27.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Appetite Loss Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Appetite Loss Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Appetite Loss Domain to Treatment Scale was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-4.8 (± 28.30)	-4.1 (± 29.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Financial Problems Domain to Treatment Discontinuation Visit

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Financial Problems Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Financial Problems Domain was scored between 0 and 100, with a higher score representing worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	19.5 (± 27.78)	10.8 (± 19.98)		
Change from BL to Cycle 3 Day 1; N = 105, 43	-7.0 (± 25.61)	-0.8 (± 18.53)		
Change from BL to Cycle 5 Day 1; N = 71, 26	-7.0 (± 27.55)	-3.8 (± 23.71)		
Change from BL to Cycle 7 Day 1; N = 57, 8	-2.9 (± 33.50)	-4.2 (± 11.79)		
Change from BL to Cycle 9 Day 1; N = 47, 6	-9.2 (± 31.62)	-5.6 (± 13.61)		
Change from BL to IP Discontinuation; N =62, 43	-4.3 (± 22.97)	1.6 (± 19.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Financial Problems Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Financial Problems Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Financial Problems Domain Scale was scored between 0 and 100, with a higher score representing

worse symptomatic expression. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)	-10.9 (± 25.32)	-2.3 (± 19.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Global Health Status / QoL Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Global Health Status / QoL Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Global Health Status / QoL Domain was scored between 0 and 100, with a higher score representing a higher quality of life. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	59.0 (± 21.45)	58.4 (± 18.58)		
Change from BL to Cycle 3 Day 1; N = 105, 43	-3.4 (± 21.89)	2.3 (± 18.66)		
Change from BL to Cycle 5 Day 1; N = 71, 26	-0.7 (± 19.96)	3.2 (± 24.50)		

Change from BL to Cycle 7 Day 1; N = 57, 8	1.0 (± 17.04)	7.3 (± 29.36)		
Change from BL to Cycle 9 Day 1; N = 47, 6	4.3 (± 21.76)	8.3 (± 22.97)		
Change from BL to IP Discontinuation;N = 62, 43	-5.8 (± 18.76)	-1.0 (± 19.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Global Health Status / QoL Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Global Health Status / QoL Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Global Health Status / QoL Domain to Treatment Scale was scored between 0 and 100, with a higher score representing a higher quality of life. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	4.6 (± 19.06)	5.6 (± 20.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-

C30 Emotional Domain ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161	74		
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (BL)	73.7 (± 21.52)	78.5 (± 18.56)		
Change from BL to Cycle 3 Day 1; N = 105, 43	3.4 (± 19.64)	1.3 (± 20.77)		
Change from BL to Cycle 5 Day 1; N = 71, 26	3.6 (± 17.01)	1.3 (± 16.11)		
Change from BL to Cycle 7 Day 1; N = 57, 8	8.1 (± 20.53)	-3.1 (± 26.33)		
Change from BL to Cycle 9 Day 1; N = 47, 6	4.5 (± 21.96)	1.4 (± 13.35)		
Change from BL to IP Discontinuation; N =62, 43	-1.3 (± 22.05)	-1.5 (± 16.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain to Treatment Discontinuation Visit

End point title	Maximum Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain to Treatment Discontinuation Visit

End point description:

The EORTC-QLQ-C30 is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Emotional Functioning Scale ranges from 0 to 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Health Related Quality of Life (QoL) Evaluable Population includes participants who had evaluable QoL assessments.

End point type	Secondary

End point timeframe:

Baseline known as screening visit, after cycle 2 (C3D1), after Cycle 4 (C5D1), after Cycle 6, (C7D1), after Cycle 8, (C9D1) and at discontinuation; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigator choice arm.

