A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

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Study ObjectivesPrimary:• To determine the effect of ixazomib maintenance therapy on progression-free survival (PFS), compared to placebo, in patients with NDMM who have had a response (complete response [CR], very good partial response [VGPR], or...

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

Summary

ID

NL-OMON54581

Source
ToetsingOnline

Brief title
C16019 NDMM

Condition

- Plasma cell neoplasms

Synonym
Kahler's disease, Multiple Myeloma (MM)

Research involving

Human

Sponsors and support

Primary sponsor: Takeda
Source(s) of monetary or material Support: Sponsor/ farmaceut

Intervention

Keyword: - Ixazomib (MLN9708), - Maintenance therapy, - 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, as evaluated by an independent review committee (IRC) using IMWG (International Myeloma Working Group) criteria, or death due to any cause, whichever occurs first

Secondary outcome

The key secondary endpoint is:

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

Study description

Background summary

Despite more therapeutic options, MM remains incurable, and there is a need for new and better agents. When patients relapse after their initial therapy, they demonstrate variable responses to subsequent treatments with decreasing likelihood and duration of response (DOR). Patients become refractory to approved therapies and ultimately are left with no alternative treatment options. In an effort to expand the therapeutic armamentarium against MM with agents that target the proteasome, Takeda Development Center Americas (Takeda) has developed ixazomib (MLN9708), a small molecule 20S proteasome inhibitor. Maintenance therapy is a long-duration, low-intensity therapy intended to

prolong the duration of a patient*s response to primary antineoplastic treatment. Requirements for a successful maintenance therapy include good long-term tolerability and adherence (low discontinuation rates due to toxicity and convenience of administration), demonstration of clinical benefit either in prolonging survival or improving quality of life without shortening survival, and a favorable benefit:risk ratio. Although there is emerging evidence for the clinical benefit of maintenance therapy following SCT, a positive benefit:risk balance is yet to be established in existing therapies, no therapy has been approved for this indication, and a true standard of care (SoC) has not been adopted
Maintenance therapy has not yet been proven to be a superior treatment strategy compared to the current paradigm of a post-ASCT treatment-free interval followed by salvage therapy at relapse. Together with the lack of a universal maintenance SoC and an evidence-based comparator with a demonstrated survival benefit for maintenance therapy post-ASCT, a strong justification is provided to conclude that a phase 3, placebo-controlled trial is an appropriate approach for determining the efficacy of single-agent ixazomib maintenance therapy.

Study objective

Study Objectives
Primary:
• To determine the effect of ixazomib maintenance therapy on progression-free survival (PFS), compared to placebo, in patients with NDMM who have had a response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to induction therapy followed by high-dose therapy (HDT) and ASCT
Key Secondary:
• To determine the effect of ixazomib maintenance therapy on overall survival (OS) compared to placebo

Study design

This is a randomized, placebo-controlled, double-blind, phase 3 study in patients with NDMM

Intervention

Patients will receive blinded study drug (ixazomib capsules or matching placebo capsules) orally on Days 1, 8, and 15 of every 28 day cycle, for a duration of approximately 24 months (26 cycles, to the nearest complete cycle), or until documented disease progression (on the basis of the IMWG criteria) or intolerable toxicities, whichever comes first. The initial dose of study drug will be 3 mg of ixazomib or matching placebo, which will be increased to 4 mg on Cycle 5, Day 1 if tolerated during the first 4 cycles.

Study burden and risks

Ixazomib can cause the following discomforts and risks. However, we might not know all the risks of ixazomib at this moment. It is possible that ixazomib can cause additional discomforts and risks other than those listed below:
- Swelling or fluid buildup in the arms or legs
- Flu-like symptoms and other upper respiratory tract infections
- Arthralgia or joint pain
- Lung infections including pneumonia or pneumonitis
- Herpes Zoster that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time

In earlier studies with ixazomib the risks listed below were reported. However, we don*t know if they were caused by Ixazomib or by the patient*s disease(s), other medications, patient related other factors or a combination of these factors:
- Feeling short of breath or difficulty breathing
- Feeling tired or week
- Cough
- Fever
- Headache
- Feeling dizzy or dizziness
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever
- Constipation
- Distortion of the sense of taste i.e. an abnormal or impaired sense of taste
- Trouble falling asleep, staying asleep or both

Acute febrile neutrophilic dermatosis (Sweet*s syndrome) and pemphigus vulgaris, have been reported in MLN9708 studies when given in combination with other drugs. These rashes are disorders of the immune system, which differ from regular skin rashes and are generally more severe.

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS), are rare, serious blood disorders that cause low levels of platelets and red blood cells, and result in blood clots in small vessels. Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders can occasionally be fatal. TMA, TTP, and HUS have been seen rarely (<0.1%) in patients treated with ixazomib.
Overdose has been reported in patients taking ixazomib. Reports of accidental overdose have been associated with risks such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death. It is important to take only one dose of ixazomib at a time, and only at the prescribed interval.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Adult male or female patients 18 years or older with a confirmed diagnosis of symptomatic multiple myeloma according to standard criteria.
2. Documented results available for cytogenetics/ fluorescence in situ hybridization (FISH) obtained at any time before transplant and for ISS staging at the time of diagnosis.
3. Underwent standard of care induction therapy (induction therapy must include PI and/or IMiD-based regimens as primary therapy for multiple myeloma), followed by a single ASCT with a high-dose melphalan (200 mg/m2) conditioning regimen, within 12 months of diagnosis. Vincristine, Adriamycin (doxorubicin), and dexamethasone (VAD) is not an acceptable induction therapy for this trial.
4. Started screening no earlier than 75 days after transplant, completed screening within 15 days, and randomized no later than 115 days after transplant.

5. Patient must have not received post-ASCT consolidation therapy.
6. Documented response to ASCT (PR, VGPR, CR/stringent complete response [sCR]) according to IMWG criteria.
7. ECOG performance status of 0 to 2.
8. Female patients who:
* If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, AND
* Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
* Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)
Male patients, even if surgically sterilized (ie, status postvasectomy), who:
* Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, AND
* Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
* Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
10. Suitable venous access for the study-required blood sampling.
11. Patient is willing and able to adhere to the study visit schedule and other protocol requirements.
12. Patients must meet the following clinical laboratory criteria at study entry:
* Absolute neutrophil count (ANC) >= 1,000/mm3 and platelet count >= 75,000/mm3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before randomization.
* Total bilirubin <= 1.5 x the upper limit of the normal range (ULN).
* Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)
* 3 <= ULN.
* Calculated creatinine clearance >= 30 mL/min.

Exclusion criteria

1. Multiple myeloma that relapsed following primary therapy or is not responsive to primary therapy. For this study, stable disease following ASCT will be considered nonresponsive to primary therapy.

2. Double (tandem) ASCT.
3. Radiotherapy within 14 days before the first dose of study drug.
4. Diagnosed or treated for another malignancy within 5 years before randomization or previously diagnosed with another malignancy with evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
5. Female patients who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.
6. Major surgery within 14 days before randomization.
7. Central nervous system involvement.
8. Infection requiring IV antibiotic therapy or other serious infection within 14 days before randomization.
9. 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.
10. 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.
11. Systemic treatment with strong inhibitors of CYP3A (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John*s wort within 14 days before randomization in the study.
12. Active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
13. 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 (eg, PN that is Grade 1 with pain or Grade 2 or higher of any cause).
14. Psychiatric illness/social situation that would limit compliance with study requirements.
15. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
16. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal (GI) procedure that could interfere with the oral absorption or tolerance of treatment.
17. Treatment with any investigational products within 60 days before the first dose of the study drug regimen.

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):	20-11-2014
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MLN9708
Generic name:	Ixazomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2023

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-09-2023
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	EUCTR2013-002076-41-NL
ClinicalTrials.gov	NCT02181413
CCMO	NL47795.029.14