A multicenter, randomized, double-blind, placebo controlled phase III study of panobinostat in combination with bortezomib and dexamethasone in patients with relapsed multiple myeloma

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON38264

Source
ToetsingOnline

Brief title
PANORAMA-1

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma

Intervention

Keyword: combination therapy, Multiple Myeloma, panobinostat (LBH589), relapsed or relapsed-refractory

Outcome measures

Primary outcome

Progession Free Survival (PFS).

Secondary outcome

Overall survival, duration of response, percentage (near) complete responses,

safety of the combination therapy, health-related quality of life and symptoms

of MM.

Study description

Background summary

Multiple myeloma (MM) is a systemic malignancy affecting the final differentiated cells of lymphoid B lineage, the plasma cells. The introduction of newer therapies such as thalidomide, bortezomib (BTZ), or intensive therapy rescued by autologous stem cell transplantation has improved outcome of patients but the disease remains incurable.

Study objective

Given the medical need for improved treatment strategies for patients with previously treated and relapsed MM, the purpose of this phase III study is to compare treatment with bortezomib/dexamethasone + panobinostat to bortezomib/dexamethasone + placebo in patients with previously treated MM whose disease has recurred or progressed. This study is intended to be included in the registration submission of panobinostat for MM.

Study design

This is a multi-center, multinational, randomized, double-blind study using a group sequential design with two interim analyses.

Intervention

Treatment phase 1: 24 weeks of combined treatment with panobinostat or placebo + bortezomib / dexamethasone (8 cycles of 21 days duration each)
Treatment phase 2: 24 weeks of combined treatment with panobinostat or placebo + bortezomib / dexamethasone (4 cycles of 42 days duration each).
All patients will receive study treatment until completion of week 24 (eight 21-day cycles). Patients with clinical benefit in phase 1 will continue study treatment up to week 48 (four additional 42-day cycles).

Study burden and risks

- every potential side effect of panobinostat, bortezomib and dexmathasone
- Physical examinations including vital signs, bone marrow aspirate, standard skeletal survey, MUGA, quality of life questionniares, ECG, blood for regular monitoring of hematology (including coagulation parameters), blood chemistry, serum/urine pregnancy.

Contacts

Public
Novartis

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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

1. Patient has a previous diagnosis of multiple myeloma, based on IMWG 2003 definitions. All three of the following criteria must have been met:
a. Monoclonal immunoglobulin (M component) on electrophoresis, and on immunofixation on serum or on total 24 hour urine
b. Bone marrow (clonal) plasma cells >= 10% or biopsy proven plasmacytoma
c. Related organ or tissue impairment (CRAB symptoms: anemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis or recurrent infections)
2. Patient with 1 to 3 prior lines of therapy who require retreatment of myeloma (cf IMWG 2003) for one of the 2 conditions below:
a. Relapsed, defined by disease that recurred in a patient that responded under a prior therapy, by reaching a MR or better, and had not progressed under this therapy nor up to 60 days of last dose of this therapy. Patients priorly treated by BTZ may be eligible.
b. Relapsed-and-refractory to a therapy, provided that meets both conditions:
- patient has relapsed to at least one prior line
- and patient was refractory to another line (except Bortezomib), by either not reaching a MR, or progressed while under this therapy, or within 60 days of its last dose
3. Patient has measurable disease on M protein at study screening defined by at least one of the following measurements as per thresholds clarified in IMWG 2003 disease definitions (Kyle, et al 2003):
• Serum M-protein >= 1 g/dL (>= 10 g/L)
• Urine M-protein >= 200 mg/24 h
4. Patients treated with local radiotherapy with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression, are eligible. Two weeks must have lapsed since last date of radiotherapy, which is recommended to be a limited field. Patients who require concurrent radiotherapy should have entry to the protocol deferred until the radiotherapy is completed and 2 weeks have passed since the last date of therapy
6. ECOG performance status of <= 2
7. Patient has the following laboratory values within 3 weeks before starting study drug
a. Absolute neutrophil count >= 1.5 x 109 /L
b. Platelet count >= 100 x 109 /L
c. Serum potassium, magnesium, phosphorus, within normal limits (WNL) for institution
d. Total calcium (corrected for serum albumin) or ionized calcium >= LLN, and not higher than CTCAE grade 1 in case of elevated value
e. AST/SGOT and ALT/SGPT <= 2.5 x ULN
f. Serum total bilirubin <= 1.5 ULN (or <= 3.0 x ULN if patient has Gilbert syndrome)
g. Serum creatinine levels <= 1.5 x ULN, or calculated creatinine clearance >= 60 ml/min

Exclusion criteria

1. Patients who have progressed under all prior lines of anti MM therapy
2. Patients who have been refractory to prior Bortezomib
3. Allogeneic stem cell transplant recipient presenting with graft versus host disease either active or requiring immunosuppression
4. Patient has shown intolerance to bortezomib or to dexamethasone or components of these drugs or has any contraindication to one or the other drug, following locally applicable prescribing information
5. Patient has grade >= 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain on clinical examination within 14 days before randomization
6. Patient received prior treatment with deacetylase inhibitors including panobinostat
7. Patient needing valproic acid for any medical condition during the study or within 5 days prior to first administration of panobinostat/study treatment
8. Patient taking any anti-cancer therapy concomitantly (bisphosphonates are permitted only if commenced prior to the start of screening period)
9. Patient has another primary malignancy < 3 years from first dose of study treatment
10. Patient who received:
a. prior anti-myeloma chemotherapy or medication including IMiDs and Dexamethasone <= 3 weeks prior to start of study.
b. experimental therapy or biologic immunotherapy including monoclonal antibodies <= 4 weeks prior to start of study.
c. prior radiation therapy <= 4 weeks or limited field radiotherapy <= 2 weeks prior start of study.
11. Patient has not recovered from all therapy-related toxicities associated with above listed treatments to < grade 2 CTCAE.
12. Patient has undergone major surgery <= 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy to < grade 2 CTCAE
13. Patients with evidence of mucosal or internal bleeding
14. Patient has unresolved diarrhea >= CTCAE grade 2
15. Patient has impaired cardiac function, including any one of the following:
a. Left Ventricular Ejection Fraction < LLN of institutional norm, as determined by ECHO or MUGA
b. obligate use of a permanent cardiac pacemaker
c. congenital long QT syndrome
d. history or presence of ventricular tachy-arrhythmias
e. resting bradycardia defined as < 50 beats per minute
f. QTcF > 450 msec on screening ECG
g. complete left bundle branch block, bifascicular block
h. any clinically significant ST segment and/or T-wave abnormalities
i. presence of unstable atrial fibrillation. Patients with stable atrial fibrillation can be enrolled provided they do not meet other cardiac exclusion criteria.
j. myocardial infarction or unstable angina pectoris <= 6 months prior to starting study drug
k. symptomatic congestive heart failure
l. other clinically significant heart disease and vascular disease
16. Patient taking medications with relative risk of prolonging the QT interval or inducing

Torsade de pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting study drug

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-10-2010
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NVT
Generic name:	panobinostat
Product type:	Medicine
Brand name:	Velcade
Generic name:	bortezomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-11-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-04-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-02-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	15-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	05-12-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2013
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	EUCTR2009-015507-52-NL
CCMO	NL30368.078.09