End point values	Lenalidomide	Investigators Choice		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	74		
Units: units on a scale				
arithmetic mean (standard deviation)	6.9 (± 21.79)	3.7 (± 17.11)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization of study drug to 30 days post-last dose; up to the study discontinuation date of 09 October 2018; median treatment duration was 24.3 weeks for lenalidomide and 13.1 weeks for the investigators choice arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Investigators Choice

Reporting group description:

Participants received a single agent investigators choice of chlorambucil 40 mg/m^2 PO every 28 days until progressive disease or toxicity, OR rituximab 375 mg/m^2 by intravenous infusion on days 1, 8, 15 and 22 of each 56-day treatment cycle until PD or toxicity, OR cytarabine 1-2 g/m^2 by IV infusion on days 1 and 2 of each 28 day treatment cycle; up to 6 cycles, OR gemcitabine 1000 mg/m^2 by IV infusion on days 1, 8 and 15 of each 28 day treatment cycle; up to 6 cycles OR oral fludarabine 40 mg/m^2 or IV fludarabine 25 mg/m^2 on days 1 through 5 of each 28-day cycle; up to 6 cycles. Participants were given the option to enter into the lenalidomide crossover phase if PD occurred and received lenalidomide 25 mg capsules daily on days 1 to 21 of each 28 day treatment cycle until PD or toxicity.

Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide 25 mg capsules orally every day for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity. Participants with moderate renal insufficiency (creatinine clearance is ≥ 30 mL/min but < 60mL/min received 10 mg lenalidomide for 21 days of each 28-day cycle (Cycles 1 and 2). After Cycle 2, if the participant remained free of Grade 3 or Grade 4 toxicity, the dose was increased to 15 mg lenalidomide for 21 days of each 28-day treatment cycle until disease progression or unacceptable toxicity.

Serious adverse events	Investigators Choice	Lenalidomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 83 (26.51%)	75 / 167 (44.91%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	0 / 83 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
BASAL CELL CARCINOMA			

subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANCER PAIN			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
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	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIPOSARCOMA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MANTLE CELL LYMPHOMA			
subjects affected / exposed	3 / 83 (3.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MENINGIOMA BENIGN			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO LUNG			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			

subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR FLARE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HAEMORRHAGE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
DEATH			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
FATIGUE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 83 (1.20%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	2 / 83 (2.41%)	5 / 167 (2.99%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
OEDEMA GENITAL			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UTERINE POLYP			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ASPIRATION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS CHRONIC			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 83 (1.20%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGEAL INFLAMMATION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURISY			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 83 (0.00%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY DISTRESS			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOCAL CORD DISORDER			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
CARDIAC FAILURE			
subjects affected / exposed	1 / 83 (1.20%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIAC FAILURE ACUTE			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEFT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIANOPIA HETERONYMOUS			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 83 (2.41%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	2 / 3	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
AUTOIMMUNE HAEMOLYTIC ANAEMIA			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	2 / 83 (2.41%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	2 / 2	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPH NODE PAIN			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			

subjects affected / exposed	0 / 83 (0.00%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	2 / 83 (2.41%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
DEAFNESS BILATERAL			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTIGO			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
RETINAL ARTERY OCCLUSION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL WALL HAEMATOMA			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 83 (0.00%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE PERFORATION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERBILIRUBINAEMIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ANURIA			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC KIDNEY DISEASE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS HAEMORRHAGIC			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OLIGURIA			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
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			
ARTHRITIS			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ARTHRITIS INFECTIVE			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPERGILLUS INFECTION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	1 / 83 (1.20%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CELLULITIS			
subjects affected / exposed	1 / 83 (1.20%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 83 (1.20%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS VIRAL			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
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 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
PNEUMONIA			
subjects affected / exposed	3 / 83 (3.61%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	5 / 5	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA MORAXELLA			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMEMBRANOUS COLITIS			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
SINUSITIS			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN INFECTION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 83 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			

subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
DEHYDRATION			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 83 (1.20%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKALAEMIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPROTEINAEMIA			
subjects affected / exposed	0 / 83 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Investigators Choice	Lenalidomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 83 (73.49%)	146 / 167 (87.43%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR FLARE			
subjects affected / exposed	0 / 83 (0.00%)	15 / 167 (8.98%)	
occurrences (all)	0	17	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	7 / 83 (8.43%)	15 / 167 (8.98%)	
occurrences (all)	12	18	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	11 / 83 (13.25%)	26 / 167 (15.57%)	
occurrences (all)	16	43	
FATIGUE			
subjects affected / exposed	4 / 83 (4.82%)	34 / 167 (20.36%)	
occurrences (all)	5	45	
OEDEMA PERIPHERAL			
subjects affected / exposed	9 / 83 (10.84%)	16 / 167 (9.58%)	
occurrences (all)	10	19	
PYREXIA			
subjects affected / exposed	9 / 83 (10.84%)	26 / 167 (15.57%)	
occurrences (all)	11	44	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	4 / 83 (4.82%)	20 / 167 (11.98%)	
occurrences (all)	5	29	
DYSPNOEA			
subjects affected / exposed	6 / 83 (7.23%)	10 / 167 (5.99%)	
occurrences (all)	7	13	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	1 / 83 (1.20%)	9 / 167 (5.39%)	
occurrences (all)	1	17	
Investigations			

ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	5 / 83 (6.02%)	8 / 167 (4.79%)	
occurrences (all)	8	12	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	0 / 83 (0.00%)	14 / 167 (8.38%)	
occurrences (all)	0	23	
PARAESTHESIA			
subjects affected / exposed	1 / 83 (1.20%)	10 / 167 (5.99%)	
occurrences (all)	1	10	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	18 / 83 (21.69%)	45 / 167 (26.95%)	
occurrences (all)	41	87	
LEUKOPENIA			
subjects affected / exposed	18 / 83 (21.69%)	29 / 167 (17.37%)	
occurrences (all)	57	102	
LYMPHOPENIA			
subjects affected / exposed	6 / 83 (7.23%)	8 / 167 (4.79%)	
occurrences (all)	26	19	
NEUTROPENIA			
subjects affected / exposed	29 / 83 (34.94%)	86 / 167 (51.50%)	
occurrences (all)	87	446	
THROMBOCYTOPENIA			
subjects affected / exposed	33 / 83 (39.76%)	63 / 167 (37.72%)	
occurrences (all)	94	194	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 83 (0.00%)	9 / 167 (5.39%)	
occurrences (all)	0	12	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	4 / 83 (4.82%)	16 / 167 (9.58%)	
occurrences (all)	5	23	
ABDOMINAL PAIN UPPER			

subjects affected / exposed	6 / 83 (7.23%)	7 / 167 (4.19%)	
occurrences (all)	6	8	
CONSTIPATION			
subjects affected / exposed	5 / 83 (6.02%)	29 / 167 (17.37%)	
occurrences (all)	7	43	
DIARRHOEA			
subjects affected / exposed	8 / 83 (9.64%)	36 / 167 (21.56%)	
occurrences (all)	10	104	
DYSPEPSIA			
subjects affected / exposed	3 / 83 (3.61%)	9 / 167 (5.39%)	
occurrences (all)	3	10	
NAUSEA			
subjects affected / exposed	13 / 83 (15.66%)	17 / 167 (10.18%)	
occurrences (all)	19	26	
VOMITING			
subjects affected / exposed	9 / 83 (10.84%)	8 / 167 (4.79%)	
occurrences (all)	9	11	
Skin and subcutaneous tissue disorders			
DERMATITIS ALLERGIC			
subjects affected / exposed	2 / 83 (2.41%)	9 / 167 (5.39%)	
occurrences (all)	2	15	
PRURITUS			
subjects affected / exposed	3 / 83 (3.61%)	15 / 167 (8.98%)	
occurrences (all)	3	21	
RASH			
subjects affected / exposed	3 / 83 (3.61%)	19 / 167 (11.38%)	
occurrences (all)	3	31	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 83 (2.41%)	12 / 167 (7.19%)	
occurrences (all)	2	14	
BACK PAIN			
subjects affected / exposed	0 / 83 (0.00%)	16 / 167 (9.58%)	
occurrences (all)	0	26	
MUSCLE SPASMS			

subjects affected / exposed	3 / 83 (3.61%)	13 / 167 (7.78%)	
occurrences (all)	4	16	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 83 (0.00%)	13 / 167 (7.78%)	
occurrences (all)	0	21	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	8 / 83 (9.64%)	15 / 167 (8.98%)	
occurrences (all)	11	22	
CONJUNCTIVITIS			
subjects affected / exposed	0 / 83 (0.00%)	9 / 167 (5.39%)	
occurrences (all)	0	11	
INFLUENZA			
subjects affected / exposed	1 / 83 (1.20%)	9 / 167 (5.39%)	
occurrences (all)	3	10	
NASOPHARYNGITIS			
subjects affected / exposed	5 / 83 (6.02%)	25 / 167 (14.97%)	
occurrences (all)	5	39	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 83 (0.00%)	10 / 167 (5.99%)	
occurrences (all)	0	20	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 83 (6.02%)	23 / 167 (13.77%)	
occurrences (all)	11	51	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	3 / 83 (3.61%)	22 / 167 (13.17%)	
occurrences (all)	4	31	
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 83 (1.20%)	9 / 167 (5.39%)	
occurrences (all)	1	11	
HYPOKALAEMIA			
subjects affected / exposed	1 / 83 (1.20%)	15 / 167 (8.98%)	
occurrences (all)	1	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2009	Eligibility criteria were updated. The exclusion criteria for corticosteroids, allowed for subjects to have prednisone ≤ 10 mg/day for purposes other than MCL. Expanded enrollment to those who received prior radiotherapy or experimental IP. Confirmation of MCL diagnosis by Central Pathology (CP) not required. Updated the timeline/tumor biopsy required for CP to confirm MCL at screening and for other assessments. Analysis of t(11;14)(q13;q32) translocation by FISH was optional. Bone marrow (BM) biopsy at screening was recommended to: 1)confirm diagnosis 2)confirm or rule out MCL BM infiltration 3)justify thrombocytopenia in screened subjects 4)gain additional tissue for the biomarker substudy. Changed the time between randomization and IP initiation to 4 days. Added 2 pregnancy tests for FCBP before starting IP. Updated dose modification for thromboembolic prophylaxis. Provided guidance on medical management of TLS for those developing LTLS or Grade ≥ 1 TLS. Updated dose modification rules for Len; included dose adjustments for neurological and liver toxicities. Limited prophylaxis for thromboembolism only to Len-treated subjects at high risk. Updated response criteria: BM required for confirmation of CR; marrow not needed. Revised treatment cycle duration. Limited the maximum duration between the Control Arm for those initiating crossover IP and subsequent Len to 10 weeks. Updated use of growth factors for severe hematologic events. Rituxan treated subjects could receive corticosteroids for prevention of cytokine release syndrome. Added QoL time points. Exploratory objectives regarding correlative biology investigation were updated; included investigation of potential predictive and PD parameter by analysis of biomarkers in archival and collected biopsy samples from tumor, blood & plasma. The 28 days wash out period required for blood, semen or sperm donation was added. Coagulation and chloride tests were deleted.
14 December 2009	The primary objective was changed from determine the ORR to compare the PFS, since PFS was a clinically relevant efficacy endpoint and acceptable endpoint for a registration trial. The ORR was defined as a secondary objective. Study design, study endpoints, analysis methods, interim analysis, sample size, and power considerations were updated. Sample size calculation was revised. Statistical test for the secondary endpoints was added to reflect the change in the nature of the study. Futility analyses were to be conducted by the DMC when approximately 80 subjects completed 2 cycles or withdrew before having 2 cycles. Eligibility criteria update: The limitation to the number of prior treatment lines was changed to number of prior relapses and was no longer limited to chemotherapy. DVT prophylaxis was no longer required for those at risk. The criterion was updated to match the Section Treatment Assignments, Thromboembolism, of the Study Protocol. A mandatory 7-day wash-out period was required for prior corticosteroid use. The upper limit of abnormal liver values were updated:the planned modification of len doses in case of toxicity. Enrollment was allowed with AST/SGOT or ALT/SGPT ≥ 3.0 x ULN (unless documented liver involvement by lymphoma). Total bilirubin > 1.5 mg/dL (except in case of Gilbert's syndrome and documented liver involvement by lymphoma) was required instead of the previous limit > 1.5 x mg/dL bilirubin (except in case of hemolytic anemia). Explorative objectives were focused on blood samples and archival/re-biopsy tumor specimens. The serial fresh lymph nodes biopsies were deleted. Clarification: participation in the biomarker substudy was optional and the sampling pertained to those who provided additional consent. Clarification: the preferred imaging method was CT, and MRI was to be used if CT was contraindicated. The guidance for toxicity management was updated to clarify: recommendations for TFR and TLS were mainly for those receiving len.

29 April 2011	Added SPMs and were regarded as SAEs and reported throughout the study, including from the time of signing the ICF through follow-up for OS. Changes to the planned protocol analysis of SPMs are in Section 9.8.2.2. A study duration item, "4 years from last subject randomized", was added to the end-of-study definition. Requirements for consent withdrawal from treatment, efficacy, and survival follow-up and allowing collection of follow-up data until study closure were clarified. A full consent withdrawal had to be documented to disallow survival follow-up. Statistical analysis was updated to include the stratified log-rank test for the main comparison, changed unstratified log-rank test to be used as supportive analysis, and added the statement that any demographic or baseline characteristics variables considered as strong predictive or prognostic factors were included as part of the SAP. The interim analysis section was updated to include the option of providing the DMC with additional data upon request. Updated the dose modification requirements as follows: specified that for len, a minimum 7-day rest period was mandatory before starting a new treatment cycle; this period had to be adhered to regardless of allowed visit windows. Updated the dose modifications and interruptions for len to include "Action required" for any other len-related AE not requiring IP discontinuation. Updated the dose reductions for len to replace the 10-mg every-other-day dose level with 5-mg every-day-dose. Changes to the planned protocol analysis of SPMs were in Section 9.8.2.2. A study duration item, "4 years from last subject randomized", was added to the end-of-study definition. Requirements for consent withdrawal from treatment, efficacy, and survival follow-up was added allowing collection of follow-up data until study closure were clarified. For subjects in the Follow-up Phase who withdrew consent for efficacy (disease progression), the follow-up continued for survival.
27 September 2011	Based on the recommendation from the third DMC held on 22 Jul 2011, the following changes were implemented: sample size was increased from 167 to 250 subjects. The sample size increase was implemented to allow a reliable estimation of potential PFS differences between the study arms. According to the DMC, the outcome observed in the Control Arm of the study was different from the initial assumptions used to calculate the sample size. The primary efficacy analysis was set 1 year after the last subject was randomized. Efficacy subgroup analyses were added to investigate the treatment effect in different subgroups or subpopulation in an exploratory manner. The changes in statistical analyses are detailed in Section 9.8.2.2. The MIPI score at baseline was added to the list of treatment and clinical characteristics. The change was implemented because the DMC had observed an imbalance in terms of risk factors between the arms, which was not mitigated by the stratification factors and, thus, recommended to include the MIPI at baseline in the stratified test (Section 9.8.2.2). Exploratory analyses were planned on the AT Population for the following endpoints: PFS, ORR, and OS. Added a fourth safety analysis after 200 subjects completed 2 cycles or withdrew before completing 2 cycles. The addition was implemented to ensure safety monitoring according to the sample size increase to 250 subjects. Added a fourth EORTC QoL compliance assessment after 200 subjects completed 2 cycles or withdrew before completing 2 cycles. This addition was implemented to ensure ongoing monitoring of EORTC QoL compliance according to the sample size increase to 250 subjects. Extended the duration of prior malignancy-free history required for enrollment (from ≥ 3 to ≥ 5 years). This modification was implemented as requested by Health Authorities to reduce the risk of SPM in subjects treated with lenalidomide. Discontinued further biomarker analysis on blood and plasma samples in the study.
22 March 2013	Thromboembolic prophylaxis had to be given to all subjects treated with lenalidomide regardless of prior thromboembolic history, instead of only to subjects at high risk of TEs. This modification was implemented following a DMC recommendation for mandatory prophylaxis of study subjects on lenalidomide because the DMC had observed an increase in TEs in the Lenalidomide Arm compared to the Control Arm and because a number of the subjects with TEs were not receiving anti-thromboembolic prophylaxis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported