



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 < 60 mL) | 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 ≥ 3 cm | 78 | 78 | |
| Low = < 5 cm 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 $\geq 50\%$ 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 progression 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 $\geq 50\%$ 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 $\geq 50\%$ 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 occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 134 (0.75%) 1 / 1 0 / 0 | | |
| BACTERAEMIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 134 (1.49%) 0 / 2 0 / 0 | | |
| BACTERIAL SEPSIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 134 (0.75%) 1 / 1 0 / 0 | | |
| BRONCHITIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 134 (0.75%) 1 / 1 0 / 0 | | |
| BRONCHOPNEUMONIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 134 (0.75%) 1 / 1 0 / 0 | | |
| BRONCHOPULMONARY ASPERGILLOSIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 134 (1.49%) 1 / 2 0 / 0 | | |
| CELLULITIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 3 / 134 (2.24%) 0 / 3 0 / 0 | | |
| CLOSTRIDIUM DIFFICILE COLITIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 134 (1.49%) 1 / 2 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 occurrences (all) | 20 / 134 (14.93%) 26 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) TUMOUR FLARE subjects affected / exposed occurrences (all) | 13 / 134 (9.70%) 16 | | |
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) DYSGEUSIA subjects affected / exposed occurrences (all) HEADACHE subjects affected / exposed occurrences (all) NEUROPATHY PERIPHERAL subjects affected / exposed occurrences (all) | 7 / 134 (5.22%) 9 8 / 134 (5.97%) 9 8 / 134 (5.97%) 9 9 / 134 (6.72%) 13 | | |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) LEUKOPENIA subjects affected / exposed occurrences (all) LYMPHOPENIA subjects affected / exposed occurrences (all) NEUTROPENIA subjects affected / exposed occurrences (all) THROMBOCYTOPENIA subjects affected / exposed occurrences (all) | 42 / 134 (31.34%) 84 22 / 134 (16.42%) 60 10 / 134 (7.46%) 20 68 / 134 (50.75%) 396 51 / 134 (38.06%) 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 | | | |

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 19 March 2009 | <p>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 \geq 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 (\pm 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 (\pm 7 days) and that scans were required every 90 days (\pm 14 days) until PD or subsequent anti-lymphoma treatment.</p> |
| 12 March 2010 | <p>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 $> 1.5 \times$ ULN were excluded, except in cases of Gilbert's syndrome or documented liver involvement by lymphoma. Subjects with ALT or AST $> 3.0 \times$ 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.</p> |

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|-------------------|---|
| 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 (\pm 7days) for the first 2 years and then every 4 months (\pm 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 remain unchanged at 4 years.) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported