A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Relapsed and/or Refractory Multiple Myeloma (RRMM)

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Primary Objective:• To evaluate the proportion of patients with a response of very good partial response (VGPR) or better to IDd treatment.Secondary Objectives:• To measure progression-free survival (PFS), time to progression (TTP), and overall...

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

Summary

ID

NL-OMON48807

Source
ToetsingOnline

Brief title
C16047

Condition

- Plasma cell neoplasms

Synonym
blood cancer, Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Takeda
Source(s) of monetary or material Support: Millennium Pharmaceuticals;Inc;a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Intervention

Keyword: C16047, Ixazomib+Daratumumab+Dexamethasone, Multiple Myeloma, Phase 2

Outcome measures

Primary outcome

The primary endpoint is response of VGPR or better as assessed by the

investigator. Additionally efficacy will be assessed by PFS, TTP, ORR, TTR,

DOR, and OS. Patients will be assessed for disease response by the investigator

according to the IMWG criteria.

Secondary outcome

Safety assessments will be evaluated through the incidence and severity of

adverse events (AEs) and changes in clinical hematology and chemistry

laboratory test results.

Study description

Background summary

See protocol (page 17), section 4.1 Background.

Study objective

Primary Objective:
• To evaluate the proportion of patients with a response of very good partial response (VGPR) or better to IDd treatment.

Secondary Objectives:
• To measure progression-free survival (PFS), time to progression (TTP), and

overall survival (OS).
• To measure overall response rate (ORR), time to response (TTR), and duration of response (DOR).
• To collect plasma concentration-time data for ixazomib to contribute to population pharmacokinetic (PK) analyses.
• To evaluate the safety/tolerability of IDd administered in a 28-day cycle.

Study design

This is a prospective, open-label, multicenter study. There will be a screening period, followed by a treatment period (divided into cycles of 28 days) with administratino of the combination of ixazomib, daratumumab and dexamethasone to the patients. All patients will receive study medication until they experience progressive disease (PD) or have an unacceptable toxicity. After the last dose of study medication, and end of study visit is done and followed by 2 follow-up periods: progression free survival (PFS) follow up (if needed) and overall survival (OS) follow up.

Intervention

For the purposes of this protocol, study treatment regimen is defined as the combination of ixazomib, daratumumab, and dexamethasone. All cycles are approximately 28 days with treatment given until PD or unacceptable toxicity. (Full details on study treatment administration are in Section 8.2.) See diagram below for details.

• Ixazomib will be administered at 4 mg orally on Days 1, 8, and 15 of each 28-day cycle. In Cycle 1 ixazomib will be given after the daratumumab infusion; in subsequent cycles, if there have been no Grade 3 or higher infusion-related reactions (IRRs) in the previous cycle, ixazomib can be given prior to or at approximately the same time as the premedications (see Section 8.2.3).

• Daratumumab will be administered intravenously (IV) at 16 mg/kg (note pre- and postinfusion medications of antipyretics and oral antihistamines listed in Section 8.2.2): Daratumumab will be given on the following schedule:
o Cycles 1 and 2: Days 1, 8, 15, and 22 (every week; total of 8 doses).
o Cycles 3 to 6: Days 1 and 15 (every 2 weeks; total of 8 doses).
o Cycles 7 and beyond: Day 1 (every 4 weeks).

• Dexamethasone will be given as 20 mg on Day 1, 2, 8, 9, 15, 16, 22, and 23 in each 28-day cycle, to achieve the standard total of 40 mg per week (2 doses of 20 mg per week). This schedule allows for dexamethasone to be given the day of (before) and the day after the daratumumab infusion on daratumumab dosing days. Dexamethasone should be given IV before the first daratumumab dose; but can be given IV or orally thereafter. The dose of dexamethasone may be reduced in some

patients (see details in Section 8.2.4).

Study burden and risks

Potential discomforts and risks of ixazomib
Based on studies of ixazomib it is possible to predict some of the discomforts and risks. However, it is possible that ixazomib may cause risks that have not yet been observed in patients. The following risks might be seen:
• Low platelet count which may increase the chance of bleeding
• Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body
• Feeling tired or weak
• Nausea
• Vomiting
• Diarrhea
• Numbness, tingling or pain feelings in hands and feet
• Constipation
• Lowered red blood 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
More information on possible discomforts and risks of ixazomib and of the study procedures can be found in Appendix F of the ICF.

Potential discomforts and risks of daratumumab
Based on previous studies of daratumumab, it is possible to predict some of the discomforts and risks associated with this drug. However, it is possible that daratumumab in combination with ixazomib may cause risks that have not yet been observed in patients. Daratumumab has not been studied in combination with ixazomib, however the following risks have been seen in association with daratumumab treatment when it is given alone and not in combination with any other medications, according to the prescribing information of the marketed product Darzalex:
• Infusion reactions that can be severe and can cause symptoms such as narrowing of the airways, low oxygen, shortness of breath, high blood pressure, swelling in the throat and fluid in the lungs, nasal congestion, cough, throat irritation, chills, vomiting, or nausea. Less common symptoms were wheezing, runny nose, fevers, chest discomfort, itching and low blood pressure. Approximately half of all patients experienced a reaction, most during the first infusion. Infusion reactins can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing daratumumab.
• Fatigue
• Fever
• Chills
• Cough
• Nasal congestion
• Shortness of breath

• Back pain
• Joint pain
• Pain in arms and legs
• Pain in the chest that is muscular pain
• Upper respiratory tract infection
• Pneumonia
• Inflammation of the nose or throat (nasopharyngitis)
• Nausea
• Diarrhea
• Constipation
• Vomiting
• Decreased appetite
• Headache
• High blood pressure
• Low levels of red blood cells
• Low levels of platelets
• Low levels of white blood cells (lymphopenia)
• Low neutrophils, a type of white blood cell (neutropenia)
More information on possible discomforts and risks of daratumumab can be found in Appendix F of the ICF.

Potential discomforts and risks of dexamethasone
Dexamethasone is a corticosteroid medication that can be associated with the following more common risks:
• Dermatologic: acne, allergic skin inflammation, dry scaly skin, easy bruising, redness of the skin, impaired wound healing, increased sweating, rash, stretching and thinning of the skin, thinning scalp hair, hives
• Metabolism: decreased sugar tolerance, high blood sugar, sugar in the urine, body hair growth, worsening of diabetes in patients who already have diabetes, irregular menstrual cycles, increased breakdown of protein
• Fluid and electrolyte changes: fluid retention, low potassium in the blood, potassium loss, sodium retention
• Gastrointestinal: increased appetite, nausea, peptic ulcer, ulcerations in the esophagus
• Musculoskeletal: damage to the head of the femur or humurus bones (long bones in the leg or arm, respectively), loss of muscle mass, muscle weakness, osteoporosis
• Neurological/Psychiatric: depression, emotional instability, headache, increased pressure inside the skull, insomnia, mood swings, psychic disorders,
• Ophthalmic: increased pressure inside the eye, cataracts, glaucoma
• Other: Abnormal fat deposits, decreased resistance to infection, hiccups, moon face, weight gain
More information on possible discomforts and risks of dexamethasone can be found in Appendix F of the ICF.

Contacts

Public
Takeda

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:
• Adult patients (aged >=18 years) who have been diagnosed with MM according to IMWG criteria.
• All patients must have measurable disease by at least 1 of the following measurements:
- Serum M-protein >=1 g/dL (>=10 g/L).
- Urine M-protein >=200 mg/24 hours.
• All patients must have documented evidence of PD on or after their last regimen as defined by IMWG criteria (see Appendix E) [1-3]. All patients must have received between 1 to 3 prior therapies for MM (a prior therapy is defined as 2 or more cycles of therapy given as a treatment plan for MM [eg, a

single-agent or combination therapy or a sequence of planned treatments such as induction therapy followed by autologous SCT and then consolidation and/or maintenance therapy]).
• All patients must have achieved a response (PR or better) to at least 1 prior therapy.
• All patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2.
• All patients must meet the following laboratory criteria:
- Absolute neutrophil count (ANC) >=1000/mm3.
- Platelet count >=75,000/mm3.
- Total bilirubin <=1.5 x the upper limit of the normal range (ULN) (except for Gilbert syndrome: direct bilirubin <=2 x ULN).
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=3 x ULN.
- Calculated creatinine clearance >=50 mL/min.
• Female patients who:
- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to use effective contraceptive measures during and for 90 days following treatment. Advise women using hormonal contraceptives to also use a barrier method of contraception (see Appendix H for details).
• Male patients, even if surgically sterilized (ie, status postvasectomy), who:
- Agree to use effective contraceptive measures during and for 90 days following treatment (see Appendix H for details).
• 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.
• Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

Exclusion criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:
• Patients have undergone prior allogenic bone marrow transplantation.
• Patients have received prior ixazomib at any time or daratumumab or other anti-CD38 therapies, except as part of initial therapy if this was stopped to move on to SCT and the patient did not progress on anti-CD38 treatment.
• Patients are refractory to bortezomib or carfilzomib at the last exposure before this study (defined as patient having PD while receiving bortezomib or carfilzomib therapy or within 60 days after ending bortezomib or carfilzomib therapy).
• Patients planning to undergo SCT prior to PD on this study (ie, these patients should not be enrolled in order to reduce disease burden prior to

transplant).
• Patients receiving systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, St. John's wort) within 14 days before randomization.
• Patient has received autologous SCT within 12 weeks before the date of study treatment.
• Patient has received an investigational drug (including investigational vaccines) within 4 weeks before study treatment (except for investigational antimyeloma agents, which cannot be taken within 2 weeks prior or 5 PK half-lives of the treatment, whichever is longer, before the date of study treatment). The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum 4 days) before treatment.
• Patients with known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note: FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
- Patients with Grade 2 or higher residual toxicities from prior therapy (including Grade 2 or higher peripheral neuropathy or any grade neuropathy with pain; excluding alopecia). This includes recovery from any major surgery. Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.
• Patients with known allergy to any of the study medications, their analogues, their excipients, mAbs or human proteins or known sensitivity to mammalian-derived products.
• Patient has uncontrolled clinically significant cardiac disease, including myocardial infarction within 6 months before date of study entry or unstable or uncontrolled angina, congestive heart failure, New York Heart Association (NYHA) Class III-IV, uncontrolled cardiac arrhythmia (Grade 2 or higher).
• Patients with ongoing or active systemic infection requiring IV medical management; patients with known HIV-RNA positivity; patients with hepatitis B virus (HBV) surface antigen or core antibody positivity,; and patients with known hepatitis C virus-RNA positivity. Patients who have positive hepatitis C antibody can be enrolled but must have hepatitis C virus-RNA negativity.
• Patient has any concurrent medical condition or disease that is likely to interfere with study procedures, results, or assessment of safety or toxicity or that in the opinion of the investigator would constitute a hazard for participating in this study.
• Patients diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any 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.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-07-2019
Enrollment:	1
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DARZALEX
Generic name:	daratumumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Depending on site
Generic name:	dexamethasone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NINLARO
Generic name:	ixazomib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	25-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	29-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	07-04-2022
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	EUCTR2017-003977-32-NL
ClinicalTrials.gov	NCT03439293
CCMO	NL65162.029.18