Clinical trial results:
A PHASE 2, MULTICENTER, SINGLE-ARM, OPEN-LABEL STUDY TO DETERMINE THE EFFICACY AND SAFETY OF SINGLE-AGENT LENALIDOMIDE (REVLIMID®) IN PATIENTS WITH MANTLE CELL NHL WHO HAVE RELAPSED OR PROGRESSED AFTER TREATMENT WITH BORTEZOMIB OR ARE REFRACTORY TO BORTEZOMIB

Summary

EudraCT number	2007-007756-34
Trial protocol	BE DE ES AT HU FR IT GB
Global end of trial date	08 November 2017

Results information

Result version number	v1 (current)
This version publication date	24 November 2018
First version publication date	24 November 2018

Trial information

Trial identification

Sponsor protocol code	CC-5013-MCL-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00737529
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	Lei Zhang, MD, Celgene Corporation, 01 908-673-2464, lei_zhang@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	30 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the tumor response and duration of response of lenalidomide monotherapy in patients with mantle cell lymphoma (MCL) who have relapsed or progressed after treatment with bortezomib or are refractory to bortezomib.

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason
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: 72
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Puerto Rico: 1
Worldwide total number of subjects	134
EEA total number of subjects	35

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)	49
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled and treated at 42 centers in 12 countries: US/ Puerto Rico, France, Israel, Belgium, Spain, Turkey, Austria, Hungary, Italy, Colombia, Germany, and Singapore.

Pre-assignment

Screening details:

All participants were required to have local histologic confirmation of Mantle Cell Lymphoma (MCL) for entry into the study.

Period 1

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

Arms

Arm title	Lenalidomide

Arm description:

Participants received lenalidomide 10 mg or 25 mg oral capsules on days 1 to 21 of each 28-day cycle and was dependent on renal function; Participants with normal renal function (defined as creatinine clearance (CrCl)) of ≥ 60 mL/min) received 25 mg of lenalidomide by mouth (PO) daily, and those with moderate renal insufficiency (CrCl) ≥ 30 mL/min but < 60 mL/min) were started at a 10 mg daily dose. Participants could continue to receive treatment until disease progression, development of unacceptable adverse events (AEs), or voluntary withdrawal.

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

Dosage and administration details:

Participants received lenalidomide 10 mg or 25 mg oral capsules on days 1 to 21 of each 28-day cycle and was dependent on renal function

Number of subjects in period 1	Lenalidomide
Started	134
Completed	1
Not completed	133
Adverse event, serious fatal	4
Consent withdrawn by subject	5
Adverse event, non-fatal	24
Unspecified	4
Disease Progression	95
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Lenalidomide
Reporting group description:	
Participants received lenalidomide 10 mg or 25 mg oral capsules on days 1 to 21 of each 28-day cycle and was dependent on renal function; Participants with normal renal function (defined as creatinine clearance (CrCl)) of ≥ 60 mL/min) received 25 mg of lenalidomide by mouth (PO) daily, and those with moderate renal insufficiency (CrCl) ≥ 30 mL/min but < 60 mL/min) were started at a 10 mg daily dose. Participants could continue to receive treatment until disease progression, development of unacceptable adverse events (AEs), or voluntary withdrawal.	

Reporting group values	Lenalidomide	Total	
Number of subjects	134	134	
Age, Customized Units: Subjects			
<65	49	49	
≥ 65	85	85	
Age Continuous Units: Years			
arithmetic mean	67.2		
standard deviation	± 8.38	-	
Sex: Female, Male Units: Subjects			
Female	26	26	
Male	108	108	
Race/Ethnicity, Customized Units: Subjects			
White or Caucasian	128	128	
Asian	3	3	
Black or African American	1	1	
Other	2	2	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group Performance Status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant 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)	43	43	
1 = (Restrictive but ambulatory)	73	73	
2 = (Ambulatory but unable to work)	17	17	
3 = (Limited self care)	1	1	
4 = (Completely Disabled)	0	0	
Renal function at baseline			
Participants with a Creatinine clearance (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 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			
Normal (CrCl > = 60 mL/min)	99	99	

Moderate Renal Insufficiency (CrCl ≥ 30 and < 60mL	28	28	
Severe Renal Insufficiency (CrCl < 30 mL/min)	1	1	
Missing	6	6	
Duration of Mantle Cell Lymphoma			
Units: Subjects			
<3 years|	52	52	
≥ 3 years|	82	82	
MCL (Ann Arbor) Stage 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 (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	2	2	
Stage II	5	5	
Stage III	19	19	
Stage IV	105	105	
Missing	3	3	
MCL International Prognostic Index (MIPI) Score Group at Enrollment			
A prognostic index predictive of the outcome in advanced Mantle Cell Lymphoma			
Units: Subjects			
Low	39	39	
Intermediate	51	51	
High	39	39	
Missing	5	5	
Prior Bone Marrow Assessment			
Baseline assessment of bone marrow involvement was not required per protocol; however, bone marrow biopsy and aspirate data previously conducted were collected if available.			
Units: Subjects			
Positive	55	55	
Negative	52	52	
Indeterminate	8	8	
Missing	19	19	
Tumor Burden			
Defined as at least one lesion that was ≥ 5 cm in diameter or ≥ 3 lesions that were ≥ 3 cm in diameter by central radiology review.			
Units: Subjects			
High = having 1 lesion ≥ 5 cm or 3 lesions ≥ 3cm	78	78	
Low = < 5cm lesions	54	54	
Missing = unable to characterize	2	2	
Bulky Disease			
Bulky disease is defined as at least one lesion ≥ 7 cm in diameter			
Units: Subjects			
Yes	44	44	
No	88	88	
Missing	2	2	

End points

End points reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide 10 mg or 25 mg oral capsules on days 1 to 21 of each 28-day cycle and was dependent on renal function; Participants with normal renal function (defined as creatinine clearance (CrCl)) of ≥ 60 mL/min) received 25 mg of lenalidomide by mouth (PO) daily, and those with moderate renal insufficiency (CrCl) ≥ 30 mL/min but < 60 mL/min) were started at a 10 mg daily dose. Participants could continue to receive treatment until disease progression, development of unacceptable adverse events (AEs), or voluntary withdrawal.

Primary: Percentage of Participants who Achieved an Overall Response According to the Independent Review Committee (IRC)

End point title	Percentage of Participants who Achieved an Overall Response According to the Independent Review Committee (IRC)[1]

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. Subjects who had 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; CR = defined as the disappearance of all clinical and radiographic evidence of disease; CRu = 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 = defined ≥50% decrease in 6 largest nodes or nodal masses. ITT population included all enrolled participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

From Day 1 of study treatment to progession or early treatment discontinuation; up to data cut-off date of 06 April 2016; median duration of treatment was 94.5 days.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis performed.

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: percentage of participants				
number (confidence interval 95%)	29.9 (22.26 to 38.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Duration of Response (DoR) According to the Independent Review Committee

End point title	Kaplan Meier Estimate of Duration of Response (DoR) According to the Independent Review Committee

End point description:

Kaplan Meier estimate for the duration of response (DoR) was calculated from the date of the first occurrence of initial response for responders (demonstrating evidence of at least a PR) to the date of first documented disease progression (any new lesion or increase by ≥ 50% of previously involved sites from nadir) or death (without documented progression) for participants who responded; participants who had not progressed (or died) were censored at the last valid assessment. Included participants from the ITT population who achieved a PR or better

End point type	Secondary

End point timeframe:

From Day 1 of study drug to progression or early treatment discontinuation; up to data cut-off date of 06 April 2016; Median duration of treatment was 94.5 days.

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: months				
median (confidence interval 95%)	16.64 (10.4219 to 29.8191)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Complete Response (CR) /Complete Response Unconfirmed (CRu) According to the Independent Review Committee

End point title	Percentage of Participants with a Complete Response (CR) /Complete Response Unconfirmed (CRu) According to the Independent Review Committee

End point description:

The percentage of participants whose best response was CR or CRu. Participants who had discontinued before CR/CRu was observed, or changed to other anti-lymphoma treatments before a CR/CRu response had been observed, were considered as non-responders. 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. The ITT population was defined as all enrolled participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 of study drug to progression or early treatment discontinuation; up to data cut-off date of 06 April 2016; Median duration of treatment was 94.5 days

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: percentage of participants				
number (confidence interval 95%)	9.0 (4.71 to 15.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Duration of Complete Response (DoCR) (CR+CRu) According to the Independent Review Committee

End point title	Kaplan Meier Estimate of Duration of Complete Response (DoCR) (CR+CRu) According to the Independent Review Committee

End point description:

Kaplan Meier estimates for the duration of CR/CRu was calculated from the date of the first occurrence of CR/CRu to the date of documented disease progression or death (without documented progression) for participants who obtained a CR/CRu; participants who had not progressed (or died) were censored at the last valid assessment. Includes participants from the ITT population who achieved a CRu or better. 99999 indicates upper limit not estimable at the time of final data cut off.

End point type	Secondary

End point timeframe:

From Day 1 of study drug to progression or early discontinuation; up to data cut-off date of 06 April 2016; median time in follow-up was 16.34 months

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: months				
median (confidence interval 95%)	24.43 (5.063 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Progression-Free Survival (PFS) According to the Independent Review Committee

End point title	Kaplan-Meier Estimate of Progression-Free Survival (PFS) According to the Independent Review Committee

End point description:

Kaplan Meier estimates of PFS was defined as the start of study drug therapy to the first observation of disease progression or death due to any cause, whichever comes first. If a participant had not progressed or died, PFS was censored at the time of last adequate 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 adequate tumor assessment with no evidence

of progression prior to the start of new anti-lymphoma treatment. ITT population defined as all enrolled participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 of study drug to first documented date of disease progression; up to data cut-off date of 06 April 2016; median time in follow-up was 16.34 months

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: months				
median (confidence interval 95%)	4.01 (3.6822 to 7.2329)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimate of Time to Progression (TTP) According to the Independent Review Committee

End point title	Kaplan Meier Estimate of Time to Progression (TTP) According to the Independent Review Committee

End point description:

Kaplan Meier estimate of time to progression was calculated as time from the start of the study drug therapy to the first observation of disease progression. Participants who died without progression were censored at the date of death; otherwise, the censoring rules presented above for PFS applied to the analysis of TTP. Progressive Disease(PD): Appearance of new lesion or increase by ≥50% from previously involved sites from nadir. ITT population was defined as all enrolled participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 of study drug to first documented time of progression; up to data cut-off date of 06 April 2016; median time in follow-up was 16.34 months

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: months				
median (confidence interval 95%)	5.46 (3.7479 to 9.4685)			

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Time to Treatment Failure (TTF) According to the Independent Review Committee

End point title	Kaplan-Meier Estimate of Time to Treatment Failure (TTF) According to the Independent Review Committee

End point description:

Time to treatment failure (TTF) was calculated from the start of study drug therapy to early discontinuation from treatment due to any cause, including disease progression, toxicity, or death and was based on site-reported data. ITT population was defined as all enrolled participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 of study drug to first documented time of treatment failure; up to data cut-off date of 06 April 2016; median duration of treatment was 94.5 days

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: months				
median (confidence interval 95%)	3.75 (2.3342 to 4.6356)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

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. Included participants from the ITT population who achieved a PR or better

End point type	Secondary

End point timeframe:

From Day 1 of study drug to time of first documented PR or better; up to data cut-off date of 06 April 2016; median duration of treatment was 94.5 days

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: months				
median (full range (min-max))	3.5 (1.7 to 15.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Complete Response (CR+CRu) According to the Independent Review Committee

End point title	Time to Complete Response (CR+CRu) According to the Independent Review Committee

End point description:

Time to Complete Response (CR+CRu) was defined as the time from the first dose of study drug to the date of the first occurrence of at least CRu and was calculated only for participants with CR or CRu. Included participants from the ITT population who achieved a CRu or better.

End point type	Secondary

End point timeframe:

From Day 1 of study drug to first documented CR/CRu or better; up to data cut-off date of 06 April 2016; median duration of treatment was 94.5 days

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: months				
median (full range (min-max))	3.9 (1.9 to 13.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Kaplan Meier estimate of overall survival was calculated from the time the first dose of study drug to death from any cause. Participants who had not died were censored at the last date the participant was known to be alive. Intent to Treat population defined as all enrolled participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From Day 1 of study drug to first documented date of progressive disease or death; up to the final data cut-off date of 30 March 2017; median duration of follow-up for surviving participants was 62.94 months

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: months				
median (confidence interval 95%)	19.50 (13.6767 to 25.5781)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

AEs were assessed using National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3: according to the following scale: Grade 1 = Mild AE, Grade 2 = Moderate AE, Grade 3 = Severe and Undesirable AE, Grade 4 = Life-threatening or Disabling AE, and Grade 5 = Death; Serious AEs (SAEs) = 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 IP and within 28 days after the last dose of IP. Included those in the safety population who received at least one dose of lenalidomide.

End point type	Secondary

End point timeframe:

From the first dose of lenalidomide through 28 days after the last dose during the follow-up phase; median (minimum, maximum) duration of treatment was 94.0 (1.0, 1950 days)

End point values	Lenalidomide			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: participants				
Any TEAE	132			
Any TEAE Related to Investigational Product (IP)	118			
Any TEAE Grade 3-5 AE	106			
Any TEAE Grade 3 AE	101			
Any TEAE Grade 4 AE	57			
Any TEAE Grade 5 AE	18			
Any Grade 3-5 AE Related to IP	90			
Any Grade 3 AE Related to IP	88			
Any Grade 4 AE Related to IP	41			

Any Grade 5 AE Related to IP	2			
Any TEAE Serious Adverse Event (SAE)	70			
Any SAE Related to IP	30			
Any TEAE Leading to Discontinuation (D/C) of IP	28			
Any Treatment Related AE Leading to D/C of IP	16			
Any AE Leading to Dose Reduction	55			
Any AE Leading to IP Interruption	81			
Any Treatment Related AE Leading to Dose Reduction	52			
Treatment Related AE Leading to IP Interruption	66			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of lenalidomide through 28 days after the last dose of lenalidomide; maximum duration of study drug was 1940 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide 10 mg or 25 mg oral capsules on days 1 to 21 of each 28-day cycle and was dependent on renal function; Participants with normal renal function (defined as creatinine clearance (CrCl)) of ≥ 60 mL/min) received 25 mg of lenalidomide by mouth (PO) daily, and those with moderate renal insufficiency (CrCl) ≥ 30 mL/min but < 60 mL/min) were started at a 10 mg daily dose. Participants could continue to receive treatment until disease progression, development of unacceptable adverse events (AEs), or voluntary withdrawal.

Serious adverse events	Lenalidomide		
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 134 (52.24%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	3 / 134 (2.24%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
MANTLE CELL LYMPHOMA			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	5 / 5		
MENINGIOMA			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
METASTATIC SQUAMOUS CELL CARCINOMA			

subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MYELODYSPLASTIC SYNDROME				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
SQUAMOUS CELL CARCINOMA OF SKIN				
subjects affected / exposed	6 / 134 (4.48%)			
occurrences causally related to treatment / all	1 / 18			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
DEEP VEIN THROMBOSIS				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
HYPOTENSION				
subjects affected / exposed	7 / 134 (5.22%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	2 / 2			
ORTHOSTATIC HYPOTENSION				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
ASTHENIA				
subjects affected / exposed	3 / 134 (2.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	1 / 1			
DEATH				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			

GENERAL PHYSICAL HEALTH DETERIORATION				
subjects affected / exposed	3 / 134 (2.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	2 / 2			
MUCOSAL INFLAMMATION				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	1 / 1			
NON-CARDIAC CHEST PAIN				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYREXIA				
subjects affected / exposed	6 / 134 (4.48%)			
occurrences causally related to treatment / all	4 / 8			
deaths causally related to treatment / all	1 / 1			
SUDDEN DEATH				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory, thoracic and mediastinal disorders				
CHRONIC OBSTRUCTIVE PULMONARY DISEASE				
subjects affected / exposed	3 / 134 (2.24%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
DYSPNOEA				
subjects affected / exposed	4 / 134 (2.99%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	1 / 1			
OBSTRUCTIVE AIRWAYS DISORDER				

subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PLEURAL EFFUSION				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
PNEUMONITIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY DISTRESS				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
RESPIRATORY FAILURE				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Investigations				
CREATININE RENAL CLEARANCE DECREASED				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
ANKLE FRACTURE				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

FALL			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BRADYCARDIA			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
HEADACHE			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MIGRAINE			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

TRANSIENT GLOBAL AMNESIA				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
ANAEMIA				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
FEBRILE NEUTROPENIA				
subjects affected / exposed	7 / 134 (5.22%)			
occurrences causally related to treatment / all	7 / 8			
deaths causally related to treatment / all	0 / 0			
LEUKOCYTOSIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	1 / 1			
LYMPH NODE PAIN				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LYMPHOCYTOSIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	1 / 1			
NEUTROPENIA				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
THROMBOCYTOPENIA				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				

ABDOMINAL PAIN				
subjects affected / exposed	4 / 134 (2.99%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
ASCITES				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CONSTIPATION				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
ENTERITIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FAECES DISCOLOURED				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTRIC HAEMORRHAGE				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL ISCHAEMIA				

subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	1 / 1			
INTRA-ABDOMINAL HAEMORRHAGE				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LOWER GASTROINTESTINAL HAEMORRHAGE				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
NAUSEA				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
PANCREATITIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
VOMITING				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
CHOLECYSTITIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
SKIN TOXICITY				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Renal and urinary disorders			
BLADDER NECK OBSTRUCTION			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HAEMATURIA			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RENAL FAILURE			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
URINARY RETENTION			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MUSCULAR WEAKNESS			
subjects affected / exposed	3 / 134 (2.24%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
NECK PAIN			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BACTERAEMIA			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
BACTERIAL SEPSIS			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHITIS			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
CELLULITIS			
subjects affected / exposed	3 / 134 (2.24%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

ENTEROCOCCAL SEPSIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	1 / 1			
ENTEROCOLITIS INFECTIOUS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
H1N1 INFLUENZA				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INFLUENZA				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LOBAR PNEUMONIA				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				
subjects affected / exposed	8 / 134 (5.97%)			
occurrences causally related to treatment / all	5 / 10			
deaths causally related to treatment / all	2 / 2			
PNEUMONIA BACTERIAL				
subjects affected / exposed	4 / 134 (2.99%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA KLEBSIELLA				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA STREPTOCOCCAL				

subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
PSEUDOMONAL SEPSIS				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SEPSIS				
subjects affected / exposed	3 / 134 (2.24%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	1 / 1			
SEPTIC SHOCK				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
STAPHYLOCOCCAL SEPSIS				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
STREPTOCOCCAL BACTERAEMIA				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
URINARY TRACT INFECTION				
subjects affected / exposed	3 / 134 (2.24%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
UROSEPSIS				

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	4 / 134 (2.99%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
FAILURE TO THRIVE			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
GOUT			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPERCALCAEMIA			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lenalidomide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 134 (93.28%)		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	9		
BLOOD CREATININE INCREASED			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	9		
WEIGHT DECREASED			

subjects affected / exposed	20 / 134 (14.93%)		
occurrences (all)	26		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR FLARE			
subjects affected / exposed	13 / 134 (9.70%)		
occurrences (all)	16		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	9		
DYSGEUSIA			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	9		
HEADACHE			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	9		
NEUROPATHY PERIPHERAL			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	42 / 134 (31.34%)		
occurrences (all)	84		
LEUKOPENIA			
subjects affected / exposed	22 / 134 (16.42%)		
occurrences (all)	60		
LYMPHOPENIA			
subjects affected / exposed	10 / 134 (7.46%)		
occurrences (all)	20		
NEUTROPENIA			
subjects affected / exposed	68 / 134 (50.75%)		
occurrences (all)	396		
THROMBOCYTOPENIA			
subjects affected / exposed	51 / 134 (38.06%)		
occurrences (all)	140		
General disorders and administration site conditions			

ASTHENIA			
subjects affected / exposed	18 / 134 (13.43%)		
occurrences (all)	22		
CHILLS			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	10		
FATIGUE			
subjects affected / exposed	47 / 134 (35.07%)		
occurrences (all)	85		
OEDEMA PERIPHERAL			
subjects affected / exposed	22 / 134 (16.42%)		
occurrences (all)	28		
PYREXIA			
subjects affected / exposed	30 / 134 (22.39%)		
occurrences (all)	54		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	10 / 134 (7.46%)		
occurrences (all)	18		
CONSTIPATION			
subjects affected / exposed	21 / 134 (15.67%)		
occurrences (all)	25		
DIARRHOEA			
subjects affected / exposed	45 / 134 (33.58%)		
occurrences (all)	107		
NAUSEA			
subjects affected / exposed	41 / 134 (30.60%)		
occurrences (all)	50		
VOMITING			
subjects affected / exposed	16 / 134 (11.94%)		
occurrences (all)	23		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	41 / 134 (30.60%)		
occurrences (all)	57		
DYSPHONIA			

subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all) PLEURAL EFFUSION subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 11 24 / 134 (17.91%) 35 14 / 134 (10.45%) 15 8 / 134 (5.97%) 9		
Skin and subcutaneous tissue disorders DRY SKIN subjects affected / exposed occurrences (all) NIGHT SWEATS subjects affected / exposed occurrences (all) PRURITUS subjects affected / exposed occurrences (all) RASH subjects affected / exposed occurrences (all)	 10 / 134 (7.46%) 10 8 / 134 (5.97%) 8 23 / 134 (17.16%) 33 30 / 134 (22.39%) 55		
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all) INSOMNIA subjects affected / exposed occurrences (all)	 11 / 134 (8.21%) 11 8 / 134 (5.97%) 10		
Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) BACK PAIN	 12 / 134 (8.96%) 13		

subjects affected / exposed	19 / 134 (14.18%)		
occurrences (all)	19		
MUSCLE SPASMS			
subjects affected / exposed	17 / 134 (12.69%)		
occurrences (all)	35		
PAIN IN EXTREMITY			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	11		
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	12		
PNEUMONIA			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	10		
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	13		
SINUSITIS			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	15		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	20 / 134 (14.93%)		
occurrences (all)	34		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	21 / 134 (15.67%)		
occurrences (all)	30		
DEHYDRATION			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	10		
HYPOCALCAEMIA			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	8		
HYPOKALAEMIA			

subjects affected / exposed occurrences (all)	19 / 134 (14.18%) 25		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2009	1. Clarified that the determination of tumor response and DOR was based on the 1999 IWRC. 2. Clarified that the evaluation of response using FDG-PET scans was based on the 2007 IWRC and that this was an exploratory evaluation. 3. Clarified that all exploratory objectives were optional for both sites and subjects. 4. Clarified that the requirement for collection of bone marrow biopsy/aspirate in cases of radiologic CR were to be obtained within 28 days from the scan confirming the CR. 5. Added language to further outline the medical management of TLS, including grading and treatment based on local standard of care with vigorous IV hydration and rasburicase. 6. Added guidance on the detection of TEEs. 7. Clarified Exclusion Criterion 6 that subjects who were candidates for high-dose chemotherapy/autologous or allogeneic transplant at the time of enrollment were not eligible unless other conditions were clearly documented (see Section 9.3.1). 8. Removed Exclusion Criterion 14, subjects with ≥ Grade 2 neuropathy. 9. Added dose modifications for subjects who developed Grade 3 peripheral neuropathy and for subjects who developed abnormal liver enzymes on study. 10. Clarified that the preferred method for assessment of tumor burden was conventional (or spiral) CT with contrast and that CT scans without contrast could be used but were not preferred. 11. Clarified that both target and non-target lesions were to be considered when assessing response and date of progression. 12. Clarified that radiographic assessments of tumor lesions were to be obtained every 56 days (± 7 days) from Cycle 1, Day 1. 13. Added language that subjects who discontinued from treatment who had not progressed were to be followed every 56 days (± 7 days) and that scans were required every 90 days (± 14 days) until PD or subsequent anti-lymphoma treatment.
12 March 2010	1. Based on a recommendation from a European Union competent authority, the section on VTEs was updated to clarify that the investigators should choose the most appropriate antithrombotic prophylaxis for each subject, taking into account the individual thrombotic risk (eg, history of venous thrombosis), bleeding risk, and the quality of compliance with antithrombotic treatment. 2. Shortened the steroid washout period from 4 weeks to 1 week and permitted treatment of exacerbated conditions with peak doses of steroids > 10 mg for a limited time. 3. Clarified Exclusion Criterion 3 for elevated serum total bilirubin and elevated AST or ALT. Subjects with serum total bilirubin > 1.5 x ULN were excluded, except in cases of Gilbert's syndrome or documented liver involvement by lymphoma. Subjects with ALT or AST > 3.0 x ULN were excluded, except those with documented liver involvement by lymphoma. 4. Dose modifications for subjects with abnormal liver function were clarified and aligned with the exclusion criterion regarding exceptions. 5. Added dose modifications for TFR and TLS. 6. Added an allowance for more than one dose reduction per cycle after consultation with the clinical research physician. 7. Changed the timing of study termination to occur after 70% of the subjects had died or a maximum of 4 years from enrollment of the last subject, whichever occurred first.

11 April 2011	1. Added the requirement that SPMs be treated as SAEs and reported from the time of informed consent up to and including study termination. 2. Clarified that tumor/lymph node biopsy specimens were to be sent to the central pathology laboratory for confirmation of MCL preferably before enrollment, but no later than 8 weeks after enrollment. 3. Added an allowance for bone marrow aspirates/biopsies to be used in rare situations when archival tumor tissue specimens were not available and re-biopsy was not possible or put the subject at risk. 4. Added an allowance for baseline radiographic scans to be conducted > 28 days prior to Cycle 1, Day 1 with prior clinical research physician approval to limit subject exposure to radiation. 5. Removed the requirement for collecting time of, and best response to, first anti-lymphoma treatment used after discontinuation from this study. 6. For sites in Germany, the following change was also included in Amendment 3.0 DE: Per the Health Authority, removed the requirement that the investigator obtain clinical research physician approval for a second dose reduction within a cycle.
05 August 2011	1. Based on a Health Authority request, added back in the requirement for collecting time of and best response to first anti-lymphoma treatment used after discontinuation from this study.
12 October 2011	1. Expanded Exclusion Criterion 10 to require subjects to be free of any other malignancies except for MCL for at least 5 years (from at least 3 years) prior to study entry. This resulted from multivariate analyses conducted by the sponsor that demonstrated that subjects with a history of prior invasive malignancies are at risk for developing another malignancy during lenalidomide-containing therapy. 2. Increased the follow-up time for subjects for the reporting of cases of SPM from 4 to 5 years after enrollment of the last subject.
16 July 2012	1. The timing of the treatment phase CT or MRI diagnostic imaging was modified to occur every 56 (± 7days) for the first 2 years and then every 4 months (± 2 weeks) until disease progression or start of a new anti-lymphoma therapy.
12 September 2013	1. Based on a postmarketing commitment issued by the FDA, the follow-up of all subjects, for both safety and efficacy, was to continue for 4 years from date the last subject enrolled, or until the time of 100% of subjects died, were lost to follow-up, or had withdrawn consent, whichever came first. 2. The follow-up time for subjects for the reporting of cases of SPM was updated to require 4 years of follow-up from date the last subject enrolled in order to concur with the 4-year follow-up of safety and efficacy.
16 May 2014	1. The SPM follow-up was extended from 4 to 5 years after last subject enrolled, until the time 100% of patients died, are lost to follow-up or have withdrawn consent, whichever comes first. (The efficacy follow-up was to remained unchanged at 4 years.)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported