



Clinical trial results:

Phase II study of carfilzomib- cyclophosphamide-dexamethasone and high-dose melphalan followed by randomization between observation or maintenance with carfilzomib and dexamethasone in patients with relapsed multiple myeloma after high-dose melphalan with autologous stem cell support

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-003789-15 |
| Trial protocol | DK FI SE NO LT |
| Global end of trial date | 01 September 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 10 May 2021 |
| First version publication date | 10 May 2021 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | NMSG#20/13 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02572492 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Nordic Myeloma Study Group |
| Sponsor organisation address | Mølleparkvej 4, Aalborg, Denmark, 9000 |
| Public contact | Clinical Trial Unit Hematology Aalborg University Hospital Mølleparkvej 4 9000 Aalborg Denmark, Nordic Myeloma Study Group, 0045 97663884, henrik.gregersen@rn.dk |
| Scientific contact | Clinical Trial Unit Hematology Aalborg University Hospital Mølleparkvej 4 9000 Aalborg Denmark, Nordic Myeloma Study Group, 0045 97663884, henrik.gregersen@rn.dk |

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 | 06 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 September 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 September 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of our study is to evaluate the effect of the combination of carfilzomib, cyclophosphamide and dexamethasone in the induction regimen and carfilzomib in the conditioning regimen of salvage HDT. In addition to evaluate the potential effect of carfilzomib/dexamethasone maintenance treatment.

Protection of trial subjects:

Exclusion criteria regarding heart disease e.g. exclusion of patients with uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrolment, NYHA Class III or IV heart failure, uncontrolled angina, clinically significant pericardial disease, uncontrolled severe arrhythmias, or cardiac amyloidosis. In addition LVEF <40%, determined by 2-D transthoracic echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA)

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 01 January 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 | Norway: 58 |
| Country: Number of subjects enrolled | Sweden: 50 |
| Country: Number of subjects enrolled | Denmark: 66 |
| Country: Number of subjects enrolled | Finland: 10 |
| Country: Number of subjects enrolled | Lithuania: 16 |
| Worldwide total number of subjects | 200 |
| EEA total number of subjects | 200 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|-----|
| wk | |
| 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) | 138 |
| From 65 to 84 years | 62 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from NMSG centers in Denmark, Sweden, Norway, Finland and Lithuania

Pre-assignment

Screening details:

Multiple myeloma patients with first relapse more than one year after single or double high-dose melphalan with stem cell support

Period 1

| | |
|------------------------------|---|
| Period 1 title | Induction and salvage ASCT (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|----------------------------|
| Arm title | CA-CY-DEX and salvage ASCT |
|------------------|----------------------------|

Arm description:

Included patients received:

Four cycles of CAR-CY-DEX (iv carfilzomib, p.o. cyclophosphamide and p.o. dexamethasone

Conditioning regimen: Iv carfilzomib on day -2 and -1 and iv melphalan 200 mg/sqm on day -2.

| | |
|--|---------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Carfilzomib |
| Investigational medicinal product code | L01XG02 |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Induction regime:

Four cycles of CAR-CY-DEX (Cycle 1 with iv carfilzomib 20 mg/sqm on days 1 and 2, and iv carfilzomib 36 mg/sqm on days 8, 9, 15 and 16. Cycle 2 - 4 with iv carfilzomib 36 mg/sqm on days 1, 2, 8, 9, 15 and 16. P.o. cyclophosphamide 300 mg/sqm on days 1, 8 and 15 and p.o. dexamethasone 20 mg on days 1, 2, 8, 9, 15 and 16 in each 28-days cycle).

Conditioning regimen:

Iv carfilzomib 27 mg/sqm on day -2 and -1

Iv melphalan 200 mg/sqm on day -2

> 2.0 x 10⁶ CD34+ stem cells/kg body weight on day 0

| Number of subjects in period 1 | CA-CY-DEX and salvage ASCT |
|--------------------------------|----------------------------|
| Started | 200 |
| Completed | 168 |
| Not completed | 32 |
| Adverse event, serious fatal | 5 |
| Consent withdrawn by subject | 7 |
| Physician decision | 1 |
| Adverse event, non-fatal | 8 |

| | |
|--------------------------|---|
| Broken bag af stem cells | 1 |
| Non-compliance | 1 |
| Progression af myeloma | 8 |
| Lost to follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Induction and salvage ASCT |
|-----------------------|----------------------------|

Reporting group description: -

| Reporting group values | Induction and salvage ASCT | Total | |
|------------------------|----------------------------|-------|--|
| Number of subjects | 200 | 200 | |
| Age categorical | | | |
| Age distribution | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 138 | 138 | |
| From 65-84 years | 62 | 62 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 84 | 84 | |
| Male | 116 | 116 | |

Subject analysis sets

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | CAR-CY-DEX and salvage ASCT |
|----------------------------|-----------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Intention-to-treat |
|---------------------------|--------------------|

Subject analysis set description:

CAR-CY-DEX and salvage ASCT

| Reporting group values | CAR-CY-DEX and salvage ASCT | | |
|------------------------|-----------------------------|--|--|
| Number of subjects | 200 | | |
| Age categorical | | | |
| Age distribution | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 84 | | |
| Male | 116 | | |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | CA-CY-DEX and salvage ASCT |
| Reporting group description: | |
| Included patients received: | |
| Four cycles of CAR-CY-DEX (iv carfilzomib, p.o. cyclophosphamide and p.o. dexamethasone | |
| Conditioning regimen: Iv carfilzomib on day -2 and -1 and iv melphalan 200 mg/sqm on day -2. | |
| Subject analysis set title | CAR-CY-DEX and salvage ASCT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| CAR-CY-DEX and salvage ASCT | |

Primary: Comparison of time to progression (TTP) after first high-dose melphalan with stem cell support (HDT) and TTP after a second HDT combined with carfilzomib-cyclophosphamide-dexamethasone (CAR-CY-DEX)

| | |
|-----------------------------------|---|
| End point title | Comparison of time to progression (TTP) after first high-dose melphalan with stem cell support (HDT) and TTP after a second HDT combined with carfilzomib-cyclophosphamide-dexamethasone (CAR-CY-DEX) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| From inclusion until end of study | |

| End point values | CA-CY-DEX and salvage ASCT | CAR-CY-DEX and salvage ASCT | | |
|---------------------------------------|----------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 168 | 168 | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| TTP after upfront ASCT | 33.2 (30.4 to 37.7) | 33.2 (30.4 to 37.7) | | |
| TTP after salvage ASCT | 26.7 (24.2 to 30.7) | 26.7 (24.2 to 30.7) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Comparison of TTP |
| Statistical analysis description: | |
| Mann-Whitney test | |
| Comparison groups | CA-CY-DEX and salvage ASCT v CAR-CY-DEX and salvage ASCT |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 336 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.0001 |
| Method | Wilcoxon (Mann-Whitney) |

Secondary: Treatment response after four cycles of CAR-CY-DEX induction

| | |
|------------------------|---|
| End point title | Treatment response after four cycles of CAR-CY-DEX induction |
| End point description: | No difference compared with VGPR, CR or sCR after induction therapy after up-front ASCT |
| End point type | Secondary |
| End point timeframe: | VGPR, CR or sCR after CAR-CY-DEX induction before salvage ASCT |

| | | | | |
|--------------------------------------|----------------------------|--|--|--|
| End point values | CA-CY-DEX and salvage ASCT | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 200 | | | |
| Units: Patients with VGPR, CR or sCR | | | | |
| number (not applicable) | 200 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to marrow regeneration (neutrophil- and platelet recovery) after the salvage ASCT

| | |
|------------------------|---|
| End point title | Time to marrow regeneration (neutrophil- and platelet recovery) after the salvage ASCT |
| End point description: | Mean time to neutrophils above $1.0 \times 10^9/\text{L}$ after salvage ASCT and mean time to thrombocytes above $100 \times 10^9/\text{L}$ after salvage ASCT. |
| End point type | Secondary |
| End point timeframe: | Time to marrow regeneration (neutrophil- and platelet recovery) after the HDT |

| | | | | |
|--------------------------------------|----------------------------------|--|--|--|
| End point values | CA-CY-DEX and salvage ASCT | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 168 | | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | | | | |
| Neutrophile recovery | 13.4 (± 3.5) | | | |
| Thrombocyte recovery | 21.1 (± 8.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Response rates of induction therapy and HDT

| | |
|-----------------|---|
| End point title | Response rates of induction therapy and HDT |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment response after CAR-CY-DEX induction and salvage ASCT

| | | | | |
|-------------------------------------|----------------------------------|--|--|--|
| End point values | CA-CY-DEX and salvage ASCT | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 168 | | | |
| Units: Different levels of response | | | | |
| SCR | 19 | | | |
| CR | 19 | | | |
| VGPR | 82 | | | |
| PR | 45 | | | |
| SD | 2 | | | |
| PD | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 60 days after salvage ASCT

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|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|---------|
| Dictionary name | NCI CTC |
|-----------------|---------|

| | |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | CAR-CY-DEX and salvage ASCT |
|-----------------------|-----------------------------|

Reporting group description:

Included patients received:

Four cycles of CAR-CY-DEX (iv carfilzomib, p.o. cyclophosphamide and p.o. dexamethasone

Conditioning regimen: Iv carfilzomib on day -2 and -1 and iv melphalan 200 mg/sqm on day -2.

| Serious adverse events | CAR-CY-DEX and salvage ASCT | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 87 / 200 (43.50%) | | |
| number of deaths (all causes) | 4 | | |
| number of deaths resulting from adverse events | 1 | | |
| Vascular disorders | | | |
| Venous thromboembolism | Additional description: Deep vein thrombosis and pulmonary embolism | | |
| subjects affected / exposed | 3 / 200 (1.50%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischemic attack | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracerebral hemorrhage | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 200 (1.50%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 200 (0.50%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | | |
| occurrences causally related to treatment / all | 2 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea and vomiting | | | |
| subjects affected / exposed | 4 / 200 (2.00%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thyphilitis | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticulitis | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 3 / 200 (1.50%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis | | | |
| subjects affected / exposed | 2 / 200 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Electrolyte disorder | | | |
| subjects affected / exposed | 3 / 200 (1.50%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Septicemia | | | |
| subjects affected / exposed | 14 / 200 (7.00%) | | |
| occurrences causally related to treatment / all | 6 / 14 | | |
| deaths causally related to treatment / all | 1 / 4 | | |
| Other bacterial infection | | | |
| subjects affected / exposed | 51 / 200 (25.50%) | | |
| occurrences causally related to treatment / all | 33 / 65 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 8 / 200 (4.00%) | | |
| occurrences causally related to treatment / all | 1 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|-----------------------------|--|--|
| Non-serious adverse events | CAR-CY-DEX and salvage ASCT | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 181 / 200 (90.50%) | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|-----------------------------|--------------------|--|--|
| subjects affected / exposed | 176 / 200 (88.00%) | | |
| occurrences (all) | 176 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 181 / 200 (90.50%) | | |
| occurrences (all) | 181 | | |
| Neutropenia | | | |
| subjects affected / exposed | 160 / 200 (80.00%) | | |
| occurrences (all) | 160 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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| No |
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Notes: