Carfilzomib, Lenalidomide and Dexamethasone versus Lenalidomide and Dexamethasone in High- Risk Smoldering Multiple Myeloma: A Randomized Phase 2 Study

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The primary objective of the study is :To assess MRD negativity rate by NGF after 9 cycles for all eligible ITT patients of KRd versus Rd in patients with high-risk SMMSecondary objectives:• To assess MRD (NGF) negativity rate after 4 cycles of...

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

Summary

ID

NL-OMON53146

Source
ToetsingOnline

Brief title
HOVON 147 SMM

Condition

- Plasma cell neoplasms

Synonym
Smoldering multiple myeloma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Amgen;Celgene,Amgen,Celgene Corporation

Intervention

Keyword: Carfilzomib, Dexamethasone, Lenalidomide, Smoldering Multiple Myeloma

Outcome measures

Primary outcome

• MRD negativity rate by NGF after cycle 9 for all eligible ITT patients;

eligible patients who achieve a MRD negativity after cycle 9 will be considered

as a success. All other eligible randomized ITT patients will be considered as

a failure, including patients going off-protocol before cycle 9, whatever the

cause.

Secondary outcome

• MRD negativity rate evaluated by means of next generation flow cytometry (cut

off 10-5) after cycle 4;

• MRD negativity rate evaluated by means of next generation flow cytometry (cut

off 10-5) after completion of maintenance

• Correlation of MRD (NGF) negativity rate with PFS

• Overall response rate (ORR; i.e. at least partial response (PR)) after 9

cycles induction treatment;

• Progression-free survival (PFS), defined as time from study entry to

progression or death, whichever comes first;

• Progression-free survival-2 (PFS2), defined at time from randomization to

progression after second-line treatment or death, whichever

comes first;

• Duration of response (DOR), defined as time from response to progression or death, whichever comes first;

• Overall survival (OS), defined as time from study entry to death from any cause. Patients still alive at the date last contact will be censored;

• Correlation of MRD (NGF) negativity rate with PFS, PFS2, DOR and OS;

• Toxicity of combination therapy (carfilzomib, lenalidomide, and dexamethasone)

• Safety (type, frequency, and severity of adverse events (AE) and relationship of AE to study drug, serious AE (SAEs))

• Disease heterogeneity in relation to clinical outcomes (molecular profiling on bone marrow samples)

Study description

Background summary

A recent study has shown that intervention with the use of novel agents in smoldering myeloma (SMM) resulted in prolonged PFS and OS without significant toxicity. A more recent pilot study in high-risk smoldering myeloma using carfilzomib, lenalidomide in combination with dexamethasone resulted in 100% CR rate and 10 out of 12 patients reached MRD negativity.
These studies formed the rationale to compare the efficacy and safety of carfilzomib, lenalidomide and dexamethasone vs. lenalidomide, dexamethasone, both followed by 24 months of lenalidomide maintenance in high-risk SMM.
This study is designed to compare 2 treatment modalities to find the optimal treatment in efficacy and safety for high-risk SMM, to define new risk stratifiers for outcome to treatment in SMM and to better understand the biology of SMM.

Study objective

The primary objective of the study is :
To assess MRD negativity rate by NGF after 9 cycles for all eligible ITT patients of KRd versus Rd in patients with high-risk SMM

Secondary objectives:
• To assess MRD (NGF) negativity rate after 4 cycles of induction treatment
• To assess MRD (NGF) negativity rate after completion of maintenance treatment
• To assess correlation of MRD (NGF) negativity rate with PFS
• To assess overall response rate (ORR) after 4 and 9 cycles induction treatment and after maintenance
• To determine progression-free survival (PFS)
• To determine progression-free survival-2 (PFS2)
• To determine duration of response (DOR)
• To determine overall survival (OS)
• To assess correlation of MRD (NGF) negativity rate with PFS, PFS2, DOR and OS
• To evaluate toxicity of combination therapy (carfilzomib, lenalidomide, and dexamethasone)
• To evaluate safety (type, frequency, and severity of adverse events (AE) and relationship of AE to study drug, serious AE (SAEs))
• To evaluate disease heterogeneity in relation to clinical outcomes (molecular profiling on bone marrow samples)

Study design

Randomized multi-center open-label phase 2 trial.

Intervention

Patients will be treated with KRd combination 9 cycles a 28 days (carfilzomib , lenalidomide , dexamethasone) or Rd combination (lenalidomide , dexamethasone); followed by extended lenalidomide dosing (for 24 cycles a 28 days).

Study burden and risks

Given the high rates of progression specific to the high risk SMM populations and low toxicity profile of combination therapy, risk of exposure does not seem to outweigh the clinical benefit that patients may derive from therapy. More importantly, much of patient morbidity in MM is associated with pain from irreversible skeletal related events. This study aims to treat or cure the disease before irreversible bone damage occurs or before aggressive clinical MM occurs. Discomfort from venipuncture, bone marrow biopsy, and CT scan is minimal and of limited risk

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

• Patients must have histologically or cytologically confirmed Smoldering Multiple Myeloma based on the 2014 International Myeloma Working Group Criteria:
o Serum M-protein >=3 g/dl
Or urinary monoclonal protein >500 mg per 24 hours
And/or monoclonal bone marrow plasma cells >=10-60 %
o Absence of CRAB symptoms and myeloma defining events.
• Patients must have high risk Smoldering Multiple Myeloma based on the Mayo Clinic and/or the PETHEMA criteria
• Measurable disease
• Age >18 years
• WHO/ECOG performance status <=2
• Patients must have normal organ and marrow function
• Calculated Creatinine Clearance >= 50 ml/min
• Females of childbearing potential must have a negative serum or urine pregnancy test within 10 - 14 days prior to entry and again within 24 hours of starting lenalidomide treatment
• Patients must be willing and capable to use adequate contraception during and after the therapy (all men, all pre-menopausal women) Patients must be able to

adhere to the requirements of the Lenalidomide Pregnancy Prevention Plan
• Written informed consent
• Patient is capable of giving informed consent

Exclusion criteria

• Patients with symptomatic multiple myeloma (i.e. having myeloma defining events)
• Amyloid Light-chain (AL) amyloidosis
• Patients who are receiving any other investigational agents.
• Concurrent systemic treatment or prior therapy within 4 weeks for SMM
• Contraindication to any concomitant medication, including antivirals, anticoagulation prophylaxis, tumor lysis prophylaxis, or hydration given prior to therapy
• History of allergic reactions attributed to immunomodulatory agents and proteasome inhibitors.
• Hypersensitive reaction to active substances or any excipients of the IMPs
• Uncontrolled hypertension or diabetes
• Pregnant or lactating females.
• Significant cardiovascular disease with NYHA grade III or IV symptoms, or hypertrophic cardiomegaly, or restrictive cardiomegaly, or myocardial infarction within 3 months prior to enrollment, or unstable angina, or unstable arrhythmia
• Active hepatitis B or C infection
• Known or suspected HIV infection
• Incidence of gastrointestinal disease that would prevent absorption
• Patients with gastric or duodenal ulcers
• Significant neuropathy >=Grade 3 or grade 2 with pain within 14 days of enrollment
• Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection.
• History of other malignancy (apart from basal cell carcinoma of the skin, or in situ cervix carcinoma) except if the patient has been free of symptoms and without active therapy during at least 5 years
• Major surgery within 1 month prior to enrollment
• Pre-existing pulmonary, cardiac or renal impairement that prevents hydration measures
• Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-01-2019
Enrollment:	25
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	dexamethasone Merck
Generic name:	Dexamethasone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	dexamethasone ratiopharm
Generic name:	Dexamethasone
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Kyprolis
Generic name:	Carfilzomib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Revlimid
Generic name:	Lenalidomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-08-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	04-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-01-2021

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-04-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2024
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	EUCTR2017-000555-10-NL
CCMO	NL62302.078.17