A Multicenter, Randomized, Double-Blind, Placebo Controlled Phase 2 Study of LY2127399 in Combination with Bortezomib and Dexamethasone in Patients with Previously Treated Multiple Myeloma

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

Summary

ID

NL-OMON39345

Source
ToetsingOnline

Brief title
H9S-MC-JDCG

Condition

- Plasma cell neoplasms
- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: combination, Multiple Myeloma, relapsed, Tabalumab

Outcome measures

Primary outcome

Interim Analysis: 2 cycles after the last patient is enrolled and at least 70

progression-free survival (PFS) events are observed

Endpoint: PFS; safety

Final Analysis: 140 PFS events

Endpoint: PFS (primary)

Secondary outcome

N/A

Study description

Background summary

Despite treatment advances over the past decade, multiple myeloma (MM) remains an incurable
malignancy. Bortezomib is an established foundational therapy as a single agent and with
dexamethasone, and shows promise with other agents, including melphalan and prednisone in the
first-line setting. New agents against novel targets, particularly those hypothesized to mediate

treatment resistance, are needed, and further improvements in MM therapy will require targeting
multiple pathways to increase responses and prolong disease control. B-cell activating factor
(BAFF) stimulation through its receptors causes NFkappaB (NF-*B) pathway activation and
resistance to apoptosis mediated by cancer therapies. BAFF levels appear to be elevated in
patients with MM, and data from a preclinical model of MM suggested that targeting BAFF may
result in antimyeloma activity and inhibit osteoclastogenesis. Data from Phase 1 Study H9S-MC-JDCF (JDCF) suggest that the combination of bortezomib and LY2127399
(tabalumab) is well-tolerated and active in the relapse setting. The pharmacokinetic (PK) profile
of tabalumab stabilizes at doses of approximately 100 mg and above; however, a recommended
dose has not been determined. Study H9S-MC-JDCG (JDCG) will establish the recommended
dose of tabalumab to be used in combination with standard doses of bortezomib and
dexamethasone in patients with MM and subsequently establish whether the addition of
tabalumab to bortezomib and dexamethasone improves the progression-free survival (PFS) of
patients with relapsed or refractory MM treated with at least 1 but not more than 3 prior lines of
therapy.

Study objective

The primary objective is to compare PFS after treatment with tabalumab, bortezomib, and
dexamethasone to that of placebo, bortezomib, and dexamethasone in patients with relapsed/refractory MM.

Secondary objectives will include comparison of treatment and placebo arms for assessment of:
Quality of response (QoR)
* Best overall response (BOR)
* Overall survival (OS)
* Time to progression (TTP)
* Time to next treatment (TNT)
* Duration of response (DOR)
* Time to first skeletal-related event (SRE)
* The incidence of clinically significant pain response
* To describe the population PK of tabalumab in patients with MM

* To describe the immunogenicity of tabalumab in patients with MM

The exploratory objectives of the study are as follows:
* Biomarker objectives may include some combination of the following, depending on the evolving science:
o determine whether serum BAFFand/or a proliferation-inducing ligand (APRIL) levels are associated with percent change from baseline in the
difference between involved and uninvolved serum free light chains (SFLC), objective response, and
response duration
o determine whether mutations in genes including, but not limited to, the NF-*B pathway in bone
marrow cells predict response to therapy that includes tabalumab
o determine whether the RNA expression of genes included in, but not limited to, the BAFF and
NF-*B pathways in bone marrow cells predicts response to therapy that includes tabalumab
o determine whether SNPs near different genes reported to affect multiple myeloma response, including BAFF, B-cell activating factor receptor (BAFF-R), transmembrane
activator and calcium-modulator and cyclophilin ligand interactor (TACI), or B-cell maturation
(BCMA) in germline or bone marrow cell DNA predict response to therapy that includes tabalumab
o determine whether surface expression of BAFF-R, TACI, or BCMA on bone marrow plasma cells
predicts response to therapy that includes tabalumab
o determine whether the percent change in the difference between the involved and uninvolved
SFLC accurately predicts response faster than standard assessments
* Health outcomes objectives
o To compare the health status, health-related quality of life, and resource utilization between the
treatment arms

Study design

This is a multicenter, randomized, double-blind, placebo-controlled, 3-arm Phase 2 study of
bortezomib and dexamethasone with placebo or tabalumab (100 mg or 300 mg) in patients with relapsed/refractory
MM previously treated with 1 to 3 lines of therapy.
The study is designed to evaluate the effect of tabalumab in combination with bortezomib, and dexamethasone in
patients with relapsed/refractory MM.
Approximately 213 patients will be randomized to 1 of the 3 treatments at a 1:1:1 ratio.

Patients will receive treatment for 8 cycles unless they meet a condition for treatment discontinuation. Efficacy
will be measured prior to each new cycle of therapy. Patients who are receiving measureable benefit at Cycle 8
may receive up to 2 additional cycles. The final database lock will occur after 140 PFS events have been observed
such that the final survival analysis may be performed.

Intervention

Reference Therapy, Dose, and Mode of Administration:
Arm A:
Dexamethasone 20 mg administered orally (po) Days 1, 2, 4, 5, 8, 9, 11, and 12 for 8 cycles
Placebo administered intravenously (IV) over 30 minutes every 21 days for 8 cycles
Bortezomib 1.3 mg/m2 Days 1, 4, 8, and 11 administered subcutaneously (SQ) every 21 days for 8 cycles
Test Product, Dosage and Mode of Administration:
Arm B:
Dexamethasone 20 mg po Days 1, 2, 4, 5, 8, 9, 11, and 12 every 21 days for 8 cycles
Tabalumab100 mg administered IV over 30 minutes every 21 days for 8 cycles
Bortezomib 1.3 mg/m2 Days 1, 4, 8, and 11 administered SQ every 21 days for 8 cycles
Arm C:
Dexamethasone 20 mg po Days 1, 2, 4, 5, 8, 9, 11, and 12 every 21 days for 8 cycles
Tabalumab 300 mg administered IV over 30 minutes every 21 days for 8 cycles
Bortezomib 1.3 mg/m2 Days 1, 4, 8, 11 administered SQ every 21 days for 8 cycles

Study burden and risks

There are risks associated with the use of the study drug tabalumab and the comparators bortezomib and dexamethasone. Please refer to attachment 3 of the patient information leaflet. There are also risks associated with the study procedrues: X-rays, CT scans (reaction to contrast), MRI (metal objects in the body; claustrophobia), and there may be complications or infections due to punctions (blood tests), IV injections, subcuteneous injections, bone marrow biopsy/aspirate. These are elucidated in attachment 3 of the patient information. In addition, the study medication and other drugs required by the protocol, the procedures and their combination may have other unknown risks. The patient taking part does not necessarily benefit from this study. Knowledge derived from this study may benefit patients in the future.

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 symptomatic and/or progressive multiple myeloma that was previously treated with at least 1 and no more than 3 prior lines of therapy
-Have measurable disease
-Are >=18 years of age
-Have given written informed consent prior to any study-specific procedures
-Have adequate organ function
-Treatment with prior autologous transplant is permitted

Exclusion criteria

-Are enrolled in or discontinued from a clinical trial of any drug or device within 21 days prior

to the first dose of assigned study treatment
-Have had less than a minimal response or have had progressive disease within 60 days of most recent therapy with a proteasome inhibitor
-Plan to proceed to autologous transplant for consolidation after treatment on Study JDCG
-Have an active infection or ongoing treatment for systemic infection (*ongoing treatment* does not include prophylactic anti-infectives), chest x-ray suggestive of tuberculosis, or history/risk of chronic/latent infection that may reactivate in the presence of study therapy
-Have any of the following:
-positive test results for human immunodeficiency virus (HIV)
-positive test for hepatitis B
-positive test results for hepatitis C virus (HCV) defined as positive for hepatitis C antibody (HepCAb) AND confirmed positive via the hepatitis C recombinant immunoblot assay.
-Have had significant allergy to human/humanized monoclonal antibodies that, in the opinion of the investigator, poses an unacceptable risk to the patient
-Have known hypersensitivity or contraindication to any of the study therapies or excipients
-Prior allogeneic hematopoietic stem cell transplant
-Prior therapy with experimental agents targeting BAFF, including LY2127399
-Have corrected QT (QTc) interval>500 msec on baseline 12-lead electrocardiogram (ECG)
-Have Waldenstrom*s macroglobulinemia
-History of malignancy for which the subject has not been disease-free for at least 3 years. Exceptions: patients with adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, in situ breast cancer, or in situ prostate cancer are eligible regardless of the time of diagnosis/treatment.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-06-2013

Enrollment:	12
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:	Tabalumab
Generic name:	Tabalumab
Product type:	Medicine
Brand name:	Velcade
Generic name:	Bortezomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-07-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-06-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2013

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2014
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	EUCTR2011-005103-32-NL
CCMO	NL40292.078.12