Clinical trial results:
A MULTICENTER, OPEN LABEL STUDY OF ORAL REVLIMID AND PREDNISONE (RP) FOLLOWED BY ORAL REVLIMID MELPHALAN AND PREDNISONE (MPR) IN NEWLY DIAGNOSED ELDERLY MULTIPLE MYELOMA PATIENTS

Summary

EudraCT number	2007-007616-28
Trial protocol	IT
Global end of trial date	21 December 2022

Results information

Result version number	v1 (current)
This version publication date	12 January 2024
First version publication date	12 January 2024

Trial information

Trial identification

Sponsor protocol code	RV-MM-PI-302

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fondazione EMN Italy Onlus
Sponsor organisation address	Via Saluzzo 1/A, Torino, Italy, 10125
Public contact	Clinical trial office, Fondazione EMN Italy Onlus, 0039 0110243236, clinicaltrialoffice@emnitaly.org
Scientific contact	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	22 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether the association of RP as induction followed by MPR as consolidation treatment is safe and induce a significant rate of PR (and CR) in elderly patients with newly diagnosed multiple myeloma.

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	04 July 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	0
From 65 to 84 years	44
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This protocol is a multicenter two-stage phase II, non comparative, open label study, designed according to Bryant and Day method (5). Potential study subjects will sign an informed consent prior to undergoing any study related procedure.
This study consists of 3 phases for each study subject: Pre-treatment, Treatment, long-term follow-up

Pre-assignment

Screening details:

after providing written informed consent, patients will undergo screening for protocol eligibility as outlined in the Schedule of Study Assessments.

Period 1

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

Arms

Arm title	RP-MPR

Arm description: -

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:

Induction
Lenalidomide will be given orally at the dose of 25 mg/die for 21 days followed by a 7 days rest period (day 22 to 28) for 4 cycles.
Consolidation
Lenalidomide will be delivered orally at the dose of 15 mg/die for 21 days followed by a 7 days rest period (day 22 to 28), for 6 cycles.
maintenance
10 mg/day from day 1 to 21, followed by a 7-day rest period (days 22 through 28). Each cycle will be repeated every 28 days, until PD.

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

Dosage and administration details:

Induction
Prednisone will be given orally at the dose of 50 mg three times a week continuously for a total of 4 months.
Consolidation
Prednisone will be given orally at the dose of 50 mg three times a week, for 6 months
maintenance
Prednisone will be given orally at the dose of 25 mg three times a week

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Consolidation
Melphalan will be given orally at the dose of 2 mg three times a week (total dose 24 mg/28 days), for 6 cycles.

Number of subjects in period 1	RP-MPR
Started	46
Completed	0
Not completed	46
Adverse event, serious fatal	4
Adverse event, non-fatal	20
Protocol deviation	1
Lack of efficacy	21

Baseline characteristics

Reporting groups

Reporting group title	RP-MPR

Reporting group description: -

Reporting group values	RP-MPR	Total	
Number of subjects	46	46	
Age categorical Units: Subjects			
Adults (18-64 years)	0	0	
From 65-84 years	44	44	
85 years and over	2	2	
Age continuous Units: years			
median	75		
full range (min-max)	65 to 88	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	30	30	
ISS Stage Units: Subjects			
ISS I	6	6	
ISS II	14	14	
ISS III	8	8	
Missing	18	18	
ECOG Units: Subjects			
ECOG 0	7	7	
ECOG 1	18	18	
ECOG 2	10	10	
ECOG 3	2	2	
Missing	9	9	

Subject analysis sets

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

Subject analysis set description:
ITT

Reporting group values	ITT		
Number of subjects	46		
Age categorical Units: Subjects			
Adults (18-64 years)	0		
From 65-84 years	44		

85 years and over	2		

Age continuous Units: years			
median	75		
full range (min-max)	65 to 88		
Gender categorical Units: Subjects			
Female	16		
Male	30		
ISS Stage Units: Subjects			
ISS I	6		
ISS II	14		
ISS III	8		
Missing	18		
ECOG Units: Subjects			
ECOG 0	7		
ECOG 1	18		
ECOG 2	10		
ECOG 3	2		
Missing	9		

End points

End points reporting groups	
Reporting group title	RP-MPR
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT	

Primary: PR Rate	
End point title	PR Rate
End point description:	
End point type	Primary
End point timeframe: ITT	

End point values	RP-MPR	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46	46		
Units: subject	37	37		

Statistical analyses

Statistical analysis title	No statistical analysis
Statistical analysis description: No statistical analysis	
Comparison groups	RP-MPR v ITT
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0 [2]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	37
Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	37
upper limit	37
Variability estimate	Standard deviation
Dispersion value	0

Notes:
[1] - No statistical analysis
[2] - No statistical analysis

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:
Progression free survival

End point values	RP-MPR	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46	46		
Units: month				
median (confidence interval 95%)	21.2 (17.1 to 34.8)	21.2 (17.1 to 34.8)		

Statistical analyses

Statistical analysis title	No statistical analysis

Statistical analysis description:
No statistical analysis

Comparison groups	RP-MPR v ITT
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0 [4]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	21.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.2
upper limit	21.2
Variability estimate	Standard deviation
Dispersion value	0

Notes:
[3] - No statistical analysis
[4] - No statistical analysis

Secondary: Time to progression

End point title	Time to progression

End point description:

End point type	Secondary
End point timeframe:	
Time to progression	

End point values	RP-MPR	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46	46		
Units: month				
median (confidence interval 95%)	29.9 (18.2 to 57.6)	29.9 (18.2 to 57.6)		

Statistical analyses

Statistical analysis title	No statistical analysis
Statistical analysis description:	
No statistical analysis	
Comparison groups	RP-MPR v ITT
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0 [6]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	29.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.9
upper limit	29.9
Variability estimate	Standard deviation
Dispersion value	0

Notes:
[5] - No statistical analysis
[6] - No statistical analysis

Secondary: Overall survival

End point title	Overall survival
End point description:	

End point type	Secondary
End point timeframe:	
Overall survival	

End point values	RP-MPR	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	46	46		
Units: month				
median (confidence interval 95%)	60.4 (49 to 81.3)	60.4 (49 to 81.3)		

Statistical analyses

Statistical analysis title	No statistical analysis
Statistical analysis description:	
No statistical analysis	
Comparison groups	RP-MPR v ITT
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0 [8]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	60.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	60.4
upper limit	60.4
Variability estimate	Standard error of the mean
Dispersion value	0

Notes:

[7] - No statistical analysis

[8] - No statistical analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

ITT

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

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	27 / 46 (58.70%)		
number of deaths (all causes)	26		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Prostate cancer			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cancer			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Hypotension				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Astringent therapy				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Hyperthermia				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperpyrexia				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary disease			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Urogram			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery occlusion			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 46 (2.17%)		
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	4 / 46 (8.70%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	5 / 46 (10.87%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Rectal haemorrhage			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative generalised			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		
Angioedema			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopulmonary disease			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infection			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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	43 / 46 (93.48%)		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	13 / 46 (28.26%)		
occurrences (all)	46		

Thrombocytopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	8 / 46 (17.39%) 46 4 / 46 (8.70%) 46 4 / 46 (8.70%) 46		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	5 / 46 (10.87%) 46 5 / 46 (10.87%) 46		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	4 / 46 (8.70%) 46		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2009	The amendments concern the revision by updating (deletion and/or replacement) of certain paragraphs of the ICF This amendment also includes changes made following the new 'Guidelines for the processing of personal data in the context of clinical trials of medicinal products - 24 July 2008 - Official Gazette No. 190 of 14 August 2008 Submission of Lenalidomide IMP dossier as a required doument to be attached to the application for authorisation according to the directive of 21 December 2007.
08 June 2011	Amendment 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 "Safety Lenalidomde" emergency, it was necessary to to inform patients about risks of increased incidence of second malignancies highlighted by the EMA in some clinical trials.
22 May 2017	Protocol: some administrative information was changed and some criteria on disease response were corrected - Information/Informed Consent Sheet: the risks associated with lenalidomide treatment were updated and the Information on the Processing of Personal Data was updated. - Pregnancy Prevention Programme (PPG):documents are sent to subjects and the physician, which are part of the Pregnancy Prevention Programme (PPG), prepared by the pharmaceutical company Celgene Corporation - Drugs Melfalan, Lenalidomide: the "Summary of Product Characteristics" document is submitted for the aforementioned drugs, downloadable from the AIFA database system. - Promoter data: change of address of the promoter's registered office - IB Lenalidomide: the updated version of the document and relative Summary of Changes
15 January 2019	a new site for the importation and release of the drug Lenalidomide was added Submitted: - Supply Chain Letter dated 21.12.2018 - Certificate of GMP compliance of manufacturer dated 06.04.2018
17 June 2019	submission of new version of the IB Lenalidomide; the new version of the Informed Consent updated with the new side effects relating to the drug Lenalidomide was released.
26 June 2020	submission of new version of the IB Lenalidomide; the new version of the Informed Consent updated with the new side effects relating to the drug Lenalidomide was released.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported