Phase I/II trial of Lenalidomide plus Bortezomib combined with Dexamethasone in elderly patients in 1st relapse or primary refractory after first line therapy for multiple myeloma.

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Phase I:-To determine the maximum tolerated dose (MTD) and recommended phase II dose level (RDL) of Bortezomib administered once weekly, and of Lenalidomide administered for 3 weeks when combined with Dexamethasone in a 28-days schedule.Phase II:-To...

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

Summary

ID

NL-OMON33820

Source
ToetsingOnline

Brief title
HOVON 86 MM

Condition

- Plasma cell neoplasms

Synonym
Kahlers disease, multiple myeloma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Celgene Corporation,Ortho Biotech,stichting HOVON;KWF

Intervention

Keyword: elderly, multiple myeloma, Phase I-II

Outcome measures

Primary outcome

Phase I:

-Dose-limiting toxicity (DLT), maximum tolerated dose (MTD) and recommended

phase II dose (RDL) of Bortezomib and of Lenalidomide when combined with

Dexamethasone

Phase II:

-stringent complete response (sCR), CR and very good partial response (VGPR)

rate

Secondary outcome

Phase I:

-Toxicity, especially myelosupression, polyneuropathy and thrombosis

Phase II:

-Overall response

-Improvement of response due to maintenance treatment

-Toxicity, especially myelosupression, polyneuropathy and thrombosis

-Progression free survival (calculated from registration and from start of

maintenance treatment)

-Overall survival (calculated from registration and from start of maintenance

treatment)

Study description

Background summary

The therapy results of multiple myeloma (MM) in elderly patients are less favorable due to several factors, including the presence of concomitant diseases and increased toxicity and poor tolerability of intensified treatment regimens. Higher age has been identified as a risk factor in many clinical trials. In addition, elderly patients with MM frequently fail to complete rescue treatment at first or later relapse.
The standard treatment of elderly patients with MM has been Melphalan plus Prednisone, Melphalan alone, Dexamathasone alone or Melphalan plus Dexamethasone. None of these regimens has been shown to be clearly superior while toxicity may differ. Recent improvement of the first-line treatment of MM of the elderly patient include the addition of Thalidomide to Melphalan/Prednisone or to Dexamethasone. These new combinations have resulted in increased overall and complete response rates and a prolonged disease-free survival. However, ultimately, patients continue to relapse and many patients suffer from debilitating side-effects, such as irreversible polyneuropathy.
The present treatment options for elderly patients with first or later relapse of MM include Thalidomide, Bortezomib and Lenalidomide as a single agent, or combined with Dexamethasone. Recently, two randomized trials showed a superior effect of Lenalidomide plus Dexamethasone over Dexamethasone alone.
Bortezomib en Lenalidomide are both effective anti-myeloma agents which have a complementary mode of action and which do not have an overlapping toxicity profile. The combination of these drugs appears to be a viable opportunity for the treatment of elderly patients with MM

Study objective

Phase I:
-To determine the maximum tolerated dose (MTD) and recommended phase II dose level (RDL) of Bortezomib administered once weekly, and of Lenalidomide administered for 3 weeks when combined with Dexamethasone in a 28-days schedule.

Phase II:
-To investigate the efficacy of a maximum of 8 cycles of Bortezomib plus Lenalidomide with Dexamethasone at the RDL, as determined by the (s)CR+VGPR

rate

Study design

The study is designed as a prospective, multicenter phase I/II study.

Intervention

Phase I:
During induction therapy a combination of Bortezomib, Lenalidomide and Dexamethasone will be adminstered in 28-days cycles untill a maximum of 8 induction cycles. The planned doses for investiagtion are as follows:
-Bortezomib: 1.3 mg/m2 i.v. on days 1, 8 and 15. Bortezomib will be escalated to a dose of 1.6 mg/m2
-Lenalidomide: 10 mg/day orally on day 1-21. lenalidomide will be escalated to a dose of 20 mg/m2
-Dexamethasone: 20 mg orally on days 1, 2, 8, 9, 15, and 16.
During maintenance therapy Lenalidomide will be administered at a dose of 10 mg on days 1-21. Maintenance cycles will be repeated at 28-days intervals untill relapse, progression or a medical condition that requires stopping the treatment

Phase II:
During induction therapy a combination of Bortezomib, Lenalidomide and Dexamethasone will be adminstered in 28-days cycles untill a maximum of 8 induction cycles. The planned doses for investiagtion are as follows:
-Bortezomib: recommanded dose level (RDL) or 1.6 mg/m2 (expected RDL) from phase I) i.v. on days 1, 8 and 15.
-Lenalidomide: RDL or 20 mg/day (excpected RDL form phase I) orally on day 1-21.
-Dexamethasone: see phase I
During maintenance therapy Lenalidomide will be administered according to the same schedule as in phase I.

Study burden and risks

Toxicity, especially myelosupression, polyneuropathy

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

-Multiple Myeloma Salmon/Durie stage II/III A+B
-Primary refractory to or first relapse after previous objective response (PR, VGPR, CR) on standard first-line treatment
-Age 60-85 years
-Not a candidate for high-dose therapy
-Measurable disease, i.e., serum M-compenent (>10 g/l), or urinary light-chain excretion (>200mg/24h), or abnormal free light chain (FLC) ratio with involved FLC > 100 mg/l or proven plasmacytoma by biopsy
-Able and/or willing to use adequate contraceptives (especially male patients)
-Written informed consent

Exclusion criteria

-Prior therapy with Bortezomib or Lenalidomide
-History of allergic reaction to compounds containing boron or mannitol
-Peripheral neuropathy or neuropathic pain grade 2 or higher as defined by NCI CTCAE version 3
-AL amyloidosis
-Uncontrolled or severe cardiovascular disease:

-New York Heart Association (NYHA) Class II or IV heart failure
-Myocardial infarction within the last 6 months of study entry
-Reduced left ventricular function with an ejection fraction *50% as measured by MUGA scan or echocardiogram (another method for measuring cardiac function is acceptable)
-Unstable angina
-Unstable cardiac arrhytmias
-Clinically significant pericardial disease
-Impaired hepatic or renal function
-ALT and/or AST > 3 x normal value
-Bilirubin > 3 x normal value
-Serum creatinin > 3 x normal value (after adequate hydration)
-Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, etc.)
-Known HIV positivity
-History of active malignancy in past 5 years

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2008
Enrollment:	68
Type:	Actual

Medical products/devices used

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 outside intended use
Product type:	Medicine
Brand name:	Velcade
Generic name:	Bortezomib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-04-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-06-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	28-04-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-06-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-12-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2013
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	EUCTR2007-002533-37-NL
CCMO	NL21715.078.08