



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 Venezzian 1, Milano, Italy, |
| Public contact | Clinical Trials Center, Fondazione IRCCS Istituto Nazionale dei Tumori, 0039 0223903146, trialcenter@istitutotumori.mi.it |
| Scientific contact | Prof. Corradini: paolo.corradini@unimi.it; Dr Montefusco: montefusco.vittorio@sancarlo.mi.it; , Fondazione IRCCS Istituto Nazionale dei Tumori, 0039 0223902950, paolo.corradini@unimi.it |

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 zoledronic 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- cyclophospham ide- dexamethason e) | RCD (lenalidomide- cyclophospham ide- dexamethason e) | | |
|-----------------------------------|--|--|--|--|
| 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 significant differences 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>