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
Scientific contact	Clinical Trial Office, Fondazione EMN Italy Onlus, Clinical Trial Office, Fondazione EMN Italy Onlus, 0039 0110243236 , clinicaltrialoffice@emnitaly.org

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 Units: Subjects			
<= 75	429	429	
> 75	225	225	
Age continuous Units: years			
median	73		
full range (min-max)	50 to 91	-	
Gender categorical Units: Subjects			
Female	335	335	
Male	319	319	
ISS Stage 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 Units: Subjects			
<= 75	429		
> 75	225		
Age continuous Units: years			
median	73		
full range (min-max)	50 to 91		
Gender categorical Units: Subjects			
Female	335		
Male	319		

ISS Stage 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: Time to the next anti-myeloma therapy	
End point type	Secondary
End point timeframe: 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				

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			

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