# Clinical trial results:
# An Open-Label, Phase 2 Study to Evaluate the Oral Combination of MLN9708 With Cyclophosphamide and Dexamethasone In Patients With Newly Diagnosed or Relapsed and/or Refractory Multiple Myeloma Requiring Systemic Treatment

## Summary

| | |
|---|---|
| EudraCT number | 2013-003113-17 |
| Trial protocol | SE GR PL |
| Global end of trial date | 29 June 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 July 2019 |
| First version publication date | 10 July 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | C16020 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02046070 |
| WHO universal trial number (UTN) | U1111-1158-2714 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited |
| Sponsor organisation address | 40 Landsdowne Street, Cambridge, United States, MA 02139 |
| Public contact | Medical Director, Clinical Science, Takeda Oncology, +1 877-825-3327, clinicaltrialregistry@tpna.com |
| Scientific contact | Medical Director, Clinical Science, Takeda Oncology, +1 877-825-3327, clinicaltrialregistry@tpna.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 | 29 June 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 29 June 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

This is a phase 2, multicenter, open-label study in patients with Newly Diagnosed Multiple Myeloma (NDMM) who have not received prior systemic treatment for multiple myeloma (MM) and who are ineligible for high-dose therapy (HDT)-stem cell transplantation (SCT) due to age (ie, ≥ 65 years) or comorbid disease(s) or with Relapsed and/or Refractory Multiple Myeloma (RRMM).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 March 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 45 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 16 |
| Country: Number of subjects enrolled | Greece: 52 |
| Country: Number of subjects enrolled | Poland: 47 |
| Country: Number of subjects enrolled | Sweden: 20 |
| Country: Number of subjects enrolled | United States: 13 |
| Worldwide total number of subjects | 148 |
| EEA total number of subjects | 119 |

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) | 43 |
| From 65 to 84 years | 102 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 23 investigative sites in Australia, Greece, Poland, Sweden and the United States from 05 March 2014 to 29 June 2018.

### Pre-assignment

Screening details:

Participants with NDMM were enrolled in 1 of 2 arms to receive 4.0 mg ixazomib in combination with 300 or 400 mg cyclophosphamide and 40 mg dexamethasone (CCd); participants with RRMM were enrolled in 1 arm to receive ixazomib 4.0 mg CCd. All arms included a safety lead-in cohort for pharmacokinetics (PK) analysis.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) |

Arm description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cyclophosphamide tablets.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dexamethasone tablets.

| | |
|---|---|
| Investigational medicinal product name | Ixazomib |
| Investigational medicinal product code | |
| Other name | MLN9708 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Ixazomib capsules.

| | |
|---|---|
| **Arm title** | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) |

Arm description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cyclophosphamide tablets.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dexamethasone tablets.

| | |
|---|---|
| Investigational medicinal product name | Ixazomib |
| Investigational medicinal product code | |
| Other name | MLN9708 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Ixazomib capsules.

| | |
|---|---|
| **Arm title** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |

Arm description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Cyclophosphamide tablets.

| | |
|---|---|
| Investigational medicinal product name | Ixazomib |
| Investigational medicinal product code | |
| Other name | MLN9708 |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Ixazomib capsules.

| | |
|---|---|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |

| Routes of administration | Oral use |
|---|---|

Dosage and administration details:

Dexamethasone tablets.

| **Number of subjects in period 1** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |
|---|---|---|---|
| Started | 36 | 34 | 78 |
| Completed | 4 | 6 | 8 |
| Not completed | 32 | 28 | 70 |
| Consent withdrawn by subject | 1 | 2 | 6 |
| Adverse event, non-fatal | 8 | 10 | 17 |
| Progressive Disease | 18 | 11 | 40 |
| Study Terminated by Sponsor | 1 | 1 | 1 |
| Reason not Specified | 4 | 4 | 6 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) |
| Reporting group description: | |
| Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM. | |
| Reporting group title | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) |
| Reporting group description: | |
| Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM. | |
| Reporting group title | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |
| Reporting group description: | |
| Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM. | |

| Reporting group values | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |
|---|---|---|---|
| Number of subjects | 36 | 34 | 78 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 0 | 2 | 41 |
| From 65-84 years | 34 | 32 | 36 |
| 85 years and over | 2 | 0 | 1 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 73.4 | 74.1 | 63.5 |
| standard deviation | ± 5.48 | ± 5.80 | ± 9.85 |
| Sex: Female, Male<br>Units: Subjects | | | |
| Female | 21 | 16 | 37 |
| Male | 15 | 18 | 41 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 0 |
| Not Hispanic or Latino | 35 | 33 | 75 |
| Unknown or Not Reported | 0 | 1 | 3 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 35 | 34 | 74 |
| Other | 1 | 0 | 2 |
| Asian | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Black or African American | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Height | | | |
| Units: centimeters (cm) | | | |
| arithmetic mean | 163.5 | 163.5 | 165.9 |
| standard deviation | ± 11.35 | ± 12.47 | ± 10.47 |
| Weight | | | |
| Units: kilograms (kg) | | | |
| arithmetic mean | 73.6 | 73.0 | 78.1 |
| standard deviation | ± 11.8 | ± 17.54 | ± 16.80 |
| Body Surface Area (BSA) | | | |
| BSA = square root (height(cm) x weight (kg) / 3600. | | | |
| Units: meters squared (m^2) | | | |
| arithmetic mean | 1.8 | 1.8 | 1.9 |
| standard deviation | ± 0.17 | ± 0.26 | ± 0.23 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 148 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 43 | | |
| From 65-84 years | 102 | | |
| 85 years and over | 3 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 74 | | |
| Male | 74 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | | |
| Not Hispanic or Latino | 143 | | |
| Unknown or Not Reported | 4 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| White | 143 | | |
| Other | 3 | | |
| Asian | 1 | | |
| Black or African American | 1 | | |
| Height | | | |
| Units: centimeters (cm) | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Weight | | | |
| Units: kilograms (kg) | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

| | | | |
|---|---|---|---|
| Body Surface Area (BSA) | | | |
| BSA = square root (height(cm) x weight (kg) / 3600. | | | |
| Units: meters squared (m^2)<br>arithmetic mean<br>standard deviation | -<br> | | |

## End points

### End points reporting groups

| Reporting group title | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) |
|---|---|

Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

| Reporting group title | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) |
|---|---|

Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

| Reporting group title | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |
|---|---|

Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM.

### Primary: Combined Response Rate during the Induction Phase in Newly Diagnosed Multiple Myeloma (NDMM) Participants

| End point title | Combined Response Rate during the Induction Phase in Newly Diagnosed Multiple Myeloma (NDMM) Participants[1][2] |
|---|---|

End point description:

Combined Response Rate is the percentage of participants with Complete Response (CR), including stringent Complete Response (sCR), and Very Good Partial Response (VGPR) according to the International Myeloma Working Group (IMWG) criteria during the Induction Phase (Cycles 1-13, 28-day cycles). CR=negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow. VGPR=serum and urine M-component detectable by immunofixation but not on electrophoresis or 90% reduction in serum M-component plus urine M-component <100 mg/24 hour. Response Evaluable Population was defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment.

| End point type | Primary |
|---|---|

End point timeframe:

Day 1 of Cycles 1-13, 28-day cycles (Up to 1 year)

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: No statistical analyses are reported for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| End point values | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 34 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 27 (13 to 46) | 24 (11 to 41) | | |

### Statistical analyses

No statistical analyses for this end point

## Primary: Overall Response Rate (ORR) in Relapsed and/or Refractory Multiple Myeloma (RRMM) Participants

| End point title | Overall Response Rate (ORR) in Relapsed and/or Refractory Multiple Myeloma (RRMM) Participants[3][4] |
|---|---|

End point description:

ORR is the percentage of participants with CR, VGPR or PR according to IMWG criteria. CR=negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas and <5% plasma cells (PC) in bone marrow. VGPR=serum and urine M-component detectable by immunofixation but not on electrophoresis or 90% reduction in serum M-component plus urine M-component <100 mg/24 hour. PR=50% reduction of serum M-protein and reduction in 24 hour urine M-protein by 90% or <200 mg/24 hour or decrease 50% difference between involved free light chain (FLC) levels or 50% reduction in bone marrow plasma cells if baseline percentage was 30%; and if present at Baseline, 50% reduction in the size of soft tissue plasmacytomas. Response Evaluable Population was defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment.

| End point type | Primary |
|---|---|

End point timeframe:

Day 1 of each 28 day cycle (Up to 45 months)

Notes:

[3] - 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: No statistical analyses are reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| End point values | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 73 | | | |
| Units: percentage of participants | | | | |
| arithmetic mean (confidence interval 95%) | 49 (37 to 61) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adverse Events (AEs), Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction and Serious Adverse Events (SAEs) in NDMM Participants

| End point title | Number of Participants with Adverse Events (AEs), Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction and Serious Adverse Events (SAEs) in NDMM Participants[5] |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of each AE to study drug was determined by the Investigator. Safety Population was defined as all participants who receive at least 1 dose of any study drug.

| End point type | Secondary |
|---|---|

End point timeframe:

First dose of study drug through 30 days after last dose of drug (Up to 45 months)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: participants | | | | |
| Any AE | 35 | 34 | | |
| Grade 3 or Higher AEs | 27 | 27 | | |
| AEs Resulting in Treatment Discontinuation | 9 | 11 | | |
| AEs Resulting in Dose Reduction | 11 | 10 | | |
| SAEs | 17 | 20 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with CR + VGPR + PR (ORR), CR, VGPR, PR and Stable Disease (SD), Progressive Disease (PD) during the Induction Phase

| End point title | Percentage of Participants with CR + VGPR + PR (ORR), CR, VGPR, PR and Stable Disease (SD), Progressive Disease (PD) during the Induction Phase[6] |
|---|---|

End point description:

Percentage of participants with CR+VGPR+PR(ORR),CR,VGPR,PR,SD,PD (IMWG criteria). CR=negative immunofixation of serum+urine; disappearance of soft tissue plasmacytomas;<5%PC in bone marrow. VGPR=serum+urine M-component by immunofixation but not on electrophoresis or 90% reduction in

serum +urine M-component <100mg/24hr. PR=50% serum M-protein and 24hr urine M-protein reduction by 90% or <200mg/24hr or decrease 50% difference in FLC levels or 50% reduction in bone marrow plasma cells if baseline=30%; and if present at Baseline, 50% reduction in size of soft tissue plasmacytomas. SD=not meeting criteria for VGPR,PR or PD. PD=25% increase in lowest value of: serum+urine M-component, difference in involved+uninvolved FLC levels, bone marrow PC%; new or increased size of existing bone lesions or soft tissue plasmacytomas. Response Evaluable Population: participants received 2 of 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and 1 postbaseline response assessment.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 of Cycles 1-13, 28-day cycles (Up to 1 year)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 34 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| CR + VGPR + PR | 79 (61 to 91) | 71 (53 to 85) | | |
| CR | 12 (3 to 28) | 9 (2 to 24) | | |
| VGPR | 15 (5 to 32) | 15 (5 to 31) | | |
| PR | 67 (48 to 82) | 62 (44 to 78) | | |
| SD | 12 (3 to 28) | 18 (7 to 35) | | |
| PD | 0 (0 to 0) | 3 (1 to 15) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with CR + VGPR + PR (ORR), CR + VGPR, CR, VGPR, PR, SD and PD Throughout the Entire Treatment Period in NDMM Participants

| End point title | Percentage of Participants with CR + VGPR + PR (ORR), CR + VGPR, CR, VGPR, PR, SD and PD Throughout the Entire Treatment Period in NDMM Participants[7] |
|---|---|

End point description:

Percentage of participants with CR+VGPR+PR(ORR),CR,VGPR,PR,SD,PD (IMWG criteria). CR=negative immunofixation of serum+urine; disappearance of soft tissue plasmacytomas;<5%PC in bone marrow. VGPR=serum+urine M-component by immunofixation but not on electrophoresis or 90% reduction in serum +urine M-component <100mg/24hr. PR=50% serum M-protein and 24hr urine M-protein reduction by 90% or <200mg/24hr or decrease 50% difference in FLC levels or 50% reduction in bone marrow plasma cells if baseline=30%; and if present at Baseline, 50% reduction in size of soft tissue plasmacytomas. SD=not meeting criteria for VGPR,PR or PD. PD=25% increase in lowest value of: serum+urine M-component, difference in involved+uninvolved FLC levels, bone marrow PC%; new or increased size of existing bone lesions or soft tissue plasmacytomas. Response Evaluable Population: participants received 2 of 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and 1 postbaseline response assessment.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 of each 28-day Cycle (Up to 45 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 34 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| CR + VGPR + PR | 82 (65 to 93) | 71 (53 to 85) | | |
| CR + VGPR | 36 (20 to 55) | 32 (17 to 51) | | |
| CR | 15 (5 to 32) | 12 (3 to 27) | | |
| VGPR | 21 (9 to 39) | 21 (9 to 38) | | |
| PR | 67 (48 to 82) | 59 (41 to 75) | | |
| SD | 18 (7 to 35) | 18 (7 to 35) | | |
| PD | 0 (0 to 0) | 6 (1 to 20) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response (TTR) in NDMM Participants during the Induction Phase

| End point title | Time to Response (TTR) in NDMM Participants during the Induction Phase[8] |
|---|---|

End point description:

TTR is defined as the time interval from the date of the first dose of study treatment to the date of the first documented confirmed response of PR or better up to the initiation of alternative therapy in a participant who responded. Participants from the Response Evaluable Population, defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment, who responded.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 1 year

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 23 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.2 (0.95 to 2.92) | 1.9 (0.95 to 1.9) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR) in NDMM Participants

| End point title | Duration of Response (DOR) in NDMM Participants[9] |
|---|---|

End point description:

DOR is defined as the time from the date of first documentation of a confirmed PR or better to the date of first documented PD up to the initiation of alternative therapy. Participants from the Response Evaluable Population, participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and at least 1 postbaseline response assessment, who responded. Responders without PD were censored at the date of SD or better prior to the date of alternative therapy. 99999 indicates 95% Confidence Interval (CI) Upper Limit was not estimable due to the low number of participants with events.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 45 Months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| End point values | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 23 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 32.2 (18.66 to 99999) | 36.6 (19.75 to 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Progression (TTP) in NDMM Participants

| End point title | Time to Progression (TTP) in NDMM Participants[10] |
|---|---|

End point description:

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of disease progression. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD were censored at the date of last response assessment that is SD or better prior to the date of the alternative therapy. 99999 indicates 95% CI Upper Limit was not estimable due to the low number of participants with events.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 45 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 30.9 (19.58 to 41.66) | 32.2 (20.27 to 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS) in NDMM Participants

| End point title | Progression Free Survival (PFS) in NDMM Participants[11] |
|---|---|

End point description:

PFS is defined as the time from the date of first dose of study treatment to the date of the first documented disease progression or death. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD or death were censored at the date of last response assessment that is SD or better prior to the date of the alternative therapy. 99999 indicates 95% CI Upper Limit was not estimable due to the low number of participants with events.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 45 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 | 34 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 23.5 (15.67 to 39.59) | 23.0 (15.90 to 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with AEs, SAEs, AEs Resulting in Discontinuation and AEs Resulting in Dose Reduction in NDMM Participants Remaining on Treatment after 13 Cycles

| End point title | Number of Participants with AEs, SAEs, AEs Resulting in Discontinuation and AEs Resulting in Dose Reduction in NDMM Participants Remaining on Treatment after 13 Cycles[12] |
|---|---|

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of each AE to study drug was determined by the Investigator. Safety Population was defined as all participants who receive at least 1 dose of any study drug. Number of participants analyzed is the number of participants who remained on treatment after 13 cycles.

| End point type | Secondary |
|---|---|

End point timeframe:

First dose of study drug through 30 days after the last dose of drug (Up to 45 months)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 22 | | |
| Units: participants | | | | |
| Any AE | 22 | 20 | | |
| SAE | 6 | 4 | | |
| AEs Resulting in Treatment Discontinuation | 1 | 2 | | |
| AEs Resulting in Dose Reduction | 5 | 4 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) during the Induction Phase in NDMM Participants

| End point title | Change from Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) during the Induction Phase in NDMM Participants[13] |
|---|---|

End point description:

EORTC QLQ-C30 is a 30 item questionnaire that consists of 5 functional scales(physical, role, emotional,

cognitive, and social functioning), 1 global health status scale, 3 symptom scales(fatigue, nausea and vomiting, and pain), 6 single items(dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Patient evaluates their health status over previous week. 28 questions answered on a 4-point scale where:1=Not at all(best) to 4=Very Much(worst), 2 questions answered on 7-point scale where 1=Very poor(worst) to 7=Excellent(best). All scales and single-item measures transformed to score:0-100. For functioning scales and global QOL higher scores indicate better functioning (a positive change from Baseline indicates improvement); for symptom scales higher scores indicate more severe symptoms (a negative change from Baseline indicates improvement). Safety Population:participants who received at least 1 dose of any study drug, with data available for analysis.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (BL) (Day 1 of Cycle 1), Day 1 of Cycle 13 (Up to 1 year)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 23 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Global Health Status/QoL, Change from BL; Cycle 13 | 3.47 (± 30.783) | -5.43 (± 24.180) | | |
| Physical functioning, Change from BL at Cycle 13 | 14.17 (± 35.675) | 17.97 (± 20.640) | | |
| Role functioning, Change from BL at Cycle 13 | 8.33 (± 43.127) | 6.52 (± 35.441) | | |
| Emotional functioning, Change from BL at Cycle 13 | 11.34 (± 27.837) | 2.54 (± 15.977) | | |
| Cognitive functioning, Change from BL at Cycle 13 | 2.78 (± 22.877) | -7.25 (± 14.058) | | |
| Social functioning, Change from BL at Cycle 13 | 9.03 (± 39.921) | -11.59 (± 29.914) | | |
| Fatigue, Change from BL at Cycle 13 | -10.88 (± 35.307) | -6.76 (± 30.473) | | |
| Nausea/Vomiting, Change from BL at Cycle 13 | -4.86 (± 26.228) | -4.35 (± 19.603) | | |
| Pain, Change from BL at Cycle 13 | -13.89 (± 52.628) | -10.87 (± 39.443) | | |
| Dyspnea, Change from BL at Cycle 13 | -11.11 (± 37.644) | -7.25 (± 40.147) | | |
| Insomnia, Change from BL at Cycle 13 | -16.67 (± 46.104) | -10.14 (± 35.441) | | |
| Appetite Loss, Change from BL at Cycle 13 | -18.06 (± 42.822) | -7.25 (± 24.529) | | |
| Constipation, Change from BL at Cycle 13 | -13.89 (± 39.215) | -5.80 (± 41.013) | | |
| Diarrhea, Change from BL at Cycle 13 | -2.78 (± 30.954) | 5.80 (± 19.207) | | |
| Financial Difficulties, Change from BL at Cycle 13 | 4.17 (± 26.580) | 1.45 (± 30.942) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with CR + VGR + PR (ORR), CR, VGPR, and PR in NDMM Participants Remaining on Treatment after 13 Cycles

| End point title | Percentage of Participants with CR + VGR + PR (ORR), CR, VGPR, and PR in NDMM Participants Remaining on Treatment after 13 Cycles[14] |
|---|---|

End point description:

Percentage of participants with Overall Response (CR + VGPR + PR), CR, VGPR and PR according to IMWG criteria. CR=negative immunofixation of serum and urine; disappearance of soft tissue plasmacytomas;<5% PC in bone marrow. VGPR=serum and urine M-component detectable by immunofixation but not on electrophoresis or 90% reduction in serum M-component plus urine M-component <100 mg/24 hour. PR=50% reduction of serum M-protein and reduction in 24 hour urine M-protein by 90% or <200 mg/24 hour or decrease 50% difference between involved FLC levels or 50% reduction in bone marrow plasma cells if baseline percentage was 30%; and if present at Baseline, 50% reduction in the size of soft tissue plasmacytomas. Participants from the Response Evaluable Population, participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and at least 1 postbaseline response assessment, with both an Induction and Maintenance response.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 of each 28-day Cycle (Up to 45 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 21 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| CR + VGPR + PR | 75.0 | 85.7 | | |
| CR | 16.7 | 19.0 | | |
| VGPR | 20.8 | 28.6 | | |
| PR | 37.5 | 38.1 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax: Maximum Observed Plasma Concentration for Ixazomib in NDMM Participants

| End point title | Cmax: Maximum Observed Plasma Concentration for Ixazomib in NDMM Participants[15] |
|---|---|

End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: nanogram/mL (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n=6,6) | 64.283 (± 36.283) | 46.600 (± 34.7722) | | |
| Cycle 1 Day 15 (n=6,5) | 53.145 (± 46.3782) | 62.280 (± 39.4249) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Tmax: Time to First Occurrence of Cmax for Ixazomib in NDMM Participants

| End point title | Tmax: Time to First Occurrence of Cmax for Ixazomib in NDMM Participants[16] |
|---|---|

End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: hour (hr) | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n=6,6) | 1.250 (0.92 to 1.58) | 1.040 (0.50 to 2.00) | | |

| | | | | |
|---|---|---|---|---|
| Cycle 1 Day 15 (n=6,5) | 1.000 (0.45 to 4.00) | 1.000 (0.50 to 1.50) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in NDMM Participants

| End point title | AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in NDMM Participants[17] |
|---|---|

End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the NDMM arms.

| End point values | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 | 6 | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n=6,5) | 885.167 (± 354.1465) | 792.600 (± 650.5665) | | |
| Cycle 1 Day 15 (n=6,5) | 1338.333 (± 746.2902) | 1226.600 (± 527.5792) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with AEs, Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction, SAEs in RRMM Participants

| End point title | Number of Participants with AEs, Grade 3 or Higher AEs, AEs Resulting in Treatment Discontinuation, AEs Resulting in Dose Reduction, SAEs in RRMM Participants[18] |
|---|---|

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical

product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. A SAE is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. Relationship of each AE to study drug was determined by the Investigator. Safety population was defined as all participants who received at least 1 dose of any study drug.

| End point type | Secondary |
|---|---|

End point timeframe:

First dose of study drug through 30 days after last dose of drug (Up to 45 months)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 78 | | | |
| Units: participants | | | | |
| Any AE | 72 | | | |
| Grade 3 or Higher AE | 49 | | | |
| AEs Resulting in Treatment Discontinuation | 19 | | | |
| AEs Resulting in Dose Reduction | 30 | | | |
| SAEs | 30 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax: Maximum Observed Plasma Concentration for Ixazomib in RRMM Participants

| End point title | Cmax: Maximum Observed Plasma Concentration for Ixazomib in RRMM Participants[19] |
|---|---|

End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| End point values | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n=6)<br>Cycle 1 Day 15 (n=7) | 47.400 (± 36.7083)<br>52.229 (± 39.6006) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Tmax: Time to First Occurrence of Cmax for Ixazomib in RRMM Participants

| End point title | Tmax: Time to First Occurrence of Cmax for Ixazomib in RRMM Participants[20] |
|---|---|

End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168) hours postdose

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| End point values | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: hr | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1 Day 1 (n=6)<br>Cycle 1 Day 15 (n=7) | 1.225 (0.50 to 3.42)<br>2.000 (0.50 to 8.00) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in RRMM Participants

| End point title | AUCtau: Area Under the Concentration-time Curve during a Dosing Interval for Ixazomib in RRMM Participants[21] |
|---|---|

End point description:

PK-Evaluable Population was defined as participants in the safety lead-in cohort who have sufficient dosing data and ixazomib concentration-time data to permit calculation of PK parameters. Number analyzed is the number of participants with data available for analysis at the given time-point.

| End point type | Secondary |
|---|---|

End point timeframe:

Cycle 1 Days 1 and 15 predose and at multiple timepoints (up to 168 hours) postdose

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1 Day 1 (n=6) | 518.167 (± 78.8274) | | | |
| Cycle 1 Day 15 (n=7) | 1241.000 (± 657.4978) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with (CR + VGPR), CR, VGPR, PR, SD and PD in RRMM Participants

| End point title | Percentage of Participants with (CR + VGPR), CR, VGPR, PR, SD and PD in RRMM Participants[22] |
|---|---|

End point description:

Percentage of participants with CR+VGPR+PR(ORR),CR,VGPR,PR,SD,PD (IMWG criteria). CR=negative immunofixation of serum+urine; disappearance of soft tissue plasmacytomas;<5%PC in bone marrow. VGPR=serum+urine M-component by immunofixation but not on electrophoresis or 90% reduction in serum +urine M-component <100mg/24hr. PR=50% serum M-protein and 24hr urine M-protein reduction by 90% or <200mg/24hr or decrease 50% difference in FLC levels or 50% reduction in bone marrow plasma cells if baseline=30%; and if present at Baseline, 50% reduction in size of soft tissue plasmacytomas. SD=not meeting criteria for VGPR,PR or PD. PD=25% increase in lowest value of: serum+urine M-component, difference in involved+uninvolved FLC levels, bone marrow PC%; new or increased size of existing bone lesions or soft tissue plasmacytomas. Response Evaluable Population: participants received 2 of 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and 1 postbaseline response assessment.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 of each 28-day Cycle (Up to 45 months)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 73 | | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| CR + VGPR | 19 (11 to 30) | | | |
| CR | 5 (2 to 13) | | | |
| VGPR | 14 (7 to 24) | | | |
| PR | 44 (32 to 56) | | | |
| SD | 37 (26 to 49) | | | |
| PD | 10 (4 to 19) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response (TTR) in RRMM Participants

| End point title | Time to Response (TTR) in RRMM Participants[23] |
|---|---|

End point description:

TTR is defined as the time interval from the date of the first dose of study treatment to the date of the first documented confirmed response of PR or better up to the alternative therapy in a participant who responded. Participants from the Response Evaluable Population, defined as participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline, and at least 1 postbaseline response assessment, who responded.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 45 months

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.1 (0.95 to | | | |

| 3.12) |
|---|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DOR) in RRMM Participants

| End point title | Duration of Response (DOR) in RRMM Participants[24] |
|---|---|

End point description:

DOR is defined as the time from the date of first documentation of a confirmed PR or better to the date of first documented PD up to the alternative therapy. Participants from the Response Evaluable Population, participants who received at least 2 of the 3 ixazomib doses during Cycle 1, had measurable disease at Baseline and at least 1 postbaseline response assessment, who responded. Responders without PD were censored at the date of SD or better prior to the date of the alternative therapy. 99999 indicates 95% CI Upper Limit was not estimable due to the low number of participants with events.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 45 months

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 26.3 (12.22 to 99999) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Progression (TTP) in RRMM Participants

| End point title | Time to Progression (TTP) in RRMM Participants[25] |
|---|---|

End point description:

TTP is defined as the time from the date of first dose of study treatment to the date of first documentation of disease progression. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD were censored at the date of last response assessment that is SD or better prior to the date of the alternative therapy.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 45 months

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 78 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 16.8 (11.30 to 24.67) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression Free Survival (PFS) in RRMM Participants

| End point title | Progression Free Survival (PFS) in RRMM Participants[26] |
|---|---|

End point description:

PFS is defined as the time from the date of first dose of study treatment to the date of the first documented disease progression or death. Safety Population was defined as all participants who received at least 1 dose of any study drug. Participants without documentation of PD or death were censored at the date of last response assessment that was SD or better prior to the date of the alternative therapy.

| End point type | Secondary |
|---|---|

End point timeframe:

Up to 45 months

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 78 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 14.2 (9.69 to 20.57) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in EORTC Quality of Life Questionnaire (QLQ-C30) in RRMM Participants

| End point title | Change from Baseline in EORTC Quality of Life Questionnaire (QLQ-C30) in RRMM Participants[27] |
|---|---|

End point description:

EORTC QLQ-C30 is a 30 item questionnaire that consists of 5 functional scales(physical, role, emotional, cognitive, and social functioning), 1 global health status scale, 3 symptom scales(fatigue, nausea and vomiting, and pain), 6 single items(dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Patient evaluates their health status over previous week. 28 questions answered on 4-point scale where:1=Not at all(best) to 4=Very Much(worst), 2 questions answered on 7-point scale where 1=Very poor(worst) to 7=Excellent(best). All scales and single-item measures transformed to score:0-100. For functioning scales and global QOL higher scores indicate better functioning (a positive change from Baseline indicates improvement); for symptom scales higher scores indicate more severe symptoms (a negative change from Baseline indicates improvement). Safety Population: participants who received at least 1 dose of any study drug, with data available for analysis.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1 of Cycle 1), Day 1 of End of Treatment (EOT) (Up to 45 months)

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable to the RRMM arm.

| **End point values** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 | | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Global Health Status/QoL, Change from BL at EOT | -5.50 (± 20.798) | | | |
| Physical functioning, Change from BL at EOT | -6.00 (± 19.806) | | | |
| Role functioning, Change from BL at EOT | -7.67 (± 30.344) | | | |
| Emotional functioning, Change from BL at EOT | -5.00 (± 23.023) | | | |
| Cognitive functioning, Change from BL at EOT | -5.33 (± 19.760) | | | |
| Social functioning, Change from BL at EOT | -11.33 (± 26.177) | | | |
| Fatigue, Change from BL at EOT | 5.11 (± 22.695) | | | |
| Nausea/Vomiting, Change from BL at EOT | 3.33 (± 14.677) | | | |
| Pain, Change from BL at EOT | 5.00 (± 28.621) | | | |
| Dyspnea, Change from BL at EOT | 10.00 (± 27.970) | | | |
| Insomnia, Change from BL at EOT | -6.00 (± 27.512) | | | |
| Appetite Loss, Change from BL at EOT | 4.67 (± 24.290) | | | |

| | | | | |
|---|---|---|---|---|
| Constipation, Change from BL at EOT | 2.00 (± 18.332) | | | |
| Diarrhea, Change from BL at EOT | 6.00 (± 19.852) | | | |
| Financial Difficulties, Change from BL at EOT | 4.00 (± 20.909) | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose of study drug through 30 days after last dose of drug (Up to 45 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) |

Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until progressive disease (PD)/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

| | |
|---|---|
| Reporting group title | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) |

Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle until PD/death or unacceptable toxicity [13 cycles in the Induction Phase continuing in the Maintenance Phase for up to 36 Months] and cyclophosphamide (CYC) 400 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle for 13 cycles or until PD/death or unacceptable toxicity in participants with NDMM.

| | |
|---|---|
| Reporting group title | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |

Reporting group description:

Ixazomib 4.0 mg, capsules, orally, on Days 1, 8, 15 of a 28-day cycle and cyclophosphamide (CYC) 300 mg/m^2, tablets, orally, on Days 1, 8 and 15 of a 28-day cycle and dexamethasone (DEX) 40 mg, tablets, orally, on Days 1, 8, 15 and 22 (dose reduced to 20 mg for patients >75 years) of a 28-day cycle until PD/death or unacceptable toxicity in participants with RRMM.

| Serious adverse events | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 17 / 36 (47.22%) | 20 / 34 (58.82%) | 30 / 78 (38.46%) |
| number of deaths (all causes) | 3 | 2 | 5 |
| number of deaths resulting from adverse events | 0 | 0 | 2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Benign bone neoplasm | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain neoplasm benign | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophageal carcinoma | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration | | | |

| | | | |
|---|---|---|---|
| site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary oedema | Additional description: 1 TE death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM), 1 with Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) and 1 with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) and all 3 are not related. | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) and is not related. | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Light chain analysis increased | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|---|---|---|
| Femur fracture | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 1 / 34 (2.94%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | Additional description: One treatment-emergent (TE) death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) and | | |

| | | | |
|---|---|---|---|
| | is not related. | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Nervous system disorders | | | |
| Cerebral haemorrhage | Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) and is related. | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Haemorrhage intracranial | Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) and is not related. | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Syncope | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper gastrointestinal haemorrhage | Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) and is not related. | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal ulcer | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Skin and subcutaneous tissue disorders** | | | |
| Pemphigus | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash macular | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Renal and urinary disorders** | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Bone pain | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteolysis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) and is not related. | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 2 / 34 (5.88%) | 3 / 78 (3.85%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 3 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 2 / 78 (2.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Localised infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomembranous colitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonal sepsis | Additional description: One treatment-emergent death occurred during treatment with Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) and is related. | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 400 mg/m^2 + DEX 40 mg (NDMM) | Ixazomib 4.0 mg + CYC 300 mg/m^2 + DEX 40 mg (RRMM) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 36 (94.44%) | 34 / 34 (100.00%) | 69 / 78 (88.46%) |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 36 (5.56%) | 7 / 34 (20.59%) | 2 / 78 (2.56%) |
| occurrences (all) | 2 | 8 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 34 (5.88%) | 2 / 78 (2.56%) |
| occurrences (all) | 1 | 2 | 2 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 8 / 36 (22.22%) | 7 / 34 (20.59%) | 15 / 78 (19.23%) |
| occurrences (all) | 10 | 10 | 22 |
| Oedema peripheral | | | |
| subjects affected / exposed | 8 / 36 (22.22%) | 9 / 34 (26.47%) | 5 / 78 (6.41%) |
| occurrences (all) | 9 | 11 | 12 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 6 / 34 (17.65%) | 4 / 78 (5.13%) |
| occurrences (all) | 6 | 16 | 5 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 1 | 1 | 5 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 1 | 1 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 4 / 34 (11.76%) | 7 / 78 (8.97%) |
| occurrences (all) | 4 | 5 | 7 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 6 / 78 (7.69%) |
| occurrences (all) | 2 | 0 | 7 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 34 (8.82%) | 10 / 78 (12.82%) |
| occurrences (all) | 1 | 3 | 16 |
| Anxiety | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 34 (5.88%) | 0 / 78 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Confusional state | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 3 | 1 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 3 / 34 (8.82%) | 1 / 78 (1.28%) |
| occurrences (all) | 4 | 3 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 2 / 34 (5.88%) | 0 / 78 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 34 (5.88%) | 2 / 78 (2.56%) |
| occurrences (all) | 1 | 2 | 2 |
| Fall | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 34 (5.88%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 2 | 1 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 34 (8.82%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 5 | 1 |
| Nervous system disorders | | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 10 / 34 (29.41%) | 10 / 78 (12.82%) |
| occurrences (all) | 7 | 17 | 17 |
| Dizziness | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 2 / 34 (5.88%) | 7 / 78 (8.97%) |
| occurrences (all) | 3 | 3 | 9 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 3 / 34 (8.82%) | 5 / 78 (6.41%) |
| occurrences (all) | 4 | 3 | 6 |
| Headache | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 3 / 34 (8.82%) | 3 / 78 (3.85%) |
| occurrences (all) | 3 | 3 | 4 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 1 / 34 (2.94%) | 3 / 78 (3.85%) |
| occurrences (all) | 6 | 1 | 3 |

| | | | |
|---|---|---|---|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 11 / 36 (30.56%) | 11 / 34 (32.35%) | 19 / 78 (24.36%) |
| occurrences (all) | 16 | 19 | 32 |
| Neutropenia | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 16 / 34 (47.06%) | 15 / 78 (19.23%) |
| occurrences (all) | 16 | 59 | 33 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 4 / 34 (11.76%) | 18 / 78 (23.08%) |
| occurrences (all) | 15 | 8 | 54 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 1 | 1 | 6 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 0 | 1 | 6 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 34 (2.94%) | 1 / 78 (1.28%) |
| occurrences (all) | 2 | 1 | 1 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 5 / 78 (6.41%) |
| occurrences (all) | 0 | 2 | 9 |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 36 (30.56%) | 9 / 34 (26.47%) | 26 / 78 (33.33%) |
| occurrences (all) | 13 | 14 | 50 |
| Nausea | | | |
| subjects affected / exposed | 8 / 36 (22.22%) | 10 / 34 (29.41%) | 19 / 78 (24.36%) |
| occurrences (all) | 16 | 12 | 34 |
| Vomiting | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 9 / 34 (26.47%) | 9 / 78 (11.54%) |
| occurrences (all) | 13 | 11 | 16 |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 8 / 36 (22.22%) | 7 / 34 (20.59%) | 8 / 78 (10.26%) |
| occurrences (all) | 11 | 8 | 11 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 34 (8.82%) | 6 / 78 (7.69%) |
| occurrences (all) | 1 | 3 | 9 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 34 (5.88%) | 4 / 78 (5.13%) |
| occurrences (all) | 3 | 2 | 7 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 34 (0.00%) | 4 / 78 (5.13%) |
| occurrences (all) | 0 | 0 | 5 |
| Gastritis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 34 (2.94%) | 1 / 78 (1.28%) |
| occurrences (all) | 2 | 1 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Rash erythematous | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 2 / 34 (5.88%) | 3 / 78 (3.85%) |
| occurrences (all) | 3 | 2 | 5 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 0 / 34 (0.00%) | 3 / 78 (3.85%) |
| occurrences (all) | 6 | 0 | 4 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 34 (2.94%) | 3 / 78 (3.85%) |
| occurrences (all) | 2 | 1 | 5 |
| Rash macular | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 2 / 34 (5.88%) | 3 / 78 (3.85%) |
| occurrences (all) | 1 | 2 | 6 |
| Alopecia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 34 (8.82%) | 1 / 78 (1.28%) |
| occurrences (all) | 1 | 3 | 1 |
| Erythema | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 4 | 0 | 1 |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 2 | 1 |

| | | | |
|---|---|---|---|
| Rash pruritic | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 34 (8.82%) | 3 / 78 (3.85%) |
| occurrences (all) | 2 | 7 | 4 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 6 / 34 (17.65%) | 6 / 78 (7.69%) |
| occurrences (all) | 7 | 9 | 9 |
| Back pain | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 5 / 34 (14.71%) | 7 / 78 (8.97%) |
| occurrences (all) | 3 | 6 | 7 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 4 / 34 (11.76%) | 2 / 78 (2.56%) |
| occurrences (all) | 6 | 6 | 2 |
| Bone pain | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 0 / 34 (0.00%) | 6 / 78 (7.69%) |
| occurrences (all) | 4 | 0 | 6 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 0 | 1 | 5 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 0 | 1 | 4 |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 34 (2.94%) | 0 / 78 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Groin pain | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 0 / 78 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Infections and infestations | | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 9 / 36 (25.00%) | 3 / 34 (8.82%) | 21 / 78 (26.92%) |
| occurrences (all) | 10 | 3 | 42 |

| | | | |
|---|---|---|---|
| Bronchitis | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 4 / 34 (11.76%) | 12 / 78 (15.38%) |
| occurrences (all) | 8 | 4 | 18 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 36 (13.89%) | 4 / 34 (11.76%) | 6 / 78 (7.69%) |
| occurrences (all) | 12 | 8 | 8 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 4 / 34 (11.76%) | 8 / 78 (10.26%) |
| occurrences (all) | 3 | 8 | 15 |
| Herpes zoster | | | |
| subjects affected / exposed | 6 / 36 (16.67%) | 3 / 34 (8.82%) | 5 / 78 (6.41%) |
| occurrences (all) | 6 | 3 | 6 |
| Influenza | | | |
| subjects affected / exposed | 3 / 36 (8.33%) | 0 / 34 (0.00%) | 6 / 78 (7.69%) |
| occurrences (all) | 3 | 0 | 6 |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 34 (2.94%) | 5 / 78 (6.41%) |
| occurrences (all) | 2 | 1 | 5 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 3 / 34 (8.82%) | 3 / 78 (3.85%) |
| occurrences (all) | 2 | 3 | 3 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 0 / 34 (0.00%) | 5 / 78 (6.41%) |
| occurrences (all) | 1 | 0 | 7 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 34 (2.94%) | 3 / 78 (3.85%) |
| occurrences (all) | 2 | 1 | 5 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 1 | 1 | 4 |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 3 / 78 (3.85%) |
| occurrences (all) | 2 | 0 | 4 |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 0 / 34 (0.00%) | 1 / 78 (1.28%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|---|---|---|---|
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 1 / 78 (1.28%) |
| occurrences (all) | 0 | 2 | 1 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 34 (5.88%) | 0 / 78 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 4 / 34 (11.76%) | 2 / 78 (2.56%) |
| occurrences (all) | 0 | 4 | 2 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 3 / 34 (8.82%) | 3 / 78 (3.85%) |
| occurrences (all) | 0 | 3 | 3 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 1 / 34 (2.94%) | 4 / 78 (5.13%) |
| occurrences (all) | 0 | 1 | 9 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 34 (2.94%) | 1 / 78 (1.28%) |
| occurrences (all) | 2 | 1 | 1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 May 2014 | Amendment 1: The protocol was amended to allow the enrollment of patients with relapsed and/or refractory multiple myeloma (RRMM) into the study. The evaluation of oral ixazomib when added to a regimen of cyclophosphamide and low-dose dexamethasone (Cd) in this patient population. Study objectives and endpoints were added, and study procedures described for this patient population. The amendment also contained minor. Updates in study procedures to improve protocol clarity and compliance and align the study conduct with the sponsor's current guidelines and practices. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported