A Randomized, Controlled, Open-Label, Phase 3 Study of Melflufen/Dexamethasone Compared with Pomalidomide/ Dexamethasone for Patients with Relapsed Refractory Multiple Myeloma who are Refractory to Lenalidomide

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Primary Objective** To compare the PFS of melflufen plus dexamethasone (Arm A) versus pomalidomide plus dexamethasone (Arm B) as assessed by the Independent Review Committee (IRC) according to the International Myeloma Working Group Uniform Response...

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

Summary

ID

NL-OMON52982

Source
ToetsingOnline

Brief title
OP-103

Condition

- Plasma cell neoplasms

Synonym
cancer of plasma cells, multiple myeolma

Research involving
Human

Sponsors and support

Primary sponsor: Oncopeptides AB
Source(s) of monetary or material Support: Oncopeptides AB

Intervention

Keyword: melflufen, pomalidomide, relapsed refractory multiple myeloma

Outcome measures

Primary outcome

Primary Endpoint*

* PFS

Secondary outcome

Key Secondary endpoints*

* ORR

* DOR

* OS

* Frequency and grade of Adverse Events (AE).

Other Secondary Endpoints*

* CBR

* TTR

* TTP

* Duration of clinical benefit

* Best response during the study (sCR, CR, VGPR, PR, MR, stable disease [SD] or

PD)

* Primary and secondary endpoints as assessed by investigators

* PK parameters of melphalan

* All tumor response and progression-dependent endpoints are as assessed by the IRC according to the IMWG-URC (Rajkumar et al. 2011, Appendix C) unless otherwise specified.

Exploratory endpoints

* PK parameters of melphalan, safety and efficacy variables specified in key secondary and other secondary endpoints

* MRD in patients that achieve a CR

• An additional Exploratory Endpoint has been added to describe the endpoints to evaluate the new study objective

Study description

Background summary

Melflufen is a peptidase-potentiated therapy designed for targeted delivery of alkylating moieties to tumor cells. In contrast to other alkylating agents that are hydrophilic, the lipophilicity of melflufen leads to rapid and extensive distribution into tissues and cells. Inside cells, melflufen may directly bind deoxyribonucleic acid (DNA) or is readily metabolized by intracellular peptidases into the well-known antitumor compound melphalan, or by esterases into desethyl-melflufen, which also has alkylating properties. Due to the high activity of peptidases and esterases in human tumor cells, the formation of melflufen*s metabolites is rapid in these cells with subsequent inflow of more melflufen (Gullbo et al. 2003c, Wickström et al. 2010). Since des-ethylmelflufen and melphalan are relatively hydrophilic, there is a possibility for intracellular trapping of these alkylators. This can be explained by a more efficient transport of melflufen into these cells, an efficient conversion into other alkylating molecules (i.e. melphalan and desethylmelflufen) inside the cells and a less rapid disappearance of these molecules from the cells.
The addition of melflufen to panels of primary cultures of human tumor cells, including multiple myeloma (MM), results in a similar pattern of activity as that of melphalan, but with 50 to 100-fold higher efficacy (Wickström et al. 2008), which is explained by the 50-fold higher intracellular exposure in MM

cells of alkylating agents compared to that observed after an equimolar dose of melphalan (Chauhan et al. 2013).
Mechanistically oriented studies have shown that melflufen-induced apoptosis is associated with (i) activation of caspases and poly ADP ribose polymerase cleavage; (ii) reactive oxygen species generation; (iii) mitochondrial dysfunction and release of cytochrome c; and (iv) induction of DNA damage (Chauhan et al. 2013).
Moreover, melflufen inhibits MM cell migration