# Clinical trial results:
# A PHASE 3, INTERGROUP MULTICENTRE, RANDOMIZED, CONTROLLED 3 ARM PARALLEL GROUP STUDY TO DETERMINE THE EFFICACY AND SAFETY OF LENALIDOMIDE IN COMBINATION WITH DEXAMETHASONE (Rd) VERSUS MELPHALAN, PREDNISONE AND LENALIDOMIDE (MPR) versus CYCLOPHOSPHAMIDE, PREDNISONE AND LENALIDOMIDE (CPR) IN NEWLY DIAGNOSED MULTIPLE MYELOMA SUBJECTS

## Summary

| | |
|---|---|
| EudraCT number | 2008-008606-52 |
| Trial protocol | IT CZ |
| Global end of trial date | 01 July 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 26 February 2025 |
| First version publication date | 26 February 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | EMN01 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01093196 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Fondazione EMN Italy Onlus |
| Sponsor organisation address | Via Saluzzo I/A, Turin, Italy, 10125 |
| Public contact | Clinical Trial Office, Fondazione EMN Italy Onlus, Clinical Trial Office, Fondazione EMN Italy Onlus, 0039 0110243236 , clinicaltrialoffice@emnitaly.org |
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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 | 27 January 2025 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of the combination Rd in comparison with MPR and CPR in newly diagnosed, symptomatic MM patients. To assess the efficacy of lenalidomide as maintenance therapy (in conjunction with prednisone) after the consolidation phase

Protection of trial subjects:

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 October 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Czechia: 39 |
| Country: Number of subjects enrolled | Italy: 615 |
| Worldwide total number of subjects | 654 |
| EEA total number of subjects | 654 |

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) | 4 |
| From 65 to 84 years | 629 |
| 85 years and over | 21 |

## Subject disposition

### Recruitment

Recruitment details:

This is an intergroup multicenter, randomized, open label study designed to compare the efficacy and safety of Rd with MPR and CPR in newly diagnosed symptomatic MM patients who are 65 years of age or older. Potential study subjects will sign an informed consent prior to undergoing any study related procedure.

### Pre-assignment

Screening details:

Patients will undergo screening for protocol eligibility within 28 dd (4 weeks) prior to randomization. Subjects who meet all the inclusion criteria will be randomized based on a computer-generated randomization schedule. The randomization will occur for induction and maintenance treatment. They will be stratified according to the ISS and age.

### Period 1

| | |
|---|---|
| Period 1 title | Induction |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | ARM A (Rd) |

Arm description:

Patients will start induction treatment with the association of lenalidomide and dexamethasone (Rd) for 9 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
• Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days in patients 65-75 years old and at the dose of 20 mg on days 1,8,15 and 22 every 28 days in patients older than 75 years.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)

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

Dosage and administration details:

Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days in patients 65-75 years old and at the dose of 20 mg on days 1,8,15 and 22 every 28 days in patients older than 75 years.

| | |
|---|---|
| **Arm title** | ARM B (MPR) |

Arm description:

Patients will start induction treatment with the association of melphalan, prednisone and lenalidomide (MPR) for 9 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)

• Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28) in patients 65-75 years old and 0.13 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28) in patients older than 75 years
• Prednisone will be given orally at the dose of 1.5 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)

| | |
|---|---|
| Investigational medicinal product name | Melphalan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28) in patients 65-75 years old and 0.13 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28) in patients older than 75 years

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

Dosage and administration details:

Prednisone will be given orally at the dose of 1.5 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28)

| | |
|---|---|
| **Arm title** | ARM C (CPR) |

Arm description:

Patients will start induction treatment with the association of cyclophosphamide, prednisone and lenalidomide (CPR) for 9 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)
• Cyclophosphamide will be given orally at the dose of 50 mg /day for 21 days followed by a 7 day rest period (days 1 to 28) in patients 65-75 years old and 50 mg every other day (days 1 to 20 followed by a 8 days rest period [day 21 to 28]) in patients older than 75 years
• Prednisone will be given orally at the dose of 25 mg every other day (days 1 to 28)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)

| | |
|---|---|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cyclophosphamide will be given orally at the dose of 50 mg /day for 21 days followed by a 7 day rest period (days 1 to 28) in patients 65-75 years old and 50 mg every other day (days 1 to 20 followed by a 8 days rest period [day 21 to 28]) in patients older than 75 years.

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

Dosage and administration details:

Prednisone will be given orally at the dose of 25 mg every other day (days 1 to 28)

| **Number of subjects in period 1** | ARM A (Rd) | ARM B (MPR) | ARM C (CPR) |
|---|---|---|---|
| Started | 217 | 217 | 220 |
| Completed | 133 | 126 | 143 |
| Not completed | 84 | 91 | 77 |
| Adverse event, serious fatal | 10 | 9 | 9 |
| Physician decision | 3 | 2 | 1 |
| Consent withdrawn by subject | 2 | 7 | 3 |
| not started | 5 | 6 | - |
| Adverse event, non-fatal | 18 | 32 | 23 |
| Lost to follow-up | 6 | 4 | 1 |
| Lack of efficacy | 40 | 30 | 40 |
| Protocol deviation | - | 1 | - |

## Period 2

| | |
|---|---|
| Period 2 title | Maintenance |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | ARM A1, B1 and C1 (R) |

Arm description:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period.

| **Arm title** | ARM A2, B2 and C2 (RP) |
|---|---|

Arm description:

• Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period.
• Prednisone will be given orally at the dose of 25 mg every other day (days 1 to 28)
Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period.

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

Dosage and administration details:

Prednisone will be given orally at the dose of 25 mg every other day (days 1 to 28)

| **Number of subjects in period 2** | ARM A1, B1 and C1 (R) | ARM A2, B2 and C2 (RP) |
|---|---|---|
| Started | 204 | 198 |
| Completed | 0 | 0 |
| Not completed | 204 | 198 |
| Adverse event, serious fatal | 8 | 11 |
| Physician decision | 5 | 15 |
| Consent withdrawn by subject | - | 3 |
| Adverse event, non-fatal | 39 | 37 |
| Other | 28 | 16 |
| Lost to follow-up | 4 | 4 |
| Treatment will be continued outside the scope of t | 2 | 2 |
| Lack of efficacy | 116 | 108 |
| Protocol deviation | 2 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Induction |

Reporting group description: -

| Reporting group values | Induction | Total | |
|---|---|---|---|
| Number of subjects | 654 | 654 | |
| Age categorical<br>Units: Subjects | | | |
| <= 75 | 429 | 429 | |
| > 75 | 225 | 225 | |
| Age continuous<br>Units: years | | | |
| median | 73 | | |
| full range (min-max) | 50 to 91 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 335 | 335 | |
| Male | 319 | 319 | |
| ISS Stage<br>Units: Subjects | | | |
| ISS I | 181 | 181 | |
| ISS II | 296 | 296 | |
| ISS III | 177 | 177 | |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:
ITT population

| Reporting group values | ITT | | |
|---|---|---|---|
| Number of subjects | 654 | | |
| Age categorical<br>Units: Subjects | | | |
| <= 75 | 429 | | |
| > 75 | 225 | | |
| Age continuous<br>Units: years | | | |
| median | 73 | | |
| full range (min-max) | 50 to 91 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 335 | | |
| Male | 319 | | |

| ISS Stage<br>Units: Subjects | | | |
|---|---|---|---|
| ISS I | 181 | | |
| ISS II | 296 | | |
| ISS III | 177 | | |

## End points

### End points reporting groups

| Reporting group title | ARM A (Rd) |
|---|---|

Reporting group description:

Patients will start induction treatment with the association of lenalidomide and dexamethasone (Rd) for 9 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28),
• Dexamethasone will be given orally at the dose of 40 mg on days 1, 8, 15 and 22 every 28 days in patients 65-75 years old and at the dose of 20 mg on days 1,8,15 and 22 every 28 days in patients older than 75 years.

| Reporting group title | ARM B (MPR) |
|---|---|

Reporting group description:

Patients will start induction treatment with the association of melphalan, prednisone and lenalidomide (MPR) for 9 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 10 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)
• Melphalan will be given orally at the dose of 0.18 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28) in patients 65-75 years old and 0.13 mg/Kg for 4 days, followed by a 24 days rest period (day 5 to 28) in patients older than 75 years
• Prednisone will be given orally at the dose of 1.5 mg/Kg for 4 days followed by a 24 day rest period (days 5 to 28)

| Reporting group title | ARM C (CPR) |
|---|---|

Reporting group description:

Patients will start induction treatment with the association of cyclophosphamide, prednisone and lenalidomide (CPR) for 9 cycles every 28 days:
• Lenalidomide will be given orally at the dose of 25 mg/day for 21 days followed by a 7 days rest period (day 22 to 28)
• Cyclophosphamide will be given orally at the dose of 50 mg /day for 21 days followed by a 7 day rest period (days 1 to 28) in patients 65-75 years old and 50 mg every other day (days 1 to 20 followed by a 8 days rest period [day 21 to 28]) in patients older than 75 years
• Prednisone will be given orally at the dose of 25 mg every other day (days 1 to 28)

| Reporting group title | ARM A1, B1 and C1 (R) |
|---|---|

Reporting group description:

Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period.

| Reporting group title | ARM A2, B2 and C2 (RP) |
|---|---|

Reporting group description:

• Lenalidomide will be given at the dose of 10 mg/day on day 1-21 followed by a 7 days rest period.
• Prednisone will be given orally at the dose of 25 mg every other day (days 1 to 28)
Each cycle will be repeated every 28 days, until any sign of disease progression (PD).

| Subject analysis set title | ITT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

ITT population

### Primary: Progression Free Survival (PFS)

| End point title | Progression Free Survival (PFS) |
|---|---|

End point description:

Progression free survival (PFS), defined as time from start of treatment to the first documentation of progressive disease based on the International Uniform Response Criteria, Appendix V or death due to any cause during the treatment phase

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

End point timeframe:

5 years

| End point values | ARM A (Rd) | ARM B (MPR) | ARM C (CPR) | ARM A1, B1 and C1 (R) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 217 | 217 | 220 | 204 |
| Units: month | | | | |
| median (confidence interval 95%) | 17.9 (15.7 to 22.4) | 22.6 (18.6 to 28.3) | 18.6 (15.4 to 22.2) | 18.6 (14.6 to 22) |

| End point values | ARM A2, B2 and C2 (RP) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 198 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | 21.6 (15.9 to 29.6) | | | |

**Statistical analyses**

| Statistical analysis title | R1 Analysis |
|---|---|
| Comparison groups | ARM A (Rd) v ARM B (MPR) |
| Number of subjects included in analysis | 434 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1072 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.104405 |

| Statistical analysis title | R1 Analysis (2) |
|---|---|
| Comparison groups | ARM A (Rd) v ARM C (CPR) |

| | |
|---|---|
| Number of subjects included in analysis | 437 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4935 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.101377 |

| **Statistical analysis title** | R2 Analysis |
|---|---|
| Comparison groups | ARM A1, B1 and C1 (R) v ARM A2, B2 and C2 (RP) |
| Number of subjects included in analysis | 402 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42957 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.107536 |

| **Secondary: Overall survival (OS)** | |
|---|---|
| End point title | Overall survival (OS) |
| End point description: | |
| Overall survival (OS), defined as time from start of treatment to death due to any cause | |
| End point type | Secondary |
| End point timeframe: | |
| 5 years | |

| End point values | ARM A (Rd) | ARM B (MPR) | ARM C (CPR) | ARM A1, B1 and C1 (R) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 217 | 217 | 220 | 204 |
| Units: month | | | | |
| median (confidence interval 95%) | 61.5 (48.2 to 80.5) | 65.2 (53.4 to 79) | 63.5 (57 to 76.1) | 71.4 (57.6 to 91.7) |

| End point values | ARM A2, B2 and C2 (RP) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 198 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | 69.9 (55.5 to 87.8) | | | |

**Statistical analyses**

| Statistical analysis title | R1 Analysis |
|---|---|
| Comparison groups | ARM A (Rd) v ARM B (MPR) |
| Number of subjects included in analysis | 434 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.90404 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.29 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.120631 |

| Statistical analysis title | Copy of R1 Analysis |
|---|---|
| Comparison groups | ARM A (Rd) v ARM C (CPR) |
| Number of subjects included in analysis | 437 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65351 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.95 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 1.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.121143 |

| | |
|---|---|
| **Statistical analysis title** | Copy of R1 Analysis |
| Comparison groups | ARM A2, B2 and C2 (RP) v ARM A1, B1 and C1 (R) |
| Number of subjects included in analysis | 402 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.65397 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.37 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.13121 |

| **Secondary: Time to progression (TTP)** | |
|---|---|
| End point title | Time to progression (TTP) |
| End point description: | |
| Time to progression (TTP), defined as time from start of treatment to the first documentation of progressive disease or death due to progressive disease during the treatment phase | |
| End point type | Secondary |
| End point timeframe: | |
| 5 years | |

| **End point values** | ARM A (Rd) | ARM B (MPR) | ARM C (CPR) | ARM A1, B1 and C1 (R) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 217 | 217 | 220 | 204 |
| Units: month | | | | |
| median (confidence interval 95%) | 18.8 (16.2 to 24.5) | 26.3 (21.7 to 34.4) | 19.1 (16.2 to 24.4) | 19.1 (15.2 to 24.3) |

| End point values | ARM A2, B2 and C2 (RP) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 198 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | 24.4 (18.7 to 30.9) | | | |

**Statistical analyses**

| Statistical analysis title | R1 Analysis |
|---|---|
| Comparison groups | ARM A (Rd) v ARM B (MPR) |
| Number of subjects included in analysis | 434 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1072 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.104405 |

| Statistical analysis title | R1 Analysis (2) |
|---|---|
| Comparison groups | ARM A (Rd) v ARM C (CPR) |
| Number of subjects included in analysis | 437 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4935 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.101377 |

| Statistical analysis title | R2 Analysis |
|---|---|

| | |
|---|---|
| Comparison groups | ARM A1, B1 and C1 (R) v ARM A2, B2 and C2 (RP) |
| Number of subjects included in analysis | 402 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.36947 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1134 |

## Secondary: VGPR rate

| | |
|---|---|
| End point title | VGPR rate |

End point description:

Objective overall response rate, including complete response (CR) and partial response (PR) using the International Uniform Response Criteria, Appendix IV

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

End point timeframe:

Overall

| End point values | ARM A (Rd) | ARM B (MPR) | ARM C (CPR) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 217 | 217 | 220 | |
| Units: patients | | | | |
| < VGPR | 130 | 131 | 145 | |
| >= VGPR | 87 | 86 | 75 | |

### Statistical analyses

| Statistical analysis title | Fisher test |
|---|---|
| Comparison groups | ARM A (Rd) v ARM B (MPR) v ARM C (CPR) |
| Number of subjects included in analysis | 654 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.361 |
| Method | Fisher exact |

| Secondary: Time to the next anti-myeloma therapy | |
|---|---|
| End point title | Time to the next anti-myeloma therapy |
| End point description:<br>Time to the next anti-myeloma therapy | |
| End point type | Secondary |
| End point timeframe:<br>7 Years | |

| End point values | ARM A (Rd) | ARM B (MPR) | ARM C (CPR) | ARM A1, B1 and C1 (R) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 217 | 217 | 220 | 204 |
| Units: month | | | | |
| median (confidence interval 95%) | 23.8 (20.8 to 30.7) | 26.4 (21.6 to 37) | 23.8 (20.2 to 28.1) | 29.4 (25.3 to 34.6) |

| End point values | ARM A2, B2 and C2 (RP) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 198 | | | |
| Units: month | | | | |
| median (confidence interval 95%) | 32.2 (27.1 to 40.3) | | | |

## Statistical analyses

| Statistical analysis title | R1 Analysis |
|---|---|
| Comparison groups | ARM A (Rd) v ARM B (MPR) |
| Number of subjects included in analysis | 434 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.20548 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.106426 |

| **Statistical analysis title** | R1 Analysis (2) |
|---|---|
| Comparison groups | ARM A (Rd) v ARM C (CPR) |
| Number of subjects included in analysis | 437 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.52519 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.31 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.103407 |

| **Statistical analysis title** | R2 Analysis |
|---|---|
| Comparison groups | ARM A1, B1 and C1 (R) v ARM A2, B2 and C2 (RP) |
| Number of subjects included in analysis | 402 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.95712 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.24 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.111566 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Safety population

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 27 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Per protocol |

Reporting group description: -

| Serious adverse events | Per protocol | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 272 / 643 (42.30%) | | |
| number of deaths (all causes) | 406 | | |
| number of deaths resulting from adverse events | 39 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute leukaemia | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenocarcinoma pancreas | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Basal cell carcinoma | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 6 / 643 (0.93%) | | | |
| occurrences causally related to treatment / all | 5 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder cancer | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Brain neoplasm | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colon cancer | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal tract adenoma | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malignant melanoma | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostate cancer | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma | | | | |
| subjects affected / exposed | 4 / 643 (0.62%) | | | |
| occurrences causally related to treatment / all | 3 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Squamous cell carcinoma of skin | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal oncocytoma | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Plasma cell leukaemia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Meningioma | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myelodysplastic syndrome | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Non-small cell lung cancer metastatic | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vascular disorders | | | | |
| Deep vein thrombosis | | | | |
| subjects affected / exposed | 8 / 643 (1.24%) | | | |
| occurrences causally related to treatment / all | 8 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Embolism | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Hypotension | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ischaemia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral artery thrombosis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Venous thrombosis | | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 3 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General disorders and administration site conditions | | | | |
| Asthenia | | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chest pain | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 1 / 2 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oedema | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pain | | | | |
| subjects affected / exposed | 11 / 643 (1.71%) | | | |
| occurrences causally related to treatment / all | 4 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 15 / 643 (2.33%) | | | |
| occurrences causally related to treatment / all | 7 / 17 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Sudden cardiac death | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Sudden death | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 1 / 2 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed | 5 / 643 (0.78%) | | | |
| occurrences causally related to treatment / all | 3 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary embolism | | | | |
| subjects affected / exposed | 6 / 643 (0.93%) | | | |
| occurrences causally related to treatment / all | 5 / 6 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Respiratory failure | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 643 (0.78%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Bronchial disorder | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Fall | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 4 / 643 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fracture | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sternal fracture | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Head injury | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rib fracture | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac disorders | | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 11 / 643 (1.71%) | | | |
| occurrences causally related to treatment / all | 5 / 11 | | | |
| deaths causally related to treatment / all | 2 / 6 | | | |
| Cardiac failure acute | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Left ventricular dysfunction | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Ventricular tachycardia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial fibrillation | | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina pectoris | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute myocardial infarction | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bradyarrhythmia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bradycardia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial hypoxia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Angina unstable | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arrhythmia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Atrioventricular block | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial ischaemia | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocarditis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Pancreatic carcinoma | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Hemiparesis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Embolic stroke | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Loss of consciousness | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transient ischaemic attack | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aphasia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Essential tremor | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hydrocephalus | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Memory impairment | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuropathy peripheral | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sciatica | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Syncope | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Blood and lymphatic system disorders | | | | |
| Anaemia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 643 (0.47%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytopenia | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 7 / 643 (1.09%) | | |
| occurrences causally related to treatment / all | 6 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 643 (0.62%) | | |
| occurrences causally related to treatment / all | 8 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|---|---|---|---|
| Abdominal pain | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Ascites | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Crohn's disease | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 7 / 643 (1.09%) | | | |
| occurrences causally related to treatment / all | 4 / 7 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Enteritis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematochezia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia strangulated | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 643 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 4 / 643 (0.62%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 643 (0.62%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 9 / 643 (1.40%) | | |
| occurrences causally related to treatment / all | 8 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash maculo-papular | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rash vesicular | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urticaria | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Decubitus ulcer | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erythema | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal and urinary disorders | | | | |
| Acute kidney injury | | | | |
| subjects affected / exposed | 10 / 643 (1.56%) | | | |
| occurrences causally related to treatment / all | 8 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Crush syndrome | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal colic | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal failure | | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 5 / 643 (0.78%) | | | |
| occurrences causally related to treatment / all | 3 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary retention | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal haemorrhage | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocrine disorders | | | | |
| Hypothyroidism | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal and connective tissue disorders | | | | |
| Bone pain | | | | |
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Back pain | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscle spasms | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Osteoarthritis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

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|---|---|---|---|---|
| Pathological fracture | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal pain | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Synovitis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |
| Bacterial sepsis | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| bronchitis | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Citrobacter infection | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Clostridium difficile infection | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| COVID-19 pneumonia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Ear infection | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Erysipelas | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Eye infection | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal infection | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 7 / 643 (1.09%) | | | |
| occurrences causally related to treatment / all | 5 / 7 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 31 / 643 (4.82%) | | | |
| occurrences causally related to treatment / all | 18 / 35 | | | |
| deaths causally related to treatment / all | 2 / 6 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Septic shock | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 3 / 643 (0.47%) | | | |
| occurrences causally related to treatment / all | 2 / 3 | | | |
| deaths causally related to treatment / all | 1 / 2 | | | |
| Systemic infection | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Upper respiratory tract infection | | | | |
| subjects affected / exposed | 2 / 643 (0.31%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| Hyperglycaemia | | | | |
| subjects affected / exposed | 4 / 643 (0.62%) | | | |
| occurrences causally related to treatment / all | 2 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypercalcaemia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypocalcaemia | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tumour lysis syndrome | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Decreased appetite | | | | |
| subjects affected / exposed | 1 / 643 (0.16%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 1 / 1 | | | |

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

| **Non-serious adverse events** | Per protocol | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 577 / 643 (89.74%) | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 39 / 643 (6.07%) | | |
| occurrences (all) | 39 | | |
| Nervous system disorders | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 37 / 643 (5.75%) | | |
| occurrences (all) | 37 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 37 / 643 (5.75%) | | |
| occurrences (all) | 37 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 410 / 643 (63.76%) | | |
| occurrences (all) | 410 | | |
| Anaemia | | | |
| subjects affected / exposed | 398 / 643 (61.90%) | | |
| occurrences (all) | 398 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 260 / 643 (40.44%) | | |
| occurrences (all) | 260 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 150 / 643 (23.33%) | | |
| occurrences (all) | 150 | | |
| Pyrexia | | | |
| subjects affected / exposed | 111 / 643 (17.26%) | | |
| occurrences (all) | 111 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 115 / 643 (17.88%) | | |
| occurrences (all) | 115 | | |
| Constipation | | | |
| subjects affected / exposed | 79 / 643 (12.29%) | | |
| occurrences (all) | 79 | | |
| Nausea | | | |
| subjects affected / exposed | 37 / 643 (5.75%) | | |
| occurrences (all) | 37 | | |
| Skin and subcutaneous tissue disorders | | | |
| Exfoliative rash | | | |
| subjects affected / exposed | 78 / 643 (12.13%) | | |
| occurrences (all) | 78 | | |
| Pruritus | | | |
| subjects affected / exposed | 37 / 643 (5.75%) | | |
| occurrences (all) | 37 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 51 / 643 (7.93%) | | |
| occurrences (all) | 51 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 March 2009 | Amendment 1: Addition of an observational substudy for asymptomatic patients. |
| 07 July 2010 | Amendment Sponsor: Change of sponsor's legal represenative. |
| 04 August 2010 | Amendment 2: Statistical updates and new MPR arm treatment scheme. |
| 03 May 2011 | Amendment 3: Regarding the modification to the information sheet/informed consent, for an update on the risks related to the use of Lenalidomide, following the AIFA communication of 6 April 2011 on the emergency "Safety Lenalidomide". |
| 01 September 2016 | Amendment PI's ECC: Change PI's ECC |
| 04 May 2017 | Amendment 4: Update protocol, ICF side effects, SAE_SUSAR form, SmPC, PPG, Sponsor contacts. |
| 28 January 2019 | Amendment 5: Added new site for import and release of drug Lenalidomide. |
| 04 November 2019 | Amendment 6: New version of the Lenalidomide IB and the updated Informed Consent with the new side effects relating to the drug Lenalidomide. |
| 20 March 2020 | Urgent Amendment 1: COVID updates. |
| 20 October 2020 | Amendment 7: New version of the Lenalidomide IB and the updated Informed Consent with the new side effects relating to the drug Lenalidomide. The drug labels and the SAE form have been updated. |
| 31 August 2023 | Amendment CEC-CET: Change from CEC to CET. |
| 27 February 2024 | Amendment 8: Central laboratory change, study duration updates and drug information |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported