Efficacy and tolerability of ixazomib, daratumumab and low dose dexamethasone (IDd) followed by ixazomib and daratumumab maintenance therapy until progression for a maximum of 2 years in unfit and frail newly diagnosed multiple myeloma patients; an open-label phase II trial

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Primary objective* To determine the efficacy, defined as overall response rate (ORR; >= partial response (PR)), of 9 cycles of ixazomib, daratumumab and low dose dexamethasoneSecondary objectives* To determine the tolerability, defined as...

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

Summary

ID

NL-OMON53051

Source
ToetsingOnline

Brief title
HOVON 143 MM

Condition

- Plasma cell neoplasms

Synonym
Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Firma's Janssen en Takeda;subsidie is aangevraagd bij KWF,Johnson & Johnson Pharmaceutical,Takeda

Intervention

Keyword: Daratumumab, Frail, Ixazomib, Multiple Myeloma

Outcome measures

Primary outcome

• Overall response rate (at least PR) on induction therapy.

Secondary outcome

• Discontinuation rate due to toxicity of maintenance therapy with Ixazomib and daratumumab.

• Safety and toxicity as defined by type, frequency and severity of adverse events as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4

• Complete Response and Very Good Partial Response rate after 9 induction cycles and on protocol

• Immunophenotypic Complete Response after 9 induction cycles and on protocol

• Minimal Residual Disease negative flow cytometry of bone marrow on protocol

• PET-CT negative, defined as disappearance of increased tracer uptake at entry, or decrease to less than mediastinal blood pool SUV or decrease to less than surrounding normal tissue

• Progression free survival, defined as time from registration to progression or death from any cause, whichever comes first

• Overall survival, measured from date of registration to death from any cause. Patients alive at the date last contact, will be censored

• Time to (maximum) response

• Improvement in response from the start of maintenance therapy

• Discontinuation rate due to toxicity of 9 cycles of Ixazomib, daratumumab and low-dose dexamethasone.

• Time to next treatment

• PFS2, defined as the time from registration to the date of objective disease progression or death from any cause after second line therapy

• Quality of life as defined by the EORTC QLQ-C30, QLQ-MY20 and EQ-5D-5L definitions

Exploratory endpoints

• Geriatric assessments (both questionnaires and physical assessments), senescence markers in fibroblasts obtained by skin biopsy and sarcopenia as determined by CT-scan that reflect biological age and predict feasibility and the toxicity of treatment

• Identification of immunological and molecular prognostic markers that predict feasibility and the toxicity of treatment

• Identification of biomarkers for response

Study description

Background summary

Data from both clinical trials and population based registries indicate that elderly patients also benefit from novel therapies. The challenge is to identify a relatively non-toxic strategy for unfit and frail patient enabling effective treatment with novel agents. With the availability of the oral proteasome inhibitor ixazomib, that does not induce grade 3 and 4 neuropathy, the way is paved for oral proteasome-inhibitor based therapy, also in the maintenance setting. The implementation of daratumumab in novel treatment regimens for unfit and frail patients is obvious, being a novel class of drugs with promising efficacy and mild and mainly infusion-related side effects, which was manageable also in the elderly patients. Therefore, the efficacy and feasibility of 9 cycles of ixazomib, daratumumab and low dose dexamethasone followed by ixazomib and daratumumab maintenance until progression for a maximum of 2 years will be investigated in unfit and frail newly diagnosed multiple myeloma (NDMM) patients

Study objective

Primary objective
* To determine the efficacy, defined as overall response rate (ORR; >= partial response (PR)), of 9 cycles of ixazomib, daratumumab and low dose dexamethasone
Secondary objectives
* To determine the tolerability, defined as discontinuation rate due to treatment related toxicity, of 9 cycles of ixazomib, daratumumab and low dose dexamethasone
* To determine adverse events of CTCAE grade 2-4
* To determine complete response (CR) and very good partial response (VGPR) after 9 induction cycles
* To determine complete response (CR) and very good partial response (VGPR) on protocol
* To determine immunophenotypic complete response after 9 induction cycles
* To determine immunophenotypic complete response on protocol
* To determine the flow Minimal Residual Disease negative complete remission
* To determine the imaging plus flow MRD negative complete remission
* To determine progression free survival (PFS)
* To determine overall survival (OS)
* To determine efficacy of therapy determined as time to response and the time to best response
* To determine the effect of maintenance therapy with ixazomib and daratumumab in terms of improvement of response during maintenance
* To determine the tolerability of maintenance therapy, defined as discontinuation rate due to treatment related toxicity of ixazomib and

daratumumab
* To determine time to next treatment
* To determine PFS2
* To evaluate quality of life (QoL)
Exploratory objectives
* To identify geriatric assessment outcomes that predict feasibility and the toxicity of treatment
* To identify biological markers; sarcopenia and senescence markers, that reflect biological age and that predict feasibility and the toxicity of treatment
* To identify immunological and molecular prognostic markers that predict outcome and toxicity
* To identify biomarkers for response
* To investigate the prognostic value of Minimal Residual Disease
* To investigate the prognostic value of FDG-PET-CT at diagnostics and in follow up

Study design

Investigator-initiated, multicenter, non-randomized, open label, phase II clinical trial

Intervention

Induction therapy with 9 cycles of ixazomib, daratumumab and dexamethasone, followed by maintenance therapy with ixazomib and daratumumab until progression for a maximum period of two years

Study burden and risks

The benefit will be that unfit and frail patients can be treated with an oral proteasome inhibitor ixazomib instead of the currently available subcutaneous proteasome inhibitor bortezomib, with considerably less polyneuropathy. Bortezomib is currently standard of care. Secondly, patients will be treated with daratumumab, a novel class drug, with pronounced effectivity in heavily pretreated patients with limited toxicity only. In this heavily pretreated patients not only response rate was high; 39%, in addition 65% of patients who responded were still in remission after one year. Moreover, the data of the addition of daratumumab to bortezomib/dexamethasone, after 1 to 3 prior lines of therapy resulted in a 61% reduction of progression, which has not been reached with other novel drugs. Therefore, this regimen is expected to result in efficacy. Secondly, less side effects as compared to the standard of care *Melphalan, Bortezomib, Prednisone - MPV* is expected, which we recently investigated in the HOVON 123 study. Preliminary data showed that 49% of frail patients and 29% of unfit patients had to discontinue therapy because of toxicity.

The burden will be that 1. Patients will receive intranvenous daratumumab instead of a combined oral/sc regimen of MPV or an oral regimen with lenalidomide/dexamethasone. 2. Following induction therapy, maintenance therapy will be given until progression for a maximum of two years. Although a benefit with respect to prolongation of PFS is expected, the extent is currently unknown. Patients may suffer from side effects, although these are generally mild with ixazomib and daratumumab and also the combination of a proteasome inhibitor with daratumamab was found to be safe with limited additional side effects to a proteasome inhibitor only.
There are additional procedures required as compared to standard care because of biological assessment of frailty, such as a CT scan to determine the presence of sarcopenia, geriatric assessments and a skin biopsy for senescence markers. Patients have to participate in QoL studies, and in case of complete response undergo a PET-CT scan and an additional BM aspirate

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

• Previously untreated patients with a confirmed diagnosis of multiple myeloma according to IMWG criteria;
• Measurable disease according to the IMWG criteria;
• Patients who are either unfit or frail according to the IMWG criteria;
• Age 18 years or older.
• Absolute neutrophil count (ANC) >= 1.0 x109/l and platelet count >= 75x109/l. Platelet transfusions and G-CSF to help patients meet eligibility criteria are not allowed;
• Written informed consent, including consent for additional bone marrow and blood sampling and a skin biopsy
• Patient is capable of giving informed consent.
• Negative pregnancy test at study entry (only for women of childbearing potential);
• Male patients and female patients of childbearing potential must agree to use adequate contraception from the time of signing the informed consent form through 90 days after the last dose of study drug.

Exclusion criteria

• Non-secretory MM;
• Plasma cell leukemia;
• Systemic Amyloid Light-chain (AL) amyloidosis;
• Central nervous system involvement;
• Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent;
• Neuropathy, grade 1 with pain or grade >= 2;
• Severe cardiac dysfunction (NYHA classification III-IV);
• Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia*s formula (QTcF) >470 msec;
• Chronic obstructive pulmonary disease (COPD) with an Forced Expiratory Volume in 1 second (FEV1) < 50% of predicted normal. ;
• Moderate or severe persistent asthma within the past 2 years or currently uncontrolled asthma of any classification..
• Significant hepatic dysfunction (total bilirubin >= 3 x ULN or transaminases >= 5 times normal level) except patients with Gilbert*s syndrome as defined by > 80% unconjugated bilirubin
• Creatinine clearance <20 ml/min or Calculated Glomerular Filtration Rate [ml/min/1.73m2] <20;
• Patients with active, uncontrolled infections;
• Patients known to be Human Immunodeficiency Virus (HIV)-positive;
• Patients seropositive for hepatitis B, defined by a positive test for

hepatitis B surface antigen [HBsAg]. Patients with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
• Patients seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
• Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing;
• Active malignancy other than MM requiring treatment or a malignancy that has been treated with chemotherapy currently affecting bone marrow capacity;
• Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John*s wort;
• Pre-treatment with cytostatic drug, immunomodulatory drugs (IMiDs) or proteasome inhibitors. Radiotherapy (provided the involved field is small and there are >= 7 days between radiotherapy and administration of ixazomib) or a short course of steroids (e.g. 4 day treatment of dexamethasone 40 mg/day or equivalent) are allowed;
• Major surgery within 14 days before enrollment;
• Any serious medical or psychiatric illness, or familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule;
• Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial;
• Female patients who are lactating.

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):	31-08-2017
Enrollment:	112
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:	Ninlaro
Generic name:	Ixazomib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-08-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2018
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:	29-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2021
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:	11-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2024
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	EUCTR2016-002600-90-NL
CCMO	NL59458.029.16
Other	NTR (TC = 6297)