A Randomized, Controlled Phase 3 Study to Evaluate Optimized Retreatment and Prolonged Therapy with Bortezomib (Velcade) in Patients with Multiple Myeloma in First or Second Relapse

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON40386

Source
ToetsingOnline

Brief title
OPTIMIZED-RETREAT

Condition

- Leukaemias

Synonym
Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: door de industrie

Intervention

Keyword: MULTIPLE MYELOMA, PROLONGED THERAPY, RELAPSE, VELCADE

Outcome measures

Primary outcome

Disease status and response to therapy will be assessed by investigators based

on the IMWG 2011 response criteria.

Response rates, TTP, DOR, TTNT, ECOG performance status, QoL measures, and MRU

data will also be

assessed. Overall survival and details of the first alternative multiple

myeloma therapy will be evaluated.

Secondary outcome

Response to therapy will be measured based on changes in the M protein in serum

and urine, as determined by SPEP and UPEP. Confirmation by immunofixation and

bone marrow assessments will be done in CR.

Response and progression will be determined according to the criteria IMWG.

Duration of response will be measured.

Time to progression, overall survival, time to new therapy will be measured.

Difference in ECOG performance status will be determined relative to

randomization and compared screening

Quality of life will be determined on the basis of EORTC QLQ-C30 questionnaire

and the EQ-5D questionnaire 5SL.

Study description

Background summary

A Randomized, Controlled, Phase 3 Study to Evaluate Optimized Retreatment and Prolonged Therapy With Bortezomib (VELCADE®) in Patients With Multiple Myeloma in First or Second Relapse (OPTIMIZED-RETREAT)
VELCADE® (bortezomib for injection) is a small molecule proteasome inhibitor, which has been approved for the treatment of multiple myeloma. It is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor *B (NF-*B) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly antiangiogenic and other effects.
This study is designed to examine whether optimized retreatment with bortezomib in combination with dexamethasone followed by prolonged therapy with bortezomib could improve progression free survival (PFS), and consequently overall survival (OS) of patients with multiple myeloma in first or second relapse.The baseline assumption is that standard retreatment with bortezomib in relapsed multiple myeloma will result in a median PFS of 11 months. The hypothesis is that optimized retreatment with bortezomib followed by prolonged therapy with bortezomib will provide a median PFS of 17 months. Due to the lower than planned total enrollment for this study, the number of evaluable subjects will be inadequate for formal testing of the hypothesis and descriptive analysis only will be performed.
Due to a reduced commitment towards enrollment of subjects, influenced by competitive recruitment for other studies, other new/developmental treatment options for relapsed/refractory patients, and expansion of the bortezomib label to include bortezomib-dexamethasone combination treatment and single-agent bortezomib retreatment options, the number of subjects needed for statistically meaningful analysis of the data will not be reached within an acceptable timeframe. Consequently, enrollment for this study will be stopped, effective 20 June 2014, and no further patients will be allowed to provide their consent or be screened for eligibility after that date. Eligible subjects who were screened before or are ongoing in the study as of that date will be randomized,

treated and clinically managed per the protocol for a maximum of 18 months after enrollment of the last subject in the study.

Study objective

The primary objective is to describe the effect of optimized retreatment with bortezomib in combination with dexamethasone followed by prolonged therapy with bortezomib versus standard retreatment with bortezomib in combination with dexamethasone on PFS.

The secondary objectives are to describe:
* Overall response rate (ORR)
* Time to progression (TTP)
* Duration of response (DOR)
* Time to next myeloma therapy (TTNT)
* Overall survival (OS)
* Eastern Cooperative Oncology Group (ECOG) Performance Status
* Quality of life (QoL: European Organisation for Research and Treatment of Cancer Quality of Life
Questionnaire-C30 [EORTC QLQ-C30] and European Quality of Life-5 Dimensions Questionnaire
[EQ-5D])
* Safety

The exploratory objectives are:
* To explore the efficacy and safety of 2 different schedules of prolonged therapy with bortezomib (once a week for first 4 weeks in 35-day cycles versus once every other week).
* To collect medical resource utilization (MRU) data to evaluate the impact of optimized retreatment with bortezomib followed by prolonged therapy with bortezomib on resource use items other than
drug costs.

Study design

This is an interventional, randomized, open-label, parallel-group, event-driven, international, multicenter, Phase 3 study to evaluate an optimized retreatment schedule of bortezomib used in combination with dexamethasone followed by prolonged therapy with single-agent bortezomib in subjects with multiple myeloma at the time of first or second relapse. The study consists of a pretreatment phase, a treatment
phase (which consists of an optimized retreatment period followed by a prolonged therapy period or a standard retreatment period followed by a posttreatment period), and a long-term follow-up phase for survival up to the end of the study. Before the premature stopping of enrollment, the end of the study iswas event-driven and is, defined as 1 year after 186 events (an *event*

being defined as disease progression or death) occur. Following the premature stopping of enrollment, effective 20 June 2014, the end of the study is defined as a maximum of 18 months after enrollment of the last subject in the study.

Intervention

There will be 2 randomizations in this study, the first will randomly assign subjects to either optimized or standard bortezomib and dexamethasone retreatment in a 2:1 ratio and the second will randomly assign eligible subjects who complete optimized bortezomib and dexamethasone retreatment to 1 of 2 prolonged single-agent bortezomib therapy groups in a 1:1 ratio. The first randomization will be stratified according to whether a subject had 1 or 2 previous lines of therapy. Before the premature stopping of enrollment, it was planned to enroll a target of 240 in this study (160 subjects in the optimized retreatment group and 80 subjects in the standard retreatment group); due to a reduced commitment towards enrollment of subjects, this number will not be reached within an acceptable timeframe.
After providing written informed consent, subjects will be evaluated for eligibility during a 14-day screening period. Baseline efficacy and safety assessments should be available on Day 1 of Cycle 1 prior to administration of study medication.
All eligible subjects will be randomly assigned to 1 of 2 different bortezomib retreatment schedules:
* Group A: optimized retreatment followed by prolonged therapy starting with retreatment with 6 cycles of bortezomib and dexamethasone (two 21-day cycles followed by four 35-day cycles) followed by a second randomization to 1 of 2 prolonged therapy schedules with single-agent
bortezomib (Group A1: once weekly for first 4 weeks in 35-day cycles; or Group A2: once every other week).
* Group B: standard retreatment with eight 21-day bortezomib and dexamethasone cycles, followed by posttreatment follow-up every 6 weeks.
Disease status and response to therapy will be evaluated on Day 1 of each cycle during optimized/standard retreatment with bortezomib and dexamethasone (Group A and Group B). Treatment will continue until completion of the retreatment period or until confirmed disease progression, unacceptable toxicity despite dose modification or delays, start of alternative multiple myeloma therapy, withdrawal from the study, death, or the end of study (a maximum of 18 months after the last subject is enrolled in the study), , whichever occurs first.
Subjects who complete optimized retreatment in Group A (6 cycles) and standard retreatment in Group B (8 cycles) and have responded to treatment (minimal response [MR], partial response [PR], very good partial response [VGPR], or complete response [CR]) or have stable disease (SD), and have not had disease progression, have not discontinued bortezomib early, or have started an alternative multiple myeloma
therapy, will enter the prolonged therapy period (Group A1 or Group A2) or posttreatment period (Group B) for up to a maximum of 18 months after the last subject is enrolled in the study), .

During prolonged therapy with single-agent bortezomib, disease status and response to therapy will be evaluated every 6 weeks in both Group A1 and Group A2. Treatment in the prolonged therapy period will continue until confirmed disease progression, unacceptable toxicity despite dose modification or delays, start of alternative multiple myeloma therapy, withdrawal from the study, death, or the end of the study (a maximum of 18 months after the last subject is enrolled in the study), whichever occurs first.
During the posttreatment period, subjects in Group B will continue to be evaluated for disease status every 6 weeks (after the end-of-treatment [EOT] visit in Week 28 [ie, 30 to 35 days after last bortezomib dose in the retreatment period]) until confirmed disease progression, start of alternative multiple myeloma treatment, withdrawal of consent for study participation, death, or the end of study, whichever occurs first.
Any subject who discontinues bortezomib before disease progression during the treatment phase (eg, unacceptable toxicity despite dose modification or delays) will continue to be evaluated for disease status after the EOT visit at a posttreatment visit every 6 weeks until confirmed disease progression, start of alternative multiple myeloma treatment, withdrawal of consent for study participation, death, or the
end of study, whichever occurs first. For a complete list of efficacy assessments and ongoing patient assessments to be performed at each posttreatment visit, and other procedures that should be performed at these visits if clinically indicated, see the Time and Events Schedule - Prolonged Therapy/Posttreatment Period.
All subjects will have an EOT visit performed 30 to 35 days after the last administration of bortezomib, or as soon as possible after bortezomib treatment discontinuation in subjects receiving alternative multiple myeloma therapy.
After confirmed disease progression or start of the first alternative multiple myeloma treatment, whichever occurs first, subjects will enter the long-term follow-up phase of the study for up to a maximum of 18 months after the last subject is enrolled in the study. During this phase,
subjects will be contacted by at least a telephone call every other month to be followed up for the first alternative multiple myeloma therapy and survival.
The final analysis will be performed at the end of the study (a maximum of 18 months after the last subject is enrolled) and will include all efficacy and safety parameters, including OS where possible.
From the end of the study in countries where bortezomib is not commercially available for prolonged
therapy or is not accessible (via a national program or access program) at that time, subjects who in the opinion of the investigator would continue to benefit from prolonged therapy with bortezomib, will continue to be supplied with bortezomib until it is accessible in that particular country or for a period of 2 years, whichever occurs first.

Study burden and risks

The risks of treatment and procedures for this study are included in the

patient information. Treatment with Velcade is a standard treatment for multiple myeloma. The study was designed to simulate normal practice. Every effort is made withiin this study **to decrease further risks and inconveniences to the minimum.

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

Have received a bortezomib containing regimen in one of the previous line(s) of therapy and have shown at least PR to the previous bortezomib therapy.;Have relapsed / progressed multiple myeloma following 1 or 2 previous lines of therapy as defined in the protocol.;Have measurable secretory multiple myeloma: measurable disease for secretory multiple myeloma is defined by at least one of the following measurements: serum M protein greater than or equal to 1 g/dL (>=10g/L], urine M-protein of >=200 mg/24 hours.;Have an ECOG

performance status of <=2. ;Have a life expectancy estimated at screening of >=6 months.

Exclusion criteria

Has received more than 2 previous lines of therapy for multiple myeloma or has received no previous bortezomib-containing regimen.;Has been refractory to bortezomib, defined as either having progressed during bortezomib therapy or relapsed/progressed within 6 months after the last dose of bortezomib.;Has oligosecretory or nonsecretory multiple myeloma.;Has a history of a myocardial infarction within 6 months of enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.;Has peripheral neuropathy or neuropathic pain of grade 2 or greater intensity, as defined by the National Cancer Institute Common Terminology Criteria of Adverse Events (NCI CTCAE), version 4.0.

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):	16-12-2013
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Velcade
Generic name:	Bortézomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-04-2013
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-07-2013
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO Date:	22-09-2014
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2011-004795-11-NL
CCMO	NL43247.008.13