A Randomized, Multicenter, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone (CRd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Relapsed Multiple Myeloma

Published: 06-07-2010
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To compare progression-free survival in subjects with relapsed multiple myeloma who are receiving CRd vs PFS in subjects receiving Rd alone.

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

Summary

ID

NL-OMON38201

Source
ToetsingOnline

Brief title
Onyx PX-171-009

Condition

- Plasma cell neoplasms

Synonym
cancer of the blood, Kahlers desease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Carfilzomib, Dexamethasone, Lenalidomide, Relapsed Multiple Myeloma

Outcome measures

Primary outcome

Progression-free survival (PFS)

Secondary outcome

• Overall survival

• Overall response rate: stringent complete response + complete response + very good partial response + partial response

• Disease control rate: overall responses + minimal response+ stable disease lasting at least 8 weeks

• Duration of response

• Change from baseline in quality of life assessments (EORTC QLQ-C30 and QLQ-MY20)

• Safety

• Time to progression (exploratory)

• QOL subscales EORTC QLQ-C30 and QLQ-MY20

• Time to next treatment (exploratory)

• Clinical Benefit Response

Study description

Background summary

This study is to compare PFS (progression free survival) in subjects with relapsed multiple myeloma who are receiving CRd vs subjects receiving Rd alone. Based on the therapeutic index of carfilzomib, nonoverlapping toxicities between carfilzomib and lenalidomide, and the apparent reduction in peripheral neuropathy compared with bortezomib, the combination of CRd is anticipated to be highly effective in the treatment of multiple myeloma. The results of the Phase 1b study using this regimen (PX-171-006) support this proposal with promising evidence of tolerability and activity in relapsed and refractory multiple myeloma.

Study objective

To compare progression-free survival in subjects with relapsed multiple myeloma who are receiving CRd vs PFS in subjects receiving Rd alone.

Study design

This is a Phase 3, randomized, open-label, multicenter study comparing two treatment regimens for subjects with relapsed multiple myeloma.

Intervention

Subjects will receive the treatment determined by randomization in 28-day cycles until disease progression or unacceptable toxicity
The general treatment plans for the Rd and CRd arms are as follows:

Rd arm
• Cycles 1 and higher (28 days each): lenalidomide (day 1-21) and dexamethasone (day 1, 8, 15, and 22)

CRd arm
• Cycles 1 through 12 (28 days each): carfilzomib (day 1, 2, 8, 9, 15 and 16), lenalidomide, and dexamethasone(day 1, 8, 15, and 22)
• Cycles 13 through 18 (28 days each): carfilzomib (day 1, 2, 15 and 16), lenalidomide, and dexamethasone (day 1, 8, 15, and 22)
• Cycles 19 and higher (28 days each): lenalidomide and dexamethasone (day 1, 8, 15, and 22) (no carfilzomib)

Study burden and risks

Carfilzomib:

Likely Side Effects: those occurring in more than 20% or more than 20 out of 100 persons who receive carfilzomib:Fatigue (tiredness), Nausea, Anemia,

Less Likely Side Effects: those occurring in 5-20% or 5 to 20 out of 100 persons who receive carfilzomib: Decreased platelet counts, Diarrhea, Mild decreases in kidney function, Vomiting, Shortness of breath, Fever, Chills, Loss of or decreased appetite, Decreased WBC count which may decrease your ability to fight infection, Headache, Constipation, Swelling of the arms or legs, Cough, Blood chemistry and electrolyte alterations, Pain or irritation at the injection site, Dizziness, Mild inflammation of the liver, Rash and/or Itching.

Lenalidomide
Side Effects of Any Grade Occurring in 10% or More of Patients: Fatigue or feeling tired; Lack or loss of strength; Problems falling asleep or staying asleep;Anemia or a decrease in red blood cells that can cause tiredness; Neutropenia or a decrease in white blood cells that can make you more prone to infections; Thrombocytopenia or a decrease in platelets which can cause you to bruise or bleed easily; Constipation or difficulty moving your bowels; Diarrhea or loose/frequent bowel movements; Nausea; Loss of appetite; Back pain; Joint pain; Muscle cramps; Swelling of the arms and legs; Fever; Cough; Shortness of breath or difficulty catching your breath; Upper respiratory infection; Rash; Itching and dry skin; Dizziness;Headache.

Dexamethasone:
Side Effects of Dexamethasone Could Include: Stomach upset, irritation or stomach ulcers; Increased blood sugar; Increased blood pressure and swelling from retaining fluid; Decreased production of your body*s stress hormone cortisol; Increased susceptibility to infection; Insomnia (trouble sleeping); Mood changes, depression, anxiety ; Restlessness ; Vomiting; Diarrhea; Fever; Decreased platelet count; Increased risk of cataracts and glaucoma; Bone thinning (osteoporosis); Muscle loss; Problems with healing; Acne; Weight gain; Easy bruising; Irregular or absent menstrual periods; Headache; Dizziness; Increased hair growth

If you experience any of the following symptoms, let your doctor know immediately: Skin rash; Swollen face, lower legs, or ankles; Vision problems; Cold or infection that lasts a long time; Muscle weakness or cramps; Black or tarry stool

Further information regarding side effects and risks are extensively described in the patient information sheet.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion
1. Symptomatic multiple myeloma
2. Measurable disease, as defined by one or more of the following (assessed within 21 days prior to randomization):
o Serum M-protein >= 0.5 g/dL
o Urine Bence-Jones protein >= 200 mg/24 hours
o For IGA patients whose disease can only be reliably measured by serum quantitative immunoglobulin (qIgA) >= 750 mg/dL (0.75 g/dL)
3. Prior treatment with at least one, but no more than three, regimens for multiple myeloma
4. Documented relapse or progressive disease on or after any regimen (subjects refractory to the most recent line of therapy are eligible)
5. Achieved a response to at least one prior regimen (defined as >= 25% decrease in M-

protein [or total protein in countries in which electrophoresis is not routinely available])
6. Age >= 18 years
7. Life expectancy >= 3 months
8. Eastern Cooperative Oncology Group performance status 0-2
9. Adequate hepatic function, with serum ALT <= 3.5 times the upper limit of normal and serum direct bilirubin <= 2 mg/dL (34 µmol/L) within 21 days prior to randomization
10. Absolute neutrophil count >= 1.0 × 109/L within 21 days prior to randomization
11. Hemoglobin >= 8 g/dL (80 g/L) within 21 days prior to randomization (subjects may be receiving red blood cell transfusions in accordance with institutional guidelines)
12. Platelet count >= 50 × 109/L (>= 30 × 109/L if myeloma involvement in the bone marrow is > 50%) within 21 days prior to randomization
13. Creatinine clearance (CrCl) >= 50 mL/minute (either measured or calculated using a standard formula such as Cockcroft and Gault) within 21 days prior to randomization
14. Written informed consent in accordance with federal, local, and institutional guidelines
15. Females of childbearing potential must agree to ongoing pregnancy testing and to practice contraception as outlined in the RevAssist program (US participants), RevAid program (Canadian participants) or Appendix F (all other participants)
16. Male subjects must agree to practice contraception as outlined in the RevAssist program (US participants), RevAid program (Canadian participants) or Appendix F (all other participants)

Exclusion criteria

Exclusion
1. If previously treated with bortezomib (alone or in combination), progression during treatment
2. If previously treated with a lenalidomide and dexamethasone (len/dex) combination:
o Progression during the first 3 months of initiating treatment
o Any progression during treatment if the len/dex regimen was the subject*s most recent line of therapy
3. Discontinuation of previous lenalidomide or dexamethasone due to intolerance; subjects who are intolerant to bortezomib are not excluded
4. Prior carfilzomib treatment
5. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
6. Waldenström*s macroglobulinemia or IgM myeloma
7. Plasma cell leukemia (> 2.0 × 109/L circulating plasma cells by standard differential)
8. Chemotherapy or investigational agent within 3 weeks prior to randomization or antibody therapy within 6 weeks prior to randomization
9. Radiotherapy to multiple sites or immunotherapy/antibody therapy within 28 days prior to randomization; localized radiotherapy to a single site within 7 days prior to randomization
10. Corticosteroid therapy at dose equivalent to dexamethasone > 4 mg/day within 21 days prior to randomization
11. Pregnant or lactating females
12. Major surgery within 21 days prior to randomization

13. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to randomization
14. Known human immunodeficiency virus infection
15. Active hepatitis B or C infection
16. Myocardial infarction within 4 months prior to randomization, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
17. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to randomization
18. Other malignancy including myelodysplastic syndrome (MDS)within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Score 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
19. Significant neuropathy (Grades 3-4, or Grade 2 with pain) within 14 days prior to randomization
20. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib)
21. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, antiviral drugs, or intolerance to hydration due to preexisting pulmonary or cardiac impairment
22. Ongoing graft-vs-host disease
23. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to randomization
24. Any other clinically significant medical disease or condition that, in the Investigator*s opinion, may interfere with protocol adherence or a subject*s ability to give informed consent

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:	Recruitment stopped
Start date (anticipated):	12-05-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	carfilzomib
Generic name:	carfilzomib
Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Revlimid
Generic name:	lenalidomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-07-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2011
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-10-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-01-2014
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:	15-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2015
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	EUCTR2009-016839-35-NL
ClinicalTrials.gov	NCT01080391
CCMO	NL32749.078.10