EU Clinical Trials Register

Clinical trial results:
A phase II open label, non comparative, non randomized study for the assessment of the efficacy and safety of lenalidomide + adriamycine and low dose dexamethasone combination (RAD) in newly diagnosed, symptomatic multiple myeloma patients who are eligible for high dose therapy and autologous stem cell transplantation.

Summary

EudraCT number	2011-001499-20
Trial protocol	GR
Global end of trial date	26 July 2016

Results information

Result version number	v1 (current)
This version publication date	27 May 2022
First version publication date	27 May 2022

Trial information

Trial identification

Sponsor protocol code	RV-MM-GMSG-392

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02471820
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Meletios-Athanasios Dimopoulos
Sponsor organisation address	80 Vas. Sofias Ave & Lourou Str, Athens, Greece, 11528
Public contact	Meletios-Athanasios Dimopoulos, Meletios-Athanasios Dimopoulos, 0030 2103381541, mdimop@med.uoa.gr
Scientific contact	Meletios-Athanasios Dimopoulos, Meletios-Athanasios Dimopoulos, 0030 2103381541, mdimop@med.uoa.gr

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 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the overall response rate to lenalidomide in combination with adriamycin and low dose of dexamethasone (RAD regiment) in newly diagnosed patients with symptomatic MM eligible for high dose therapy and ASCT.

Protection of trial subjects:

55% of the patients received prophylactic granulocyte colony stimulating factor during the treatment course.
All of the efficacy and safety assessments were standard i.e. widely used and generally recognized as reliable, accurate and relevant (able to discriminate between effective and ineffective agents).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 November 2014
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	Greece: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	43
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period was from November 2014 to February 2016. Recruitment took place in 3 sites in Greece.

Pre-assignment

Screening details:

Newly diagnosed patients with symptomatic MM, according to the criteria of the IMWG who were candidates for ASCT in good performance and hematological status were deemed eligible for inclusion in the study. Patients not fulfilling the above-mentioned criteria or with serious comorbidities were excluded.

Period 1

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

Arms

Arm title	1st Arm

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:

Lenalidomide was administered per os at a dose of 25 mg daily, on days 1 to 21 of a 28-day cycle for 4 cycles.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone was administered per os at a dose of 40 mg, on days 1, 8, 15, and 22 of a 28-day cycle for 4 cycles.

Investigational medicinal product name	Doxorubicin/adriamycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Doxorubicin/adriamycin was administered as intravenous bolus infusion at a dose of 9 mg/m², on days 1-4 of a 28-day cycle for 4 cycles.

Number of subjects in period 1	1st Arm
Started	45
Completed	40
Not completed	5
Toxicity	3
Lost to follow-up	2

Number of subjects in period 1	1st Arm
Started	45
Completed	40
Not completed	5

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	43	43	
From 65-84 years	2	2	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	24	24	
Male	21	21	

End points

End points reporting groups

Reporting group title	1st Arm
Reporting group description: -	
Subject analysis set title	Baseline control
Subject analysis set type	Per protocol

Subject analysis set description:

Baseline measurements used as self control for comparison with RAD treatment after 4 cycles.
In addition to study subjects, 30 healthy individuals (18 males and 12 females) were also tested for markers of bone remodeling and angiogenic cytokines and served as controls.

Subject analysis set title	After RAD x 4
Subject analysis set type	Per protocol

Subject analysis set description:

Patients that have received 4 cycles of RAD treatment.

Primary: Overall Response Rate

End point title	Overall Response Rate[1]
End point description:	

Overall Response Rate was 66.7%.

End point type	Primary
End point timeframe:	

End of study.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was performed for this outcome measure.

End point values	1st Arm			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Patients				
Complete Response	1			
Very Good Partial Response	8			
Partial Response	21			

Attachments (see zip file)	Supplemental Figure 2.tiff

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) and Time-to Progression (TTP)

End point title	Progression-free survival (PFS) and Time-to Progression (TTP)
End point description:	

Median PFS and TTP not reached

End point type	Secondary

End point timeframe:

End of study

End point values	1st Arm			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percent				
number (not applicable)				
1-year PFS and TTP probability	88.6			
2-year PFS and TTP probability	60			

Attachments (see zip file)	Figure 1.tiff

Statistical analyses

No statistical analyses for this end point

Secondary: Grade 3 or 4 adverse events

End point title	Grade 3 or 4 adverse events

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	1st Arm			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Patients				
Anemia	4			
Neutropenia	3			
Febrile respiratory infection	2			
Febrile neutropenia	1			
Respiratory infection	1			
Hypocalcemia	1			
Acute renal failure	1			
Pulmonary embolism	1			
Lumbar pain	1			
Pathological fracture	1			
Leukopenia	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: C-terminal cross-linking telopeptide of collagen type I levels

End point title	C-terminal cross-linking telopeptide of collagen type I levels
End point description:	
End point type	Other pre-specified
End point timeframe:	
End of study	

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: ng/ml				
arithmetic mean (standard deviation)	0.74 (± 0.30)	0.54 (± 0.14)		

Attachments (see zip file)	CTX.png

Statistical analyses

Statistical analysis title	CTX analysis
Comparison groups	Baseline control v After RAD x 4
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Versus baseline.

Other pre-specified: Tartrate-resistant acid phosphatase isoform 5b levels

End point title	Tartrate-resistant acid phosphatase isoform 5b levels
End point description:	
End point type	Other pre-specified

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: U/L				
arithmetic mean (standard deviation)	3.42 (± 1.28)	1.25 (± 1.10)		

Attachments (see zip file)	TRACP.png

Statistical analyses

Statistical analysis title	TRACP-5b analysis
Comparison groups	Baseline control v After RAD x 4
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.01
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Versus baseline.

Other pre-specified: Bone-specific alkaline phosphatase levels

End point title	Bone-specific alkaline phosphatase levels

End point description:

End point type	Other pre-specified

End point timeframe:

End of study

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: µg/L				
arithmetic mean (standard deviation)	11.5 (± 5.1)	15.3 (± 6.7)		

Attachments (see zip file)	bALP.png

Statistical analyses

Statistical analysis title	bALP analysis
Comparison groups	Baseline control v After RAD x 4
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.036
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Versus baseline.

Other pre-specified: Procollagen type 1 amino-terminal propeptide levels

End point title	Procollagen type 1 amino-terminal propeptide levels

End point description:

End point type	Other pre-specified

End point timeframe:

End of study

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: mg/L				
arithmetic mean (standard deviation)	45 (± 15)	110 (± 57)		

Attachments (see zip file)	PINP.png

Statistical analyses

Statistical analysis title	P1NP analysis
Comparison groups	Baseline control v After RAD x 4
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.028
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Versus baseline.

Other pre-specified: Angiogenin levels

End point title	Angiogenin levels

End point description:

End point type	Other pre-specified

End point timeframe:

End of study

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: ng/mL				
arithmetic mean (standard deviation)	420 (± 120)	250 (± 110)		

Attachments (see zip file)	Ang.png

Statistical analyses

Statistical analysis title	Ang analysis
Comparison groups	Baseline control v After RAD x 4
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.02
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Versus baseline.

Other pre-specified: Vascular endothelial growth factor levels

End point title	Vascular endothelial growth factor levels

End point description:

End point type	Other pre-specified

End point timeframe:

End of study

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: pg/mL				
arithmetic mean (standard deviation)	260 (± 97)	108 (± 66)		

Attachments (see zip file)	VEGF.png

Statistical analyses

Statistical analysis title	VEGFanalysis
Comparison groups	Baseline control v After RAD x 4
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.01
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Versus baseline.

Other pre-specified: Fibroblast growth factor-basic levels

End point title	Fibroblast growth factor-basic levels

End point description:

End point type	Other pre-specified

End point timeframe:

End of study

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: pg/mL				
arithmetic mean (standard deviation)	1.23 (± 0.42)	0.32 (± 0.18)		

Attachments (see zip file)	bFGF.png

Statistical analyses

Statistical analysis title	bFGF analysis
Comparison groups	Baseline control v After RAD x 4

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.01
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Versus baseline.

Other pre-specified: Angiopoietin-1 to angiopoietin-2 ratio

End point title	Angiopoietin-1 to angiopoietin-2 ratio

End point description:

End point type	Other pre-specified

End point timeframe:

End of study

End point values	Baseline control	After RAD x 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	40		
Units: Ratio				
arithmetic mean (standard deviation)	13.3 (± 10.9)	18.8 (± 12.6)		

Attachments (see zip file)	Ang1-Ang2.png

Statistical analyses

Statistical analysis title	Ang-1/Ang-2 analysis
Comparison groups	Baseline control v After RAD x 4
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.022
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Versus baseline.

Other pre-specified: Stem cell collection post-RAD induction

End point title	Stem cell collection post-RAD induction

End point description:

End point type	Other pre-specified

End point timeframe:

End of study

End point values	1st Arm			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Patients				
number (not applicable)				
Adequate stem cell collection	40			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

End of study

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	1st Arm

Reporting group description: -

Serious adverse events	1st Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 45 (22.22%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Fainting			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dysautonomia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Septicemia			

subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Liver disease			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Maculopapular rash			
subjects affected / exposed	1 / 45 (2.22%)		
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 / 45 (2.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Deterioration of renal function			

subjects affected / exposed	2 / 45 (4.44%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Pathological fracture				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Febrile neutropenia				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile respiratory tract infection				
subjects affected / exposed	3 / 45 (6.67%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	2 / 45 (4.44%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
CMV Reactivation				
subjects affected / exposed	1 / 45 (2.22%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Metabolism and nutrition disorders				
Transaminases abnormal				
subjects affected / exposed	1 / 45 (2.22%)			
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	1st Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 45 (68.89%)		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	18 / 45 (40.00%)		
occurrences (all)	36		
Thrombocytopenia			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	7		
Neutropenia			
subjects affected / exposed	8 / 45 (17.78%)		
occurrences (all)	20		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	23 / 45 (51.11%)		
occurrences (all)	30		
Musculoskeletal and connective tissue disorders			
Fatigue			
subjects affected / exposed	5 / 45 (11.11%)		
occurrences (all)	8		
Bone pain			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	2		
Lumbar pain			

subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Infections and infestations

Fever
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Respiratory infection
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Metabolism and nutrition disorders

Hyponatremia
subjects affected / exposed	6 / 45 (13.33%)			
occurrences (all)	6			

Hypokalemia
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			

Elevated GGT
subjects affected / exposed	7 / 45 (15.56%)			
occurrences (all)	11			

Elevated AST levels
subjects affected / exposed	2 / 45 (4.44%)			
occurrences (all)	2			

Hypocalcemia
subjects affected / exposed	8 / 45 (17.78%)			
occurrences (all)	12			

Hypercalcemia
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Ypercholirethryaimia
subjects affected / exposed	1 / 45 (2.22%)			
occurrences (all)	1			

Hyponatremia
subjects affected / exposed	6 / 45 (13.33%)			
occurrences (all)	8			

Elevated ACT levels

subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Elevated ALT levels			
subjects affected / exposed	2 / 45 (4.44%)		
occurrences (all)	2		
Elevated ALP levels			
subjects affected / exposed	3 / 45 (6.67%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2014	The main reason behind the substantial protocol amendment was the implementation of further measures for pregnancy prevention plans.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported