A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma

Published: 06-04-2010
Last updated: 30-11-2024

*To assess the efficacy of VMP versus high-dose therapy (HDT) and stem cell transplantation in patients with previously untreated multiple myeloma, as measured by the progression free survival.**To evaluate the effect of consolidation with VRD...

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

Summary

ID

NL-OMON54491

Source
ToetsingOnline

Brief title
HOVON 95 MM

Condition

- Plasma cell neoplasms

Synonym
Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Celgene Corporation,Janssen-Cilag,KWF

Intervention

Keyword: Bortezomib, Lenalidomide, Multiple Myeloma

Outcome measures

Primary outcome

- For all registered patients: progression free survival (PFS) as defined by

time from registration to progression or death from any cause whichever occurs

first).

- For all patients included in R1; PFS as defined by time from randomization R1

to progression or death from any cause whichever comes first

- For all patients included in R2; PFS as defined by time from randomization R2

to progression or death from any cause whichever comes first

Secondary outcome

- Response (PR, VGPR, CR and stringent CR), and improvement of response during

the various stages of the treatment

- Overall survival measured from the time of registration/randomization R !/

randomization R2.

- Toxicity

- Quality of life defined by the EORTC QLQ-C30 and QLQ-MY20 definitions.

Study description

Background summary

This is a phase III study to test the efficacy and feasibility of Bortezomib combined with Melphalan and Prednisone (VMP) versus intensive treatment (HDM) followed by ASCT(s) and secondly to evaluate the role of short term consolidation treatment with VRD (Bortezomib, Lenalidomide, Dexamethasone) versus no consolidation. In a subgroup of patients, 2 cycles of HDM + ASCT will be compared to 1 cycle of HDM + ASCT. Finally, the overall efficacy of these treatments in relation to clinical and molecular prognostic factors in multiple myeloma will be evaluated.

The rationale for including Bortezomib in VCD induction chemotherapy is based on the different mechanisms of actions and the potential synergism of Bortezomib with Cyclophosphamide and/or Dexamethasone. It has been shown that Bortezomib (1.3 mg/m2) can be safely combined with Doxorubicin and/or Dexamethason (BD, PAD) or Cyclophosphamide and/or Dexamethasone. Furthermore the combination of Bortezomib, Lenalidomide and Dexamethasone has been used for induction in refractory/relapsed as well as previously untreated patients with good results
Bortezomib has also been combined with Melphalan/Prednisone for patients who were not eligible for transplantation resulting in an high CR (35 %) and significant prolongation of remission duration and survival
These results have prompted the rationale for the use of Bortezomib during induction therapy of MM. In addition, it seems feasible to compare the standard treatment of induction followed by high-dose therapy and stem cell transplantation with a Bortezomib based approach that includes the same induction followed by VMP.
Secondly, it is time to examine whether consolidation treatment using an effective combination of Bortezomib and Lenalidomide (VRD) may further improve the CR rate, progression-free survival and overall survival.

Study objective

*To assess the efficacy of VMP versus high-dose therapy (HDT) and stem cell transplantation in patients with previously untreated multiple myeloma, as measured by the progression free survival.
**To evaluate the effect of consolidation with VRD followed by Lenalidomide maintenance with no consolidation but Lenalidomide maintenance alone on progression free survival.
*To compare VMP versus single HDT+ ASCT; or VMP versus tandem HDT + ASCT; or single versus tandem HDT + ASCT.
*To compare overall response rate and CR + VGPR (complete and very good partial response) after induction therapy, after VMP or HDT, after consolidation and during maintenance.

*To evaluate overall survival.
*To assess safety and toxicity
*To assess the prognostic value of risk factors at diagnosis, including b2-microglobulin, FISH abnormalities del1p, ampli 1q, t(4;14), t(14;16), t(11;14), ampli 9, del13q/13-, del17p as analyzed in purified bone marrow plasma cells with respect to progression free survival.
*To analyze the prognostic value of myeloma gene expression profiles on the overall response on induction of all patients and of patients treated in the different randomization arms.
- To assess quality of life.

Study design

Prospective, multicenter, intrergroup, randomized phase 3

Intervention

All patients will be treated with 3 induction cycles with VCD, followed by cyclophosphamide for stem cell mobilization and collection.
After induction patients will be randomized to compare two intensification regimens VMP vs. HDM (R1), except if a patient will proceed to allogenic SCT.
In hospitals with a policy of double intensification, all patients will be randomized at R1 between VMP, 1 HDM and 2 HDM, in order also to evaluate 1 HDM vs. 2 HDM
After intensification treatment there will be a 2nd randomization to compare VRD consolidation vs. no consolidation (R2), followed by lenalidomide maintenance in both arms.

Study burden and risks

No extra risk.
Longer duration of treatment with VMP

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Patients with a confirmed diagnosis of symptomatic multiple myeloma stage I to III according to the International Staging System ISS (see appendix A), i.e. at least one of the CRAB criteria should be present;, -Measurable disease as defined by the presence of M-protein in serum or urine (serum M-proteïn > 10 g/l or urine M-proteïn > 200 mg/24 hours) or abnormal free light chain ratio with involved free light chain (FLC) > 100 mg/l or proven plasmacytoma by biopsy, - Age 18-65 years inclusive;, - WHO performance status 0-3 (WHO=3 is allowed only when caused by MM and not by co-morbid conditions) , - Negative pregnancy test at inclusion if applicable;, - Written informed consent.

Exclusion criteria

- Known intolerance of Boron;, - Systemic AL amyloidosis;, - Primary Plasmacell Leukemia;, - Non-secretory MM;, - Previous chemotherapy or radiotherapy except local radiotherapy in case of local myeloma progression or corticosteroids maximum 5 days for symptom control;, - Severe cardiac dysfunction (NYHA classification II-IV, see appendix E);, - Significant hepatic dysfunction (serum bilirubin >= 30 mmol/l or transaminases >= 2.5 times normal level), unless related to myeloma;, - Patients with GFR <15 ml/min,, - Patients known to be HIV-positive;, - Patients with active, uncontrolled infections;, - Patients with neuropathy, CTC grade 2 or higher;, - Patients with a history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma;, - Patients who are not willing or capable to use adequate contraception during the therapy

(all men, all pre-menopausal women);, -Lactating women;

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:	Completed
Start date (anticipated):	21-01-2011
Enrollment:	356
Type:	Actual

Medical products/devices used

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:	06-04-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	04-11-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	06-04-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	03-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	10-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	30-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-02-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-10-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-02-2023
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	EUCTR2009-017903-28-NL
ClinicalTrials.gov	NCT01208766
CCMO	NL31466.078.10