Clinical trial results:
A Phase 2/3 Multicenter, Randomized Open-Label Study to Compare the Efficacy and Safety of Lenalidomide (Revlimid®) Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma

Summary

EudraCT number	2009-013483-38
Trial protocol	SE CZ AT GB ES IT FR
Global end of trial date	05 April 2018

Results information

Result version number	v1 (current)
This version publication date	21 April 2019
First version publication date	21 April 2019

Trial information

Trial identification

Sponsor protocol code	CC-5013-DLC-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01197560
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	Adrian Kilcoyne, MD, Celgene Corporation, 01 908-739-5549, AKilcoyne@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 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Stage 1: To select adequate (e.g., p-value <0.15 in favor of lenalidomide) subtype(s) for Stage 2. Germinal center B-cell (GCB), non-GCB, both subtypes, or neither subtype will be selected based on the overall response rate (ORR) in the individual subtype to lenalidomide monotherapy versus single agent of Investigator's choice. Stage 2: To compare the progression free survival (PFS) of lenalidomide monotherapy versus single agent of Investigator's choice in the subtype(s) selected in Stage 1.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection, Archiving of Essential Documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 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	United States: 26
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	111
EEA total number of subjects	75

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)	45
From 65 to 84 years	65
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Screening and enrollment occurred at 43 sites, including 11 in the United States, 9 in France, 8 in the United Kingdom; 5 in Spain, 4 in Italy, 3 each in Austria and Australia, 2 in the Czech Republic, and 1 in Sweden.

Pre-assignment

Screening details:

Participants were stratified into germinal center B-cell (GCB) or non-GCB subtypes and randomized 1:1 to receive lenalidomide or investigator's choice treatment (one of the single-agent reference therapies [gemcitabine, rituximab, etoposide, or oxaliplatin).

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 25 mg orally once daily for 21 days in each 28-day cycle until progressive disease. For participants with creatinine clearance ≥ 30 mL/min but < 60 mL/min, lenalidomide 10 mg once daily for 21 days for 2 cycles. After Cycle 2 the dose may have been increased to a maximum of 15 mg lenalidomide once daily for 21 days in each 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or voluntary withdrawal.

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 orally once daily for 21 days in each 28-day cycle until progressive disease. For participants with creatinine clearance ≥ 30 mL/min but < 60 mL/min, lenalidomide 10 mg once daily for 21 days for 2 cycles. After Cycle 2 the dose may have been increased to a maximum of 15 mg lenalidomide once daily for 21 days in each 28-day cycle.

Arm title	Investigators Choice (Control Arm)

Arm description:

Participants received a single agent reference therapy (either gemcitabine, oxaliplatin, rituximab or etoposide) based on published data for up to 6 cycles or until disease progression, unacceptable toxicity or withdrawal. Participants with documented progressive disease had the option to receive crossover lenalidomide at the same dosage as participants randomized to lenalidomide.

Arm type	Active comparator
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 1250 mg/m^2 intravenous (IV) days 1, 8, 15 every 28 days for 6 Cycles or 1,000 mg/m^2 IV days 1 and 15 in each 28- day cycle for 6 Cycles

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

Dosage and administration details:

Oxaliplatin 100 mg/m^2 IV day 1 in each 21-day cycle for 6 Cycles

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

Dosage and administration details:

Rituximab 375 mg/m^2 IV days 1, 8, 15, 22 during Cycle 1, and if stable disease at Week 12, also on Day 1 of Cycles 4, 6, 8, and 10 (CD20+ patients only)

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	VP-16
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Etoposide doses:
100 mg/m^2 IV days 1-5 in each 28-day cycle for 6 Cycles, or 100 mg/m^2 IV days 1-3 in each 28-day cycle for 6 Cycles, or 50 mg/m^2 oral days 1-21 in each 28-day cycle for 6 Cycles, or 50 mg/m^2 oral days 1-14 in each 28-day cycle for 6 Cycles, or 50 mg/m^2 oral days 1-10 in each 28-day cycle for 6 Cycles

Number of subjects in period 1	Lenalidomide	Investigators Choice (Control Arm)
Started	54	57
Received ≥ one dose study drug	54	55
Lenalidomide Crossover	0	29
Discontinued treatment after ≥ 6 cycles	14	0 [1]
Completed	0	4
Not completed	54	53
Adverse event, serious fatal	3	5
Consent withdrawn by subject	1	1
Disease progression	40	35
Adverse event, non-fatal	6	8
Miscellaneous	4	3
Missing	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Some subjects elected to stop treatment early and did not complete the entire study.

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide
Reporting group description:	
Participants received lenalidomide 25 mg orally once daily for 21 days in each 28-day cycle until progressive disease. For participants with creatinine clearance ≥ 30 mL/min but < 60 mL/min, lenalidomide 10 mg once daily for 21 days for 2 cycles. After Cycle 2 the dose may have been increased to a maximum of 15 mg lenalidomide once daily for 21 days in each 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or voluntary withdrawal.	
Reporting group title	Investigators Choice (Control Arm)
Reporting group description:	
Participants received a single agent reference therapy (either gemcitabine, oxaliplatin, rituximab or etoposide) based on published data for up to 6 cycles or until disease progression, unacceptable toxicity or withdrawal. Participants with documented progressive disease had the option to receive crossover lenalidomide at the same dosage as participants randomized to lenalidomide.	

Reporting group values	Lenalidomide	Investigators Choice (Control Arm)	Total
Number of subjects	54	57	111
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)	17	28	45
From 65-84 years	36	29	65
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	65.0	62.9	
standard deviation	± 13.50	± 13.96	-
Sex: Female, Male Units: Subjects			
Female	22	22	44
Male	32	35	67
Race/Ethnicity, Customized Units: Subjects			
Asian	1	1	2
Black/African American	0	1	1
White	40	41	81
Missing	10	12	22
Other (Unspecified)	3	2	5
Eastern Cooperative Oncology Performance Status (ECOG)]			
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 (Most Favorable Activity); 1 = Restricted activity			

but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, No self-care (Least Favorable Activity)			
Units: Subjects			
0 = (Fully Active)	20	15	35
1 (Restrictive but Ambulatory)	25	33	58
2 (Ambulatory but Unable to Work)	7	9	16
3 (Limited Self-Care)	1	0	1
4 (Completely Disabled)	0	0	0
Missing	1	0	1
Creatinine Clearance (CrCl)			
Creatinine is a waste product from the normal breakdown of muscle tissue. As creatinine is produced, it's filtered through the kidneys and excreted in urine. Doctors measure the blood creatinine level as a test of kidney function. Participants with a CrCl (as calculated by the Cockcroft-Gault formula, utilizing actual body weight or ideal body weight, whichever was less) of ≥ 60 mL/min received a starting dose of 25 mg lenalidomide once daily. Participants with moderate renal insufficiency (ie, CrCl ≥ 30 mL/min but < 60 mL/min) received a starting dose of 10 mg lenalidomide once daily.			
Units: Subjects			
≥ 60 mL/min	34	43	77
≥ 30 but < 60 mL/min	19	11	30
Missing	1	3	4
Diffuse Large B-Cell Lymphoma (DLBCL) Subtypes - Germinal Center B-Cell (GCB) and non-GCB			
DLBCL is comprised of different pathophysiological subtypes that influence patient prognosis and response to treatment. Based on immunohistochemistry (IHC), DLBCL can be classified into germinal center B-cell and non-GCB subtypes. Patients with non-GCB have a worse prognosis compared with the GCB subtype.			
Units: Subjects			
Germinal Center B-Cell Type	24	25	49
Non-Germinal Center B-Cell Type	28	30	58
Missing	2	2	4
Disease Stage of DLBCL at Enrollment			
Units: Subjects			
Stage IA	1	3	4
Stage IB	1	0	1
Stage IIA	9	7	16
Stage IIB	3	1	4
Stage IIIA	13	14	27
Stage IIIB	2	5	7
Stage IVA	19	16	35
Stage IVB	6	11	17

End points

End points reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide 25 mg orally once daily for 21 days in each 28-day cycle until progressive disease. For participants with creatinine clearance ≥ 30 mL/min but < 60 mL/min, lenalidomide 10 mg once daily for 21 days for 2 cycles. After Cycle 2 the dose may have been increased to a maximum of 15 mg lenalidomide once daily for 21 days in each 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or voluntary withdrawal.

Reporting group title	Investigators Choice (Control Arm)

Reporting group description:

Participants received a single agent reference therapy (either gemcitabine, oxaliplatin, rituximab or etoposide) based on published data for up to 6 cycles or until disease progression, unacceptable toxicity or withdrawal. Participants with documented progressive disease had the option to receive crossover lenalidomide at the same dosage as participants randomized to lenalidomide.

Subject analysis set title	Lenalidomide
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received lenalidomide 25 mg orally once daily for 21 days in each 28-day cycle until progressive disease. For participants with creatinine clearance ≥ 30 mL/min but < 60 mL/min, lenalidomide 10mg once daily for 21 days for 2 cycles. After Cycle 2 the dose may be increased to a maximum of 15 mg lenalidomide once daily for 21 days in each 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or voluntary withdrawal.

Subject analysis set title	Investigator's Choice (Control Arm)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received a single agent reference therapy (either gemcitabine, oxaliplatin, rituximab or etoposide) based on published data for up to 6 cycles or until disease progression, unacceptable toxicity or withdrawal. Participants with documented progressive disease had the option to receive crossover lenalidomide at the same dosage as participants randomized to lenalidomide.

Subject analysis set title	Lenalidomide
Subject analysis set type	Safety analysis

Subject analysis set description:

Lenalidomide 25 mg orally once daily for 21 days in each 28-day cycle until progressive disease. For participants with creatinine clearance ≥ 30 mL/min but < 60 mL/min, lenalidomide 10mg once daily for 21 days for 2 cycles. After Cycle 2 the dose may be increased to a maximum of 15 mg lenalidomide once daily for 21 days in each 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or voluntary withdrawal.

Subject analysis set title	Investigator's Choice
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received a single agent reference therapy (either gemcitabine, oxaliplatin, rituximab or etoposide) based on published data for up to 6 cycles or until disease progression, unacceptable toxicity or withdrawal. Participants with documented progressive disease had the option to receive crossover lenalidomide at the same dosage as participants randomized to lenalidomide.

Primary: Stage 1: Percentage of Participants with an Overall Response Rate According to the International Working Group (IWG) Response Criteria for Non Hodgkin's Lymphoma (NHL), Cheson 1999 and Evaluated by the Independent Response Adjudication Committee (IRAC)

End point title	Stage 1: Percentage of Participants with an Overall Response Rate According to the International Working Group (IWG) Response Criteria for Non Hodgkin's Lymphoma (NHL), Cheson 1999 and Evaluated by the Independent Response Adjudication Committee (IRAC)

End point description:

An overall response is a complete response (CR), unconfirmed complete response (CRu) or partial

response (PR) and was evaluated by the IRAC. A CR = complete disappearance of disease and related symptoms. Lymph nodes and nodal masses regressed on computed tomography to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy and ≤ 1.0 cm in their short axis for nodes 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to therapy). Spleen and/or liver not palpable on exam, normal size by imaging, and absence of nodules related to lymphoma. If bone marrow was involved prior to therapy, infiltrate must have cleared on repeat biopsy. PR = ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. No increase in other nodes, liver, or spleen. Splenic and hepatic nodules regressed by ≥ 50% in their SPD or for single nodules, in the greatest transverse diameter;no new disease.

End point type	Primary

End point timeframe:

From date of randomization to the data cut-off of 4 July 2013; when all patients reached the scheduled 16-week assessment or had progressed/died before the scheduled 16-week assessment); the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: percentage of participants				
number (confidence interval 95%)				
ORR for All Participants	27.5 (15.9 to 41.7)	11.8 (4.4 to 23.9)		
GCB Subtype (N = 23 and 25)	26.1 (10.2 to 48.4)	12.0 (2.5 to 31.2)		
Non-GCB (N = 28, 26)	28.6 (13.2 to 48.7)	11.5 (2.4 to 30.2)		

Statistical analyses

Statistical analysis title	Comparison of All Participants
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	Fisher exact

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Pertains to GCB Subtype in row 2

Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279
Method	Fisher exact

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Pertains to non-GCB Sub-type; row 3	
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179
Method	Fisher exact

Primary: Stage 1: Percentage of Participants with an Overall Response According to the IWG Response Criteria Based on the Investigators Assessment at the Final Data Cut During the Core Treatment Phase

End point title	Stage 1: Percentage of Participants with an Overall Response According to the IWG Response Criteria Based on the Investigators Assessment at the Final Data Cut During the Core Treatment Phase

End point description:

Response was defined as participants with a CR, CR or PR, based on IWG 1999 Response Criteria for NHL as evaluated by the investigators. CR is a complete disappearance of all disease with the exception of nodes. No new lesions. Previously enlarged organs must have regressed and not be palpable. Bone marrow must be negative if positive at baseline. Normalization of markers. CRu does not qualify for CR above, due to a residual nodal mass or an indeterminate BM. PR is a 50% decrease in the sum of the products of diameters for up to 6 dominant lesions, including spleenic and hepatic nodules from baseline. No new lesions and no increase in the size of liver, spleen or other nodes. The mITT population = randomized subjects who had a DLBCL diagnosis and either germinal center B-cell subtype or non-GCB subtype confirmed by central pathology, and who received at least one dose of study drug.

End point type	Primary

End point timeframe:

From date of randominzation to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: Percentage of participants				
number (confidence interval 95%)	29.4 (17.5 to 43.8)	13.7 (5.7 to 26.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Pertains to all participants	
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.091
Method	Fisher exact

Secondary: Number of Participants with Treatment Emergent Events (TEAEs) in the Overall Treatment Phase by Initial Treatment Assignment

End point title	Number of Participants with Treatment Emergent Events (TEAEs) in the Overall Treatment Phase by Initial Treatment Assignment

End point description:

A TEAE = an AE that begins or worsens in intensity of frequency on or after the first dose of study drug through 28 days after the last dose. A serious AE = an AE which results in death;is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The investigator determined the relationship of an AE to study drug based on the timing of the AE relative to drug delivery and whether or not other drugs, interventions, or underlying conditions could provide a sufficient explanation for the event. The severity of an AE was evaluated according to National Cancer Institute Common Terminology Criteria for AE (NCI CTCAE) Version 3.0 where Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death. Safety population = all subjects who received at least one dose of either regimen

End point type	Secondary

End point timeframe:

From first dose of study drug to the final data cut-off date of 18 May 2018; median study duration for participants given lenalidomide was 30.9 weeks (range 2.3 to 356.1 weeks) and 24.6 weeks for those treated in the IC arm (range 1.3-303.9 weeks)

End point values	Lenalidomide	Investigator's Choice		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	55		
Units: Participants				
Any TEAEs	54	55		
Any TEAE Grade ≥ 3	43	43		
Any TEAE Grade ≥ 4	29	28		
Any TEAE Grade 5	9	11		
Any TEAE Grade 3 or 4	42	42		

Any Treatment Related TEAE	49	44		
Any Treatment Related TEAE Grade ≥ 3	30	31		
Any Treatment Related TEAEs Grade ≥ 4	15	16		
Any Treatment Related TEAE Grade 5	0	2		
Any Treatment Related TEAE Grade 3 or 4	30	31		
Any Serious Adverse Events (SAEs)	31	31		
Any Treated Related SAEs	14	18		
Any AE leading to stopping of study drug	11	12		
Any drug related AE leading to halt of study drug	5	3		
Any AE leading to dose interruption/reduct	32	27		
Any drug related AE leading to interruption/reduct	27	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Overall Response Rate (ORR)

End point title	Stage 2: Overall Response Rate (ORR)

End point description:

ORR is defined as: Complete Response + Complete Response unconfirmed + Partial Response based on the International Lymphoma Workshop Response Criteria [IWRC] (Cheson 1999).

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[1]	0[2]		
Units: percentage of participants				
number (not applicable)				

Notes:

[1] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

[2] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Duration of Response (DoR)

End point title	Stage 2: Duration of Response (DoR)

End point description:

Length of time of overall response (Complete Response + Complete Response unconfirmed + Partial Response) based on the International Lymphoma Workshop Response Criteria [IWRC] (Cheson 1999).

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[3]	0[4]		
Units: weeks				
number (not applicable)				

Notes:

[3] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

[4] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Overall Survival (OS)

End point title	Stage 2: Overall Survival (OS)

End point description:

Overall survival was defined as time from randomization until death of any cause.

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: months				
number (not applicable)				

Notes:

[5] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

[6] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Duration of Complete Response

End point title	Stage 2: Duration of Complete Response

End point description:

Duration of complete response was defined as the time from the first documented complete response (CR + CRu) until the first disease progression or death for participants who had a CR.

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	0[8]		
Units: weeks				
number (not applicable)				

Notes:

[7] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2
[8] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Overall Response Rate for with a Duration of Response Lasting ≥ 16 weeks

End point title	Stage 2: Overall Response Rate for with a Duration of Response Lasting ≥ 16 weeks

End point description:

Response was defined as participants with a complete response (CR), unconfirmed complete response (CRu) or partial response (PR), based on IWG 1999 Response Criteria for NHL as evaluated by the IRAC. CR is a complete disappearance of all disease with the exception of nodes. No new lesions. Previously enlarged organs must have regressed and not be palpable. Bone marrow must be negative if positive at baseline. Normalization of markers. CRu does not qualify for CR above, due to a residual nodal mass or an indeterminate BM. PR is a 50% decrease in the sum of the products of diameters for up to 6 dominant lesions, including spleenic and hepatic nodules from baseline. No new lesions and no increase in the size of liver, spleen or other nodes

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[9]	0[10]		
Units: weeks				
number (not applicable)				

Notes:

[9] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2
[10] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Time to Progression

End point title	Stage 2: Time to Progression

End point description:

Time to progression (TTP) was defined as the time from randomization until objective tumor progression

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[11]	0[12]		
Units: weeks				
number (not applicable)				

Notes:

[11] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2
[12] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Health Related Quality of Life Questionnaires

End point title	Stage 2: Health Related Quality of Life Questionnaires

End point description:

Quality of Life based on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and the EQ-5D assessments

End point type	Secondary

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[13]	0[14]		
Units: Participants				
number (not applicable)				

Notes:

[13] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2
[14] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Stage 1: Percentage of Participants with a Durable Overall Response Rate (dORR) According to the IWG Response Criteria as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point title	Stage 1: Percentage of Participants with a Durable Overall Response Rate (dORR) According to the IWG Response Criteria as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point description:

Durable overall response rate was defined as the percentage of participants who maintained a response for at least 16 weeks after initial response. Includes participants who achieved an overall response.

End point type	Other pre-specified

End point timeframe:

From date of randomization to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: percentage of participants				
median (confidence interval 95%)	23.5 (12.8 to 37.5)	9.8 (3.3 to 21.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.109
Method	Fisher exact

Other pre-specified: Stage 1: Percentage of Participants with a Complete Response Rate According to the IWG Response Criteria as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point title	Stage 1: Percentage of Participants with a Complete Response Rate According to the IWG Response Criteria as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point description:

A complete response was defined as participants with a complete response , or unconfirmed complete response based on IWG 1999 Response Criteria for NHL as assessed by the investigator. A CR is a complete disappearance of all disease with the exception of nodes. No new lesions. Previously enlarged organs must have regressed and not be palpable. Bone marrow(BM) must be negative if positive at baseline. Normalization of markers. CR Unconfirmed (CRu) does not qualify for CR above, due to a residual nodal mass or an indeterminate BM. Includes participants with a CR.

End point type	Other pre-specified

End point timeframe:

From date of randomization to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: percentage of participants				
number (confidence interval 95%)	13.7 (5.7 to 26.3)	3.9 (0.5 to 13.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Pertains to the all participants; row 1

Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Fisher exact

Other pre-specified: Stage 1: Kaplan Meier Estimates of Duration of Overall Response (DoR) as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point title	Stage 1: Kaplan Meier Estimates of Duration of Overall Response (DoR) as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point description:

Duration of overall response was calculated as the time of initial response (CR+CRu+PR) until documented disease progression determined by computerized tomography scan or magnetic resonance imaging (MRI) or death due to lymphoma, whichever occurred earlier, for participants who responded. The mITT population = randomized subjects who had a DLBCL diagnosis and either germinal center B-cell subtype or non-GCB subtype confirmed by central pathology, and who received at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From date of randomization to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: Weeks				
median (confidence interval 95%)	64.7 (29.1 to 141.6)	63.1 (15.3 to 79.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.529
Method	Logrank

Other pre-specified: Stage 1: Kaplan Meier Estimates of Duration of Complete Response (DoCR) as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point title	Stage 1: Kaplan Meier Estimates of Duration of Complete Response (DoCR) as Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point description:

Duration of complete response was defined as the time from the first documented complete response

(CR + CRu) until the first disease progression or death for participants who had a CR. The mITT population = randomized subjects who had a DLBCL diagnosis and either germinal center B-cell subtype or non-GCB subtype confirmed by central pathology, and who received at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From date of randomization to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51[15]	51		
Units: Weeks				
median (confidence interval 95%)	66.4 (22.1 to 99999)	179.3 (63.1 to 295.4)		

Notes:

[15] - 99999 = not estimable due to

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.972
Method	Logrank

Other pre-specified: Stage 1: Kaplan Meier Estimates of Progression-Free Survival As Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point title	Stage 1: Kaplan Meier Estimates of Progression-Free Survival As Assessed by the Investigators at the Final Data Cut During the Core Treatment Phase

End point description:

Progression-free survival was defined as the time from randomization to the first documented disease progression or death due to any cause. The mITT population = randomized subjects who had a DLBCL diagnosis and either germinal center B-cell subtype or non-GCB subtype confirmed by central pathology, and who received at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From randomization to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: Weeks				
median (confidence interval 95%)	9.6 (7.6 to 17.1)	7.1 (6.0 to 8.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Logrank

Other pre-specified: Stage 1: Kaplan Meier Estimates of Overall Survival at the Final Data Cut During the Core Treatment Phase

End point title	Stage 1: Kaplan Meier Estimates of Overall Survival at the Final Data Cut During the Core Treatment Phase

End point description:

Overall survival was defined as time from randomization until death of any cause. The mITT population = randomized subjects who had a DLBCL diagnosis and either germinal center B-cell subtype or non-GCB subtype confirmed by central pathology, and who received at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From randomization to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively.

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	51		
Units: Weeks				
median (confidence interval 95%)	31.0 (16.6 to 43.7)	24.6 (12.7 to 34.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide v Investigator's Choice (Control Arm)

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.211
Method	Logrank

Other pre-specified: Stage 2: Progression-Free Survival

End point title	Stage 2: Progression-Free Survival

End point description:

Progression-free survival was defined as the time from randomization to the first documented disease progression or death due to any cause.

End point type	Other pre-specified

End point timeframe:

Approximately 3.5 years

End point values	Lenalidomide	Investigator's Choice (Control Arm)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[16]	0[17]		
Units: months				
number (not applicable)				

Notes:

[16] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

[17] - The IRAC determined that neither subtype met the pre-specified requirement to be studied in Stage 2

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug to the final data cut-off date of 18 May 2018; the median study duration of 27.0 and 19.7 weeks, respectively. Two participants in the investigator choice arm elected to discontinue before cycle 1.

Adverse event reporting additional description:

The AEs were based on the overall treatment phase that includes both core treatment phase and crossover phase. Two participants in the investigator choice arm elected to discontinue before cycle 1; secondary primary malignancies were monitored up to final database lock of 18 May 2018.Two

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Participants received Lenalidomide 25 mg orally once daily for 21 days in each 28-day cycle until progressive disease. For participants with creatinine clearance ≥ 30 mL/min but < 60 mL/min, lenalidomide 10 mg once daily for 21 days for 2 cycles. After Cycle 2 the dose may have been increased to a maximum of 15 mg lenalidomide once daily for 21 days in each 28-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or voluntary withdrawal.

Reporting group title	Investigator's Choice

Reporting group description:

Participants received a single agent reference therapy (either gemcitabine, oxaliplatin, rituximab or etoposide) based on published data for up to 6 cycles or until disease progression, unacceptable toxicity or withdrawal. Participants with documented progressive disease had the option to receive crossover lenalidomide at the same dosage as participants randomized to lenalidomide.

Serious adverse events	Lenalidomide	Investigator's Choice	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 54 (57.41%)	42 / 55 (76.36%)	
number of deaths (all causes)	9	18	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	4 / 54 (7.41%)	10 / 55 (18.18%)	
occurrences causally related to treatment / all	0 / 6	3 / 13	
deaths causally related to treatment / all	0 / 4	1 / 6	

GASTROINTESTINAL TRACT ADENOMA			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKAEMIA			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOMA			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-HODGKIN'S LYMPHOMA			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RECTOSIGMOID CANCER METASTATIC			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR FLARE			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
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 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 54 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
FATIGUE			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 54 (1.85%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERFORMANCE STATUS DECREASED			

subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
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 / 54 (3.70%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	2 / 54 (3.70%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARYNGEAL OBSTRUCTION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGEAL INFLAMMATION			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
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 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			

subjects affected / exposed	2 / 54 (3.70%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
STRIDOR			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CAUDA EQUINA SYNDROME			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

DIZZINESS			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVE ROOT COMPRESSION			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 54 (7.41%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	1 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE BONE MARROW APLASIA			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	4 / 54 (7.41%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPH NODE PAIN			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS ULCERATIVE			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL OBSTRUCTION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LOWER GASTROINTESTINAL HAEMORRHAGE			

subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (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 / 54 (0.00%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILE DUCT OBSTRUCTION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
FUNGATING WOUND			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	0 / 54 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

HYDRONEPHROSIS			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROTIC SYNDROME			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT SWELLING			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 54 (0.00%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
CELLULITIS			
subjects affected / exposed	0 / 54 (0.00%)	4 / 55 (7.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA INFECTIOUS			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

INFECTION			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ABSCESS			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPH NODE ABSCESS			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
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 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	3 / 54 (5.56%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS			

subjects affected / exposed	1 / 54 (1.85%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
SEPTIC SHOCK			
subjects affected / exposed	1 / 54 (1.85%)	2 / 55 (3.64%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
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	2 / 54 (3.70%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			

subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	1 / 1	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	Lenalidomide	Investigator's Choice	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 54 (98.15%)	52 / 55 (94.55%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
DIFFUSE LARGE B-CELL LYMPHOMA			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
TUMOUR FLARE			
subjects affected / exposed	5 / 54 (9.26%)	0 / 55 (0.00%)	
occurrences (all)	5	0	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	3 / 54 (5.56%)	3 / 55 (5.45%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	10 / 54 (18.52%)	13 / 55 (23.64%)	
occurrences (all)	12	15	
CHILLS			
subjects affected / exposed	4 / 54 (7.41%)	2 / 55 (3.64%)	
occurrences (all)	4	2	
FATIGUE			
subjects affected / exposed	19 / 54 (35.19%)	16 / 55 (29.09%)	
occurrences (all)	28	25	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	4 / 54 (7.41%)	1 / 55 (1.82%)	
occurrences (all)	4	1	
OEDEMA PERIPHERAL			

subjects affected / exposed	9 / 54 (16.67%)	10 / 55 (18.18%)	
occurrences (all)	12	11	
PYREXIA			
subjects affected / exposed	16 / 54 (29.63%)	18 / 55 (32.73%)	
occurrences (all)	17	33	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	13 / 54 (24.07%)	10 / 55 (18.18%)	
occurrences (all)	15	11	
DYSPNOEA			
subjects affected / exposed	6 / 54 (11.11%)	12 / 55 (21.82%)	
occurrences (all)	11	13	
EPISTAXIS			
subjects affected / exposed	0 / 54 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	4	
OROPHARYNGEAL PAIN			
subjects affected / exposed	2 / 54 (3.70%)	4 / 55 (7.27%)	
occurrences (all)	4	4	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	4 / 54 (7.41%)	5 / 55 (9.09%)	
occurrences (all)	5	5	
DEPRESSION			
subjects affected / exposed	3 / 54 (5.56%)	3 / 55 (5.45%)	
occurrences (all)	3	3	
INSOMNIA			
subjects affected / exposed	3 / 54 (5.56%)	2 / 55 (3.64%)	
occurrences (all)	4	2	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 54 (0.00%)	4 / 55 (7.27%)	
occurrences (all)	0	7	

BLOOD CREATININE INCREASED			
subjects affected / exposed	2 / 54 (3.70%)	4 / 55 (7.27%)	
occurrences (all)	2	7	
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	0 / 54 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	4	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 54 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	4	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 54 (0.00%)	7 / 55 (12.73%)	
occurrences (all)	0	14	
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 54 (0.00%)	9 / 55 (16.36%)	
occurrences (all)	0	36	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 54 (0.00%)	5 / 55 (9.09%)	
occurrences (all)	0	27	
Injury, poisoning and procedural complications			
DRUG PRESCRIBING ERROR			
subjects affected / exposed	5 / 54 (9.26%)	1 / 55 (1.82%)	
occurrences (all)	5	1	
Cardiac disorders			
TACHYCARDIA			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	3 / 54 (5.56%)	5 / 55 (9.09%)	
occurrences (all)	4	7	
DYSGEUSIA			
subjects affected / exposed	2 / 54 (3.70%)	3 / 55 (5.45%)	
occurrences (all)	2	3	
HEADACHE			

subjects affected / exposed	3 / 54 (5.56%)	6 / 55 (10.91%)	
occurrences (all)	3	6	
HYPOAESTHESIA			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
LETHARGY			
subjects affected / exposed	4 / 54 (7.41%)	1 / 55 (1.82%)	
occurrences (all)	7	1	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	2 / 54 (3.70%)	5 / 55 (9.09%)	
occurrences (all)	4	5	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	17 / 54 (31.48%)	31 / 55 (56.36%)	
occurrences (all)	32	89	
LEUKOPENIA			
subjects affected / exposed	3 / 54 (5.56%)	8 / 55 (14.55%)	
occurrences (all)	9	28	
LYMPHOPENIA			
subjects affected / exposed	1 / 54 (1.85%)	5 / 55 (9.09%)	
occurrences (all)	5	13	
NEUTROPENIA			
subjects affected / exposed	23 / 54 (42.59%)	18 / 55 (32.73%)	
occurrences (all)	81	45	
THROMBOCYTOPENIA			
subjects affected / exposed	13 / 54 (24.07%)	17 / 55 (30.91%)	
occurrences (all)	59	50	
Ear and labyrinth disorders			
HYPOACUSIS			
subjects affected / exposed	0 / 54 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
VERTIGO			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
Gastrointestinal disorders			

ABDOMINAL DISTENSION			
subjects affected / exposed	4 / 54 (7.41%)	1 / 55 (1.82%)	
occurrences (all)	4	1	
ABDOMINAL PAIN			
subjects affected / exposed	10 / 54 (18.52%)	12 / 55 (21.82%)	
occurrences (all)	14	14	
CONSTIPATION			
subjects affected / exposed	16 / 54 (29.63%)	16 / 55 (29.09%)	
occurrences (all)	16	31	
DIARRHOEA			
subjects affected / exposed	18 / 54 (33.33%)	16 / 55 (29.09%)	
occurrences (all)	31	21	
DRY MOUTH			
subjects affected / exposed	7 / 54 (12.96%)	3 / 55 (5.45%)	
occurrences (all)	10	3	
DYSPEPSIA			
subjects affected / exposed	3 / 54 (5.56%)	3 / 55 (5.45%)	
occurrences (all)	3	4	
NAUSEA			
subjects affected / exposed	10 / 54 (18.52%)	23 / 55 (41.82%)	
occurrences (all)	15	31	
STOMATITIS			
subjects affected / exposed	1 / 54 (1.85%)	5 / 55 (9.09%)	
occurrences (all)	1	5	
VOMITING			
subjects affected / exposed	9 / 54 (16.67%)	11 / 55 (20.00%)	
occurrences (all)	13	14	
Skin and subcutaneous tissue disorders			
DRY SKIN			
subjects affected / exposed	3 / 54 (5.56%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
ERYTHEMA			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
PRURITUS			

subjects affected / exposed	3 / 54 (5.56%)	3 / 55 (5.45%)	
occurrences (all)	4	3	
PRURITUS GENERALISED			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
RASH			
subjects affected / exposed	9 / 54 (16.67%)	2 / 55 (3.64%)	
occurrences (all)	14	7	
RASH MACULO-PAPULAR			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	5	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	7 / 54 (12.96%)	5 / 55 (9.09%)	
occurrences (all)	7	7	
BACK PAIN			
subjects affected / exposed	3 / 54 (5.56%)	8 / 55 (14.55%)	
occurrences (all)	3	8	
MUSCLE SPASMS			
subjects affected / exposed	4 / 54 (7.41%)	2 / 55 (3.64%)	
occurrences (all)	4	2	
MUSCULAR WEAKNESS			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	3 / 54 (5.56%)	0 / 55 (0.00%)	
occurrences (all)	3	0	
MYALGIA			
subjects affected / exposed	4 / 54 (7.41%)	4 / 55 (7.27%)	
occurrences (all)	5	8	
PAIN IN EXTREMITY			
subjects affected / exposed	6 / 54 (11.11%)	5 / 55 (9.09%)	
occurrences (all)	7	7	
Infections and infestations			

BRONCHITIS			
subjects affected / exposed	6 / 54 (11.11%)	0 / 55 (0.00%)	
occurrences (all)	7	0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 54 (5.56%)	6 / 55 (10.91%)	
occurrences (all)	6	7	
LUNG INFECTION			
subjects affected / exposed	0 / 54 (0.00%)	3 / 55 (5.45%)	
occurrences (all)	0	3	
NASOPHARYNGITIS			
subjects affected / exposed	3 / 54 (5.56%)	1 / 55 (1.82%)	
occurrences (all)	7	2	
PNEUMONIA			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	
occurrences (all)	1	6	
RHINITIS			
subjects affected / exposed	3 / 54 (5.56%)	4 / 55 (7.27%)	
occurrences (all)	4	4	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 54 (9.26%)	5 / 55 (9.09%)	
occurrences (all)	16	5	
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 54 (5.56%)	4 / 55 (7.27%)	
occurrences (all)	4	5	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	8 / 54 (14.81%)	15 / 55 (27.27%)	
occurrences (all)	9	15	
HYPERGLYCAEMIA			
subjects affected / exposed	3 / 54 (5.56%)	6 / 55 (10.91%)	
occurrences (all)	8	14	
HYPOCALCAEMIA			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
HYPOKALAEMIA			

subjects affected / exposed	6 / 54 (11.11%)	10 / 55 (18.18%)	
occurrences (all)	20	13	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2010	1. A formal interim analysis was implemented for Stage 1. This change was made based on a recommendation from an IRB at a US site. 2. Eligibility according to specific WHO subcategories for DLBCL was implemented. 3. Subjects in whom combination chemotherapy was considered appropriate were excluded from the study. 4. Baseline HBV testing was required for eligibility and definitions for HBV positive were added. This change was made based on recommendations from several European investigators. 5. Exceptions to laboratory requirements for eligibility (ie, ANC < 1,500 cells/mm3 and platelet counts < 50,000/mm3) were allowed, if they were secondary to bone marrow involvement by lymphoma (as demonstrated by recent bone marrow aspiration and bone marrow biopsy). 6. To be eligible, subjects who received SCT within 28 days of D1 dosing had to recover from all acute toxicity and be transfusion independent. 7. The toxicity recovery time before lenalidomide start for crossover subjects was extended from eight weeks to 12 weeks. 8. New starting doses and schedules for etoposide and gemcitabine were implemented. This change was made to accommodate investigator requests to follow common clinical practice, and to allow a lower starting dose schedule for subjects who could not tolerate a high starting dose schedule. 9. Instructions for lenalidomide dose modification in case of TFR and TLS were implemented. This change was made for enhanced guidance on subject management and safety. 10. Venous thromboembolic event prophylaxis was recommended instead of required. This change was made based on a recommendation from an EU competent Health Authority. 11. For safety assessments, NCI CTCAE Version 4.03 grading was used (instead of Version 4.0); it was also noted that NCI CTCAE Version 3.0 was used solely for TFR grading. 12. A global pregnancy prevention plan replaced two regional plans.
22 April 2011	1. The period for submission of the archival lymph node biopsy to central pathology was extended for subjects who needed urgent treatment upon medical monitor approval. If locally determined subtype data were available, that information was used to stratify the subject. However, a retrospective central pathology subtype designation was the basis for analysis in the mITT Population. This change was made based on investigator feedback and as an attempt to eliminate treatment delays. 2. The Screening requirement of CT/MRI scans could be fulfilled by CT/MRI scans acquired as SOC up to 28 days prior to C1 D1, as long as all required fields were images and they fulfilled the standard specified by central radiology. This change was made based on investigators feedback and as an attempt to eliminate treatment delays. 3. A CT/MRI scan was required in the Control Arm who desired to cross over to lenalidomide, even if they had clinical progression alone. The scan had to be forwarded to central radiology; however, local radiology approval was sufficient for determining PD and allowing crossover. Upon request, subtype could be unblinded for these subjects. This change was made to reduce bias and ensure that control drugs were given an adequate trial before switching treatment arms. 4. Local laboratory results could be used for eligibility as long as a concurrent central laboratory samples were drawn. This change was made based on investigator feedback and as an attempt to eliminate treatment delays. 5. Second primary malignancies were required to be treated as SAEs and reported for the study duration from ICF through follow-up for OS. 6. Subjects who exited the Treatment Phase for reasons other than PD were followed to the date of progression. This change was made to improve data collection for PFS endpoint. 7. Systemic corticosteroid doses above 10 mg/day (prednisone or equivalent) for up to 24 h after each dose of IV chemotherapy were allowed for antiemetic prophylaxis.

03 October 2011	1. The exclusionary time period for prior malignancies was extended from ≥ 3 to ≥ 5 years. Follow-up time for SPM during the study was extended. This change was implemented because Health Authorities in France and Austria had requested that Celgene further restrict the exclusion criteria for previous malignancies. 2. Lenalidomide dose modification could be made, as per investigator's discretion, for reasons other than those previously listed (Table 4). This change allowed the investigators to be more conservative with dosing. 3. A window (ie, ± 3 days) was added to visits on C1 D8 and C1 D15 in the Core Treatment Phase and during the Crossover Phase. 4. Treatment Discontinuation laboratory tests and physical examination performed during the Core Treatment Phase were allowed to fulfill the crossover C1 D1 assessments if they had been collected within seven days of the first dose of lenalidomide in the Crossover Phase. The reason was to avoid unnecessary subject blood draws and examinations and to apply the same standard previously set for Screening and C1 D1 laboratory tests and physical examinations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

On 29 January 2013 the Stage 1 portion of the study was met and enrollment stopped. The Stage 1 results as assessed by the IRAC demonstrated that neither subtype met the prespecified requirement to be further studied in Stage 2.

Notes: