A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma

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To determine whether the addition of oral ixazomib to the background therapy of lenalidomide and dexamethasone improves progression-freesurvival (PFS) in patients with relapsed and/or refractory multiple myeloma (RRMM) The objective has been met.…

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

Summary

ID

NL-OMON55577

Source
ToetsingOnline

Brief title
Millennium C16010

Condition

- Plasma cell neoplasms

Synonym
Kahler's disease, Multiple Myeloma (MM)

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: sponsor/farmaceut

Intervention

Keyword: dexamethasone, lenalidomide, relapsed and/or refractory Multiple Myeloma

Outcome measures

Primary outcome

The primary endpoint is PFS, defined as the time from the date of randomization to the date of first documentation of disease progression based on central laboratory results and international myeloma working group (IMWG) criteria as evaluated by an independent review committee (IRC), or death due to any cause, whichever occurs first

The endpoint has been met. Upon implementation of Amendment 8, evaluation of the safety profile of MLN9708 and/or LenDex is the only endpoint being assessed. Analysis of all other study endpoints will be complete at the final analysis and no further formal statistical analyses will be performed. However, the complete list of endpoints is retained for reference.

Secondary outcome

The key secondary endpoints are:

• OS, measured as the time from the date of randomization to the date of death

• OS in high-risk patients carrying del(17)

The endpoint has been met. Upon implementation of Amendment 8, evaluation of

the safety profile of MLN9708 and/or LenDex is the only endpoint being

assessed. Analysis of all other study endpoints will be complete at the final

analysis and no further formal statistical analyses will be performed. However,

the complete list of endpoints is retained for reference.

Study description

Background summary

Multiple myeloma (MM) is a clonal disease of plasma cells that is characterized by the accumulation of plasma cells in the bone marrow (and other organs) and sometimes results in bone marrow failure, bone destruction, hypercalcemia, and renal failure.
Although MM is uniformly fatal, survival has improved over the last 2 decades because of newer and more effective treatment options. Multiple myeloma is sensitive to a number of cytotoxic drugs such as alkylating agents, anthracyclines, and corticosteroids for initial treatment and for relapsed disease.
Despite the increase in the number of therapeutic options, the disease remains incurable and there is a need for new and better agents. Patients who relapse after their initial therapy demonstrate variable response to subsequent treatments with decreasing likelihood and duration of response (DOR). Patients ultimately become refractory to approved therapies and have no alternative treatment options. In an effort to further target the proteasome with improved activity in MM and other cancers, Millennium has developed ixazomib citrate.

Study objective

To determine whether the addition of oral ixazomib to the background therapy of lenalidomide and dexamethasone improves progression-free survival (PFS) in patients with relapsed and/or refractory multiple myeloma (RRMM)

The objective has been met. Upon implementation of Amendment 8, the objective is to continue to collect long-term safety data from patients who are continuing on ixazomib (MLN9708) and LenDex or LenDex (note the placebo capsule will be discontinued) because of continuing clinical benefit. Data collection for all other study objectives will be complete at the time of the final analysis and no further formal analyses will be conducted. The original lists of objectives are retained for reference only.

Study design

randomized, double-blind, placebo-controlled study

Intervention

Ixazomib citrate Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone

Patients will receive study drug (ixazomib citrate 4.0 mg or matching placebo capsule) on Days 1, 8, and
15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15,
and 22 of a 28-day cycle. Patients may continue to receive treatment until PD or unacceptable
toxicity, whichever comes first. Dose modifications may be made based on toxicities. Patients with
creatinine clearance of 30 to 50 mL/min will receive a reduced lenalidomide dose of 10 mg once
daily on Days 1 through 21 of a 28-day cycle. The lenalidomide dose may be escalated to 15 mg
once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment.

Study burden and risks

Additional tests/assessments related to study participation are:
• questionnaires and review of status;
• elektrocardiogram (ecg);
• farmacokinetic bloodsamples;
• patient diary.
Based on studies in an early stage with patients treated with ixazomib citrate, the following discomforts and risks could occur:
• a low numer of platelets (an increase of the chance of bleedings);
• skin rash, which can vary from a few red spots that may or may not itch or spots over the entire body;
• vfatigue or weakness, nausea, vomiting, diarrheae.

Contacts

Public
Millenium Pharmaceuticals

Landsdowne Street Cambridge 40

MA 02139
US
Scientific
Millenium Pharmaceuticals

Landsdowne Street Cambridge 40
MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1.Multiple myeloma diagnosed according to standard criteria either currently or at the time of initial diagnosis.
2.Patients must have measurable disease defined by at least 1 of the following 3 measurements:
•Serum M-protein >= 1 g/dL (>= 10 g/L).
•Urine M-protein >= 200 mg/24 hours.
•Serum free light chain assay: involved free light chain level >=10 mg/dL (>= 100 mg/L), provided that the serum free light chain ratio is abnormal.
3.Patients with relapsed and/or refractory MM who have received 1 to 3 prior therapies.
4.ECOG performance status of 0, 1, or 2.

Exclusion criteria

1. Patient was refractory to lenalidomide or proteasome inhibitor-based therapy at any line.
2. Female patients who are lactating or pregnant.
3. Failure to have fully recovered (ie, < Grade 1 toxicity) from the effects

of prior chemotherapy regardless of the interval since last treatment.
4. Major surgery within 14 days before randomization.
5. Radiotherapy within 14 days before randomization.
6. Central nervous system involvement.
7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before randomization.
8. Diagnosis of Waldenstrom*s macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
9. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
10. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John*s wort within 14 days before randomization in the study.
11. Ongoing or active systemic infection, active hepatitis B virus infect, active hepatitis C infection, or known human immunodeficiency virus (HIV) positive.
12. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of
the prescribed regimens.
13. Psychiatric illness/social situation that would limit compliance with study requirements.

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:	Recruitment stopped
Start date (anticipated):	03-09-2013
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MLN9708
Generic name:	Ixazomib citrate

Ethics review

Approved WMO Date:	05-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2014
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-005496-17-NL
ClinicalTrials.gov	NCT01564537
CCMO	NL40132.018.12

Study results

Results posted: 10-02-2023

First publication
07-02-2023