Clinical trial results:
PHASE II MULTICENTER CLINICAL TRIAL TO INVESTIGATE THE EFFICACY AND SAFETY OF BENDAMUSTINE, DEXAMETHASONE AND THALIDOMIDE IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA PATIENTS AFTER TREATMENT WITH LENALIDOMIDE AND BORTEZOMIB OR WHICH ARE INELIGIBLE TO ONE OF THESE DRUGS.

Summary

EudraCT number	2011-001775-39
Trial protocol	IT
Global end of trial date	08 April 2017

Results information

Result version number	v1 (current)
This version publication date	24 June 2021
First version publication date	24 June 2021

Trial information

Trial identification

Sponsor protocol code	BDT-01-2011

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	U.O. Ematologia & CBMT, Hospital Bolzano
Sponsor organisation address	Via Lorenz Böhler 5, Bolzano, Italy,
Public contact	DIVISIONE DI EMATOLOGIA E TMO, AZIENDA OSPEDALIERA DI BOLZANO, +39 0471908807, michael.mian@asbz.it
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of BDT in relapsed or refractory multiple myeloma as measured by the rate of responses (time frame 18 months).

Protection of trial subjects:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator(s).
Patients will receive prophylactic aspirin (acetylsalicylic acid, ASA) (70-100mg) daily unless contraindicated. Patients who are at high risk for a thromboembolic event in whom ASA is contraindicated, the use of low molecular weight heparin or warfarin (or equivalent vitamin K antagonist) to keep the INR in the range of 2-3 may be considered or other anti-thrombotic therapy according to hospital guidelines or physician preference is acceptable.
All concomitant treatments for other pathologies except B-NHL as well as supportive therapies other than anti-cancer treatments are permitted as clinically indicated.
Prophylaxis against hepatitis B reactivation with Lamivudine 100 mg/die from the start of the treatment to one year after the end of the treatment is recommended in HBcAb positive patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2011
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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	14
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Age ≥ 18 years at the time of signing the informed consent form; Life expectancy of at least 3 months; Relapsed or refractory active MM after treatments containing bortezomib and lenalidomide or ineligible to both of these drugs with detectable myeloma protein in blood or urine; Disease free of prior malignancies for at least 5 years.

Pre-assignment

Screening details:

No screening details

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Single Arm

Arm description: -

Arm type	Single arm study
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

60 mg/m2 i.v. days 1, 8, 15

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg daily p.o. days 1-28; initial dose of 50mg/day, with an increment to 100mg after the first 15 days of treatment.

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

Dosage and administration details:

20 mg p.o. days 1,8 , 15, 22

Number of subjects in period 1[1]	Single Arm
Started	26
Completed	26

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Four patients were excluded from the present analyses: two were screening failures, one patient died and another one left the country
before treatment was started.

Baseline characteristics

Reporting groups	
Reporting group title	Single Arm

Reporting group description: -

Reporting group values	Single Arm	Total	
Number of subjects	26	26	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	66		
full range (min-max)	41 to 78	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	10	10	
ISS stage Units: Subjects			
Stage I	12	12	
Stage II	4	4	
Stage III	8	8	
missing	2	2	
Durie & Salmon stage Units: Subjects			
Stage I	5	5	
Stage II	4	4	
Stage III	16	16	
missing	1	1	
Renal failure Units: Subjects			
No	22	22	
Yes	3	3	
missing	1	1	
Bence-Jones proteinuria Units: Subjects			
No	10	10	

Yes	16	16	
missing	0	0	
ECOG PS Units: Subjects			
PS 0	15	15	
PS 1	8	8	
PS 2	2	2	
missing	1	1	
Lactate dehydrogenase Units: Subjects			
Normal	16	16	
Elevated	8	8	
missing	2	2	
Beta-2-microglobulin Units: Subjects			
Normal	6	6	
Elevated	17	17	
missing	3	3	
Type of monoclonal component Units: Subjects			
IgG kappa	8	8	
IgG lambda	7	7	
IgA kappa	4	4	
IgA lambda	4	4	
Lambda chains only	2	2	
IgD lambda	1	1	
Previous treatment lines Units: number			
median	3.5		
full range (min-max)	1 to 7	-	

End points

End points reporting groups	
Reporting group title	Single Arm
Reporting group description: -	
Subject analysis set title	Comparator
Subject analysis set type	Intention-to-treat
Subject analysis set description: fictional arm of comparison	

Primary: Overall Response (ORR)	
End point title	Overall Response (ORR)
End point description: teh overall response rate (ORR) was defined as the number of complete remissions (CR), very good partial remissions (VGPR) and partial responses (PR).	
End point type	Primary
End point timeframe: End of treatment: 6 months after registration.	

End point values	Single Arm	Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	26		
Units: category				
ORR	10	10		
less tahn ORR	16	16		

Statistical analyses

Statistical analysis title	Overall Response Rate
Statistical analysis description: Percent frequency with 95% confidence interval	
Comparison groups	Single Arm v Comparator
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	other[1]
Parameter estimate	Frequency
Point estimate	38.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.2
upper limit	59.4

Notes:

[1] - Was reported the percentage frequency with 95%CI according to Clopper-Pearson binomial confidence intervals.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival: from the date of registration to the date of death for any cause or date of last clinical control.

End point type	Secondary

End point timeframe:

18 months from registration in the study

End point values	Single Arm	Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	26		
Units: Probability at 18 months				
number (confidence interval 95%)	0.40 (0.22 to 0.63)	0.40 (0.22 to 0.63)		

Statistical analyses

Statistical analysis title	Estimate Overall survival at 18 months

Statistical analysis description:

Estimated OS at 18 months by means of Kaplan-Meier method.

Comparison groups	Single Arm v Comparator
Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	other
Parameter estimate	Kaplan-Meier estimate
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.63

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Time from date of registration to treatment interrumption, progression or death for any cause.

End point type	Secondary

End point timeframe:

18 months from date of registration.

End point values	Single Arm	Comparator		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	26	26		
Units: probability at 18 months				
number (confidence interval 95%)	0.22 (0.01 to 0.59)	0.22 (0.01 to 0.59)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 18 months from date of registration	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	Single arm study
Reporting group description: Report of adverse events observed.	

Serious adverse events	Single arm study		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neuropenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Single arm study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 26 (84.62%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Nervous system disorders			
Neurology			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Blood and lymphatic system disorders			

anemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all)	11 / 26 (42.31%) 11 4 / 26 (15.38%) 4 14 / 26 (53.85%) 14 7 / 26 (26.92%) 7 1 / 26 (3.85%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Poor clinical condition subjects affected / exposed occurrences (all)	 5 / 26 (19.23%) 5 1 / 26 (3.85%) 1		
Eye disorders Retinal tear subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1		
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	 4 / 26 (15.38%) 4		
Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1		
Skin and subcutaneous tissue disorders			

Dermatology subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Infections and infestations Infection subjects affected / exposed occurrences (all) fever subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	 4 / 26 (15.38%) 4 6 / 26 (23.08%) 6 3 / 26 (11.54%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2015	Change of the principal investogator, Prolongation of the enrolment period. Prolongation of the insurance period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported