Clinical trial results:
A PHASE II, MULTI-CENTER STUDY OF MELPHALAN 100 mg/m2 (MEL 100) as transplant, REVLIMID and PREDNISONE (RP) as consolidation and REVLIMID ALONE as maintenance IN ELDERLY NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS.

Summary

EudraCT number	2005-004730-41
Trial protocol	IT
Global end of trial date	14 August 2023

Results information

Result version number	v1 (current)
This version publication date	22 May 2024
First version publication date	22 May 2024

Trial information

Trial identification

Sponsor protocol code	GIMEMA-MM-05-05

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	FONDAZIONE EMN ITALY ONLUS, FONDAZIONE EMN ITALY ONLUS, clinicaltrialoffice@emn.org
Scientific contact	FONDAZIONE EMN ITALY ONLUS, FONDAZIONE EMN ITALY ONLUS, 011 0243236, clinicaltrialoffice@emn.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	28 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives
Determine whether the sequence MEL100-Revlimid and Prednisone (RP) and Revlimid is safe and provides clinical benefits in patients with newly diagnosed myeloma

Secondary study objectives
Determine the effect of the sequence MEL100-Revlimid and Prednisone (RP) and Revlimid on progression-free survival and overall survival. Verify the duration of molecular remissions and their association with progression free survival.
Determine whether tumor response and survival might significantly change in particular subgroups of patients defined on prognostic factors (2-microglobulin, C-reactive protein, cytogenetics, gene expression profile).

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	03 October 2005
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	Italy: 102
Worldwide total number of subjects	102
EEA total number of subjects	102

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)	32
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

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	pad-mel100-RP_R (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	pad-mel100_RP_R

Arm description:

Cyclophosphamide (CY) for 2 courses and stem cell collection, MEL100 for 2 courses. In order to assess the toxicity of treatment, patients will attend the study center visits at least every 2 weeks.
After MEL100 patients will receive RP for 4 months as consolidation therapy. In order to assess the toxicity of treatment, patients will attend the study center visits at least every 2-4 weeks.
After the 4th course of consolidation therapy (RP) patients will receive REVLIMID alone as maintenance until progression. The duration of the maintenance treatment should be approximately 1.5 years. All patients are to attend study center visits on an every 4 week basis, until development of confirmed Progressive Disease (PD) – short term follow up

Arm type	pad-mel100_RP_R
Investigational medicinal product name	MEL100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

CY: Cyclophosphamide will be given iv at 3 gr/m2 followed by G-CSF administration at the dose of 10 ug/kg, stem-cell collection will be performed 10 days later when the number of WBC > 2 x 109/L . Each cycle will be repeated every 60 days for a total of 2 courses.
MEL100: After 30 days from last CY, Melphalan will be delivered iv at the dose of 100 mg/m2 followed by stem cell infusion. Each cycle will be repeated every 60 days for a total of 2 courses.

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Other use

Dosage and administration details:

Lenalidomide will be given orally at the dose of 25 mg once daily on days 1-21 every 28 days cycle for a total of 4 courses.

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

Dosage and administration details:

Prednisone will be administered orally at the dose of 50 mg every other day for a total of 4 months

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

REVLIMID alone will be used as maintenance at the dose of 10 mg once daily on days 1-21 every 28 days until development of confirmed progressive disease.

Number of subjects in period 1	pad-mel100_RP_R
Started	102
Completed	33
Not completed	69
Adverse event, serious fatal	9
Consent withdrawn by subject	3
Adverse event, non-fatal	23
Other	2
Lost to follow-up	4
Lack of efficacy	28

Baseline characteristics

Reporting groups	
Reporting group title	pad-mel100-RP_R

Reporting group description: -

Reporting group values	pad-mel100-RP_R	Total	
Number of subjects	102	102	
Age categorical Units: Subjects			
< 70	76	76	
>= 70	26	26	
Age continuous Units: years			
median	67		
full range (min-max)	46 to 74	-	
Gender categorical Units: Subjects			
Female	53	53	
Male	49	49	
International Staging System stage Units: Subjects			
ISS I	48	48	
ISS II	30	30	
ISS III	12	12	
NA	12	12	

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	102		
Age categorical Units: Subjects			
< 70	76		
>= 70	26		
Age continuous Units: years			
median	67		
full range (min-max)	46 to 74		
Gender categorical Units: Subjects			
Female	53		
Male	49		

International Staging System stage Units: Subjects			
ISS I	48		
ISS II	30		
ISS III	12		
NA	12		

End points

End points reporting groups

Reporting group title	pad-mel100_RP_R

Reporting group description:

Cyclophosphamide (CY) for 2 courses and stem cell collection, MEL100 for 2 courses. In order to assess the toxicity of treatment, patients will attend the study center visits at least every 2 weeks.
After MEL100 patients will receive RP for 4 months as consolidation therapy. In order to assess the toxicity of treatment, patients will attend the study center visits at least every 2-4 weeks.
After the 4th course of consolidation therapy (RP) patients will receive REVLIMID alone as maintenance until progression. The duration of the maintenance treatment should be approximately 1.5 years. All patients are to attend study center visits on an every 4 week basis, until development of confirmed Progressive Disease (PD) – short term follow up

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

Subject analysis set description:

ITT

Primary: Safety and Benefits

End point title	Safety and Benefits

End point description:

The safety will be assessed by showing:
Less than 30% of patients presenting the following toxicities during consolidation or maintenance: Grade 4 neutropenia a week, or Grade 4 hematologic toxicity except neutropenia, or any Grade 3 non-hematologic toxicity
The benefit will be assessed by showing:
A nCR rate > 35%
At least 20% of patients in molecular remission (PCR negativity) following the proposed treatment

End point type	Primary

End point timeframe:

CR rate

End point values	pad-mel100_RP_R	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	102	102		
Units: Patients				
>= CR	56	56		
< CR	46	46		

Statistical analyses

Statistical analysis title	No statistical analysis
Comparison groups	pad-mel100_RP_R v ITT

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	56
Confidence interval	
level	Other: 0 %
sides	2-sided
lower limit	56
upper limit	56
Variability estimate	Standard deviation
Dispersion value	0

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

PFS was defined as time
from enrollment until the date of progression, relapse, or death from any cause
(whichever occurred first).
Percentage at 24 monhts

End point values	pad-mel100_RP_R	ITT		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	102	102		
Units: percent				
number (confidence interval 95%)	69 (60 to 78)	69 (60 to 78)		

Statistical analyses

Statistical analysis title	No statistical analysis
Comparison groups	pad-mel100_RP_R v ITT
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0 [1]
Method	No statistical analysis
Parameter estimate	No statistical analysis
Point estimate	69

Confidence interval	
level	95 %
sides	2-sided
lower limit	60
upper limit	78
Variability estimate	Standard deviation
Dispersion value	0

Notes:

[1] - No statistical analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: ITT	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26

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	29 / 102 (28.43%)		
number of deaths (all causes)	21		
number of deaths resulting from adverse events	7		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colorectal neoplasm			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome with excess blasts			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Myelosuppression			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Maxillofacial operation			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Death			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Disease progression			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Embolism pulmonary			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Aneurysm			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric dilatation			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal cyst			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Myopathy			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Polymyositis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis B reactivation			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Septic shock			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Per Protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 102 (85.29%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	17 / 102 (16.67%)		
occurrences (all)	17		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	87 / 102 (85.29%)		
occurrences (all)	87		
Thrombocytopenia			
subjects affected / exposed	83 / 102 (81.37%)		
occurrences (all)	83		
Anaemia			
subjects affected / exposed	13 / 102 (12.75%)		
occurrences (all)	13		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	13 / 102 (12.75%)		
occurrences (all)	13		

Fatigue subjects affected / exposed occurrences (all)	7 / 102 (6.86%) 7		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 7 / 102 (6.86%) 7 6 / 102 (5.88%) 6		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 5 / 102 (4.90%) 5		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all) Sepsis subjects affected / exposed occurrences (all)	 15 / 102 (14.71%) 15 8 / 102 (7.84%) 8		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	 5 / 102 (4.90%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2006	Reduction of sites participants Clarification for acceptable toxicity assessment changing the requirements for pregnancy protection evaluation of minimum platelet level evaluation of the administration of Revlimid during maintenance therapy inclusion of a paragraph on revlimid toxicity delete of quality of life questonnaire inclusion of prophylaxis with ASA delete co-trimoyxazole and allopurinol as concomitant therapies adverse events report changes new version of ICF
15 May 2011	ICF updated for urgent information supplied by AIFA regarding lenalidomide
06 February 2018	Protocol: some administrative information was changed and some criteria on disease response were corrected Information sheet/informed consent: the risks associated with lenalidomide treatment have been updated and the information on the processing of personal data has been updated SAE_SUSAR form: the new form for reporting serious adverse events and/or SUSARs has been submitted. Drugs Prednisione, Melfalan, Lenalidomide: updated the 'Summary of Product Product Characteristics' for these drugs submission of document for pts regarding the Pregnancy Prevention Programme (PPG) Sponsor data: change of address of the promoter's registered office
15 January 2019	a new site has been added for the import and release of the drug Lenalidomide.
17 June 2019	updated Lenalidomide IB and ICF
20 March 2020	COVID-19 health emergency: urgent procedures in order in order to limit the risk of coronavirus infection by subjects enrolled in the trial.
17 June 2020	Updated Lenalidomide IB and ICF

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26596670