Clinical trial results:
A phase III trial comparing bortezomib, cyclophosphamide and dexamethasone versus lenalinomide cyclophosphamide and dexamethasone in patients with multiple myeloma at first relapse

Summary

EudraCT number	2010-021557-40
Trial protocol	IT
Global end of trial date	28 February 2017

Results information

Result version number	v1 (current)
This version publication date	20 February 2020
First version publication date	20 February 2020
Summary attachment (see zip file)	Br J Haematology 2020 (Montefusco_et_al-2020-British_Journal_of_Haematology_Suppl.pdf)

Trial information

Trial identification

Sponsor protocol code	MM-Rel

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fondazione IRCCS Istituto Nazionale dei Tumori
Sponsor organisation address	via Venezian 1, Milano, Italy,
Public contact	Clinical Trials Center, Fondazione IRCCS Istituto Nazionale dei Tumori, 0039 0223903146, trialcenter@istitutotumori.mi.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	01 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2017
Global end of trial reached?	Yes
Global end of trial date	28 February 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the CR and VGPR rate at 6 weeks after the end of consolidation in patients treated with VCD (velcade-cyclophosphamide-dexamethasone) versus RCD (revlimid-cyclophosphamide-dexamethasone).

Protection of trial subjects:

Each subject, or the subject's representative, signed an informed consent form prior to screening

Background therapy:

All patients received acyclovir 400 mg bid for herpes viruses prophylaxis.
Prophylaxis with quinolones, cotrimoxazole, and fluconazole was prescribed as clinically indicated.
All subjects were allowed to receive Biphosphonates therapy (intravenous pamidronate or zolendronic acid) according to the current guidelines or when clinically indicated.

Evidence for comparator:

Bortezomib- and lenalidomide-containing regimens are well-established therapies in multiple myeloma. However, despite their extensive use, head-to-head comparisons have never been performed. Therefore, we conducted a phase III randomized trial comparing cyclophosphamide and dexamethasone plus bortezomib (VCD, i.e. Test Products) or lenalidomide (RCD, i.e. Reference Therapy) in MM patients at first relapse.

Actual start date of recruitment	03 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 159
Worldwide total number of subjects	159
EEA total number of subjects	159

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)	85
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 159 patients were enrolled from March 2011 until February 2015. The study was prematurely closed due to regional regulatory issues.

Pre-assignment

Screening details:

MM patients at first symptomatic relapse were eligible. Key entry criteria were age ≥18 and ≤75 years, and measurable disease according to the International Myeloma Working Group (IMWG) criteria.

Pre-assignment period milestones

Number of subjects started	159
Number of subjects completed	155

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Screening failure: 2
Reason: Number of subjects	death of unknown cause: 1

Period 1

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

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	VCD (bortezomib-cyclophosphamide-dexamethasone)

Arm description:

Induction treatment: cyclophosphamide 500 mg/sqm, iv, on day 1 and 8, and dexamethasone 20 mg, oral or iv, on days 1-2, 8-9, 15-16, and 22-23 in combination with subcutaneous bortezomib 1.3 mg/sqm on days 1, 8, 15, 22 (VCD) in six 35-day cycles.
Consolidation phase: after the first six cycles, patients received consolidation with 3 further cycles of VCD therapy, administered every 2 months (i.e. the duration of the cycle was 35 days, followed by a 25 days rest).
Patients who did not achieve at least a minimal response (MR) after the third cycle, or at least a PR after the sixth cycle, were allowed to go off study.

Arm type	Experimental
Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/sqm, on day 1 and 8 of each 35-day cycle

Investigational medicinal product name	dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Tablet

Routes of administration	Intravenous use, Oral use
Dosage and administration details: 20 mg, oral or iv, on days 1-2, 8-9, 15-16, and 22-23 of each 35-day cycle	
Investigational medicinal product name	bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: 1.3 mg/sqm on days 1, 8, 15, 22 of each 35-day cycle	
Arm title	RCD (lenalidomide-cyclophosphamide-dexamethasone)

Arm description:

Induction treatment: cyclophosphamide 500 mg/sqm, iv, on day 1 and 8, and dexamethasone 20 mg, oral or iv, on days 1-2, 8-9, 15-16, and 22-23 in combination with oral lenalidomide 15 mg on days 1 to 21 (RCD) in six 28-day cycles.
Consolidation phase: after the first six cycles, patients received consolidation with 3 further cycles of RCD therapy, administered every 2 months (i.e. the duration of the cycle was 28 days, followed by a 32 days rest).
Patients who did not achieve at least a minimal response (MR) after the third cycle, or at least a PR after the sixth cycle, were allowed to go off study.
RCD arm patients received anti-thrombotic prophylaxis with low molecular weight heparin at 100 IU/Kg/die during the first three courses.

Arm type	Active comparator
Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 500 mg/sqm, iv, on day 1 and 8 of each 28 days cycle	
Investigational medicinal product name	dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use
Dosage and administration details: 20 mg, oral or iv, on days 1-2, 8-9, 15-16, and 22-23 of each 28 days cycle	
Investigational medicinal product name	lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 15 mg on days 1-21 of each 28 days cycle	

Number of subjects in period 1[1]	VCD (bortezomib-cyclophosphamide-dexamethasone)	RCD (lenalidomide-cyclophosphamide-dexamethasone)
Started	76	79
Mid-Induction (after the third cycle)	53	61
End of Induction (after the sixth cycle)	41	49
Completed	31	43
Not completed	45	36
Lack of partial response after the sixth cycle	9	7
Physician decision	4	6
Consent withdrawn by subject	3	-
Adverse event, non-fatal	-	1
Progressive disease during consolidation	6	6
Lost to follow-up	3	3
Lack of minimal response after the third cycle	20	13

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: A total number of 186 patients was required to evaluate the primary endpoint. The required sample size was increased up to 200 patients (100 for each arm) to account for about 5% drop-in and drop-outs. However, only 159 patients were enrolled as the study was prematurely closed due to regional regulatory issues. Among patients enrolled, 155 were randomized to receive VCD (n = 76) or RCD (n = 79), and were included in the ITT analysis.

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	155	155	
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)	83	83	
From 65-84 years	72	72	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	83	83	
Male	72	72	

End points

End points reporting groups

Reporting group title	VCD (bortezomib-cyclophosphamide-dexamethasone)

Reporting group description:

Induction treatment: cyclophosphamide 500 mg/sqm, iv, on day 1 and 8, and dexamethasone 20 mg, oral or iv, on days 1-2, 8-9, 15-16, and 22-23 in combination with subcutaneous bortezomib 1.3 mg/sqm on days 1, 8, 15, 22 (VCD) in six 35-day cycles.
Consolidation phase: after the first six cycles, patients received consolidation with 3 further cycles of VCD therapy, administered every 2 months (i.e. the duration of the cycle was 35 days, followed by a 25 days rest).
Patients who did not achieve at least a minimal response (MR) after the third cycle, or at least a PR after the sixth cycle, were allowed to go off study.

Reporting group title	RCD (lenalidomide-cyclophosphamide-dexamethasone)

Reporting group description:

Induction treatment: cyclophosphamide 500 mg/sqm, iv, on day 1 and 8, and dexamethasone 20 mg, oral or iv, on days 1-2, 8-9, 15-16, and 22-23 in combination with oral lenalidomide 15 mg on days 1 to 21 (RCD) in six 28-day cycles.
Consolidation phase: after the first six cycles, patients received consolidation with 3 further cycles of RCD therapy, administered every 2 months (i.e. the duration of the cycle was 28 days, followed by a 32 days rest).
Patients who did not achieve at least a minimal response (MR) after the third cycle, or at least a PR after the sixth cycle, were allowed to go off study.
RCD arm patients received anti-thrombotic prophylaxis with low molecular weight heparin at 100 IU/Kg/die during the first three courses.

Primary: VGPR and CR rate

End point title	VGPR and CR rate

End point description:

Since we compared two fixed-duration therapies and we were mainly interested in discerning the depth of response obtained with the two treatments, we chose as primary endpoint the achievement of a very good partial response (VGPR) or better (i.e. CR) at 6 weeks after the end of consolidation. Response was assessed according to the IMWG criteria.

End point type	Primary

End point timeframe:

At six weeks after 9 treatment cycles

End point values	VCD (bortezomib-cyclophosphamide-dexamethasone)	RCD (lenalidomide-cyclophosphamide-dexamethasone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	43		
Units: subjects				
Stringent Complete Response (sCR)	4	1		
Complete response (CR)	5	5		
Very Good Partial Response (VGPR)	3	8		
Partial Response (PR)	10	20		
Stable Disease (SD)	3	1		
Progressive disease (PD)	4	6		

Not assessable	2	2		

Statistical analyses

Statistical analysis title	Depth of response (VGPR and CR rate)

Statistical analysis description:

The primary endpoint was achievement of a very good partial response (VGPR) or better at six weeks after 9 treatment cycles. The expected VGPR and CR rate in the VCD and RCD treatment groups were 40% and 20%, respectively. Allowing for a significance level (alpha) of 5%, and a 85% power, then a total number of 186 patients were required. Statistical analysis was performed on an Intention-To-Treat basis. Statistical analyses were conducted using SAS (version 9.4) and R (version 3.3.1) software.

Comparison groups	VCD (bortezomib-cyclophosphamide-dexamethasone) v RCD (lenalidomide-cyclophosphamide-dexamethasone)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≤ 0.05 [2]
Method	Regression, Cox

Notes:

[1] - For regulatory issues on use of drugs in clinical trials, we enrolled only 159 patients, in spite of at least 186 patients being necessary to keep a statistical power of 85%. After 9 cycles of therapy, 12 VCD and 14 RCD patients achieved a VGPR or better (p=0.70); thus the primary endpoint of the study was not met.
[2] - We planned to use a standard p-value

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Median follow-up was 34 months, specifically 34 months in the VCD group, and 32 months in the RCD group. One-year PFS was 60%(95% CI: 50–72%) and 64% (95% CI: 53–75%), two-year PFS was 34% (95% CI: 25–47%) and 40% (95% CI: 30–53%), and median PFS was 16.3 (95% CI: 12.1–22.4) and 18.6 (95% CI: 14.7–25.5), in the VCD and in RCD arms respectively. No statistically significan tdifferences in PFS were observed with VCD and RCD according to age(<65 or ≥65 years), first-line therapy (chemotherapy or bortezomib-based regimen), ISS stage (I vs. II–III), and time-to-progression with first-line therapy (>3 years vs. ≤3 years).

End point type	Secondary

End point timeframe:

PFS was calculated as the time from randomization to the date of first evidence of PD or death without evidence of PD or to the last date the patient was known to be progression-free. Median follow-up was calculated by the reverse Kaplan–Meier method.

End point values	VCD (bortezomib-cyclophosphamide-dexamethasone)	RCD (lenalidomide-cyclophosphamide-dexamethasone)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	79		
Units: not progressed living patients				
1-year not progressed living patients	45	49		

2-year not progressed living patients	21	26		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization up to 6 weeks after the end of consolidation

Adverse event reporting additional description:

Toxicities are graded according to the Common Terminology Criteria for Adverse Events v.3.0 (CTCAE)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12

Reporting groups

Reporting group title	All treated patients

Reporting group description:

A total of 52 patients, 26 in each arm, experienced at least one toxicity.
All deaths occurred during follow-up and were not recorded as serious adverse events. No toxicity related deaths were observed. The majority of patients in both study groups (n = 42) died from relapse or progression: 25 in the VCD and 17 in the RCD arm respectively. Among others, 9 patients died for other causes: 2 in the VCD arm and 7 in the RCD arm respectively. For 6 patients (3 in each arm) the cause of death is unknown.

Serious adverse events	All treated patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 155 (21.94%)		
number of deaths (all causes)	57		
number of deaths resulting from adverse events	0		
Investigations			
Neutropenia	Additional description: Grade 3-4 neutropenia was observed in 4 VCD patients and 9 RCD patients		
subjects affected / exposed	13 / 155 (8.39%)		
occurrences causally related to treatment / all	20 / 20		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia	Additional description: Grade 3-4 Thrombocytopenia occurred in 3 VCD patients and in 5 RCD patients		
subjects affected / exposed	8 / 155 (5.16%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Second primary malignancy			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Infection	Additional description: Grade 3-4 infections occurred in 9 VCD patients and in 3 RCD patients		
subjects affected / exposed	12 / 155 (7.74%)		
occurrences causally related to treatment / all	12 / 12		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All treated patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 155 (30.32%)		
Investigations			
Neutropenia	Additional description: Grade 1-2 neutropenia occurred in 8 RCD patients (none in VCD patients)		
subjects affected / exposed	8 / 155 (5.16%)		
occurrences (all)	8		
Nervous system disorders			
Peripheral sensory neuropathy	Additional description: any grade peripheral sensory neuropathy occurred in a total of 12 VCD and 4 RCD patients		
subjects affected / exposed	16 / 155 (10.32%)		
occurrences (all)	16		
Infections and infestations			
Infection	Additional description: Grade 1-2 infections were observed in 7 VCD patients and in 16 RCD patients		
subjects affected / exposed	23 / 155 (14.84%)		
occurrences (all)	23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2011	Amendment 1: clarifications on the evaluation of the response after the third cycle; increase in the number of participating sites.
16 July 2012	Amendment 2: changes in exclusion criteria to specify that "active hepatitis B virus (HBV DNA positivity) or hepatitis C virus (HCV RNA positivity) are not, per se, a contraindication to the study, unless, in the opinion of the treating physician, these conditions can be predicted to interfere with treatment administration"; clarifications on the consolidation phase; increase in the number of participating sites.
27 January 2014	Amendment 3: extension of study enrolment (from 2 to 4 years); change in the route of bortezomib administration (from intravenous to subcutaneous).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 July 2015	Amendment 4: early termination of enrolment due to regional regulatory issues, leading the National Healthcare System to stop bortezomib and lenalidomide free supply for the study.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Our results should be considered with caution, since, for regulatory issues on use of drugs in clinical trials, we enrolled only 159 patients, in spite of at least 186 patients being necessary to keep a statistical power of 85%.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31898319