A Randomized, Open-label Phase 3 Study of Carfilzomib, Melphalan, and Prednisone versus Bortezomib, Melphalan, and Prednisone in Transplant ineligible Patients with Newly Diagnosed Multiple Myeloma

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Primary Objective:To compare the progression-free survival (PFS) of transplant-ineligible subjects with newly diagnosed multiple myeloma who are treated withcarfilzomib, melphalan, and prednisone (CMP) versus those treated with bortezomib (Velcade...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON44957

Source
ToetsingOnline

Brief title
CLARION

Condition

- Plasma cell neoplasms

Synonym
Multiple myeloma

Research involving

Human

Sponsors and support

Primary sponsor: Onyx Therapeutics, Inc.
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Multiple Myeloma

Outcome measures

Primary outcome

Primary Objective:

To compare the progression-free survival (PFS) of transplant-ineligible subjects with newly diagnosed multiple myeloma who are treated with carfilzomib, melphalan, and prednisone (CMP) versus those treated with bortezomib (Velcade), melphalan, and prednisone (VMP).

Secondary outcome

Secondary Objectives:

To compare the following between the treatment groups:

1. Overall survival (OS)

2. Overall response (OR) status

3. Complete response (CR) status

4. Neuropathy Events

5. EORTC QLQ-C30 Global Health Status/QoL scale

6. Safety and tolerability

Study description

Background summary

Please refer to the study protocol section 1.6 "Study rationale"

Study objective

Primary Objective:
To compare the progression-free survival (PFS) of transplant-ineligible subjects with newly diagnosed multiple myeloma who are treated with carfilzomib, melphalan, and prednisone (CMP) versus those treated with bortezomib (Velcade), melphalan, and prednisone (VMP).
Secondary Objectives:
To compare the following between the treatment groups:
1. Overall survival (OS)
2. Overall response rate (ORR; defined as the proportion of best overall response of stringent complete response [sCR], complete response [CR], very good partial response [VGPR], and partial response [PR])
3. Complete response rate (CRR; defined as the proportion of best overall response of stringent complete response [sCR] or complete Response [CR])
4. Neuropathy events (defined as the incidence of grade 2 or higher peripheral neuropathy [PN] events)
5. European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire (QLQ) C30 Global Health Status/QoL scale
6. Safety and tolerability

Study design

This is a Phase 3 multicenter, open-label, randomized study in transplant-ineligible subjects with newly diagnosed multiple myeloma.
Subjects will be randomized to receive 1 of 2 treatment regimens, CMP or VMP, as outlined in the Study Treatment section.
The randomization will be stratified on the basis of the following criteria:
International Staging System (ISS) stage: Stage 1 versus Stages 2 or 3
Choice of route of bortezomib administration (if the subject were to receive bortezomib): intravenous (IV) versus subcutaneous (SC)
Region: (1) North America, (2) Europe, (3) Asia Pacific, or (4) other
Age: < 75 years versus >= 75 years
A permuted-block randomization will be used to randomize subjects within each stratum. The estimated sample size is 882 subjects.
Subjects will receive the treatment determined by randomization until confirmed disease progression, unacceptable toxicity, withdrawal of consent, death, or completion of nine 6-week treatment cycles (whichever occurs first). No

crossover between the 2 treatment arms will be allowed. Subjects in both treatment arms will be assessed for multiple myeloma disease response according to the International Myeloma Working Group (IMWG)-Uniform Response Criteria (URC) using central laboratory test results every 3 weeks, irrespective of treatment delays or the timing of treatment cycles, during the first 54 weeks of the study. Afterwards, disease response assessments will be extended to every 6 weeks until confirmed progressive disease (PD).
For subjects who discontinue treatment before PD occurs (such as for an AE, noncompliance), disease response assessments using central laboratory results will be performed every 3 weeks during the first 54 weeks of the study and every 6 weeks thereafter, until confirmed PD.
Long-term follow up (LTFU) for survival and PFS2 will continue approximately every 12 weeks (± 1 week) for each subject after their disease progresses, until the subject has withdrawn consent for further participation, is lost to follow-up, has died, a total of 400 deaths have occurred, or the study is closed, whichever is earliest. For any subject who is lost to follow-up, the study site will attempt to ascertain survival information via public database search.
This study is designed to detect a 35% improvement in PFS (hazard ratio [HR] = 0.74) for CMP over VMP with 85% power and a 1-sided significance level of 0.025. It is assumed that the PFS for the control arm (VMP regimen) is 21 months. One interim analysis will be performed when 75% (302) of the total 403 PFS events have occurred.

Intervention

Study Treatment Regimens
CMP Regimen: 9 cycli of 42 days

Cyclus/cycli Days Study Treatment
1 1, 2 Carfilzomib 20 mg/m2
1 8, 9, 22, 23, 29, 30 Carfilzomib 36 mg/m2
2-9 1, 2, 8, 9, 22, 23, 29, 30 Carfilzomib 36 mg/m2
1-9 1-4 Melfalan 9 mg/m2
1-9 1-4 Prednison 60 mg/m2
1 8, 9, 22, 23, 29, 30 Dexamethason 4 mg

VMP Regimen: 9 cycli of 42 days
Cyclus/cycli Days Study Treatment
1-4 1, 4, 8, 11, 22, 25, 29, 32 Bortezomib 1,3 mg/m2
5-9 1, 8, 22, 29 Bortezomib 1,3 mg/m2
1-9 1-4 Melfalan 9 mg/m2
1-9 1-4 Prednison 60 mg/m2

Study burden and risks

Patients may experience drug-related side effect. For full list of side effects please refer to Appendix III of the main patient information sheet and infomed consent from.
In addition to side effects patients may experience discomforts and risks associated with the study procedures such as blood drawing, bone marrow sampling, ECHO, X-rays exposure.
Carfilzomib has an adequate safety profile without apparent long-term toxicity, including in patients with renal impairment, and those on dialysis. The benefit/risk ratio of carfilzomib appears favorable and may be preferable to some available agents, allowing for improved therapy for patients with multiple myeloma and possibly other neoplastic conditions.
The results of preclinical and clinical studies to date suggest that a clinical study of efficacy and safety of carfilzomib in patients with multiple myeloma is advisable and justifiable with regard to the risk/benefit ratio.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

• Newly diagnosed symptomatic multiple myeloma
• Transplant-ineligibility
• Males and females >= 18 years of age
• Left ventricular ejection fraction (LVEF) >= 40%

Exclusion criteria

• POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
• Plasma cell leukemia
• Waldenström macroglobulinemia (WM)
• Known amyloidosis
• Significant neuropathy (Grades >= 2) within 14 days prior to randomization

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-06-2014
Enrollment:	19
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alkeran
Generic name:	Melphalan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kyprolis
Generic name:	Carfilzomib
Product type:	Medicine
Brand name:	Prednison HEXAL
Generic name:	Prednisone
Product type:	Medicine
Brand name:	Velcade
Generic name:	Bortezomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-05-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2014

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	08-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-005283-97-NL
ClinicalTrials.gov	NCT01818752
CCMO	NL44557.078.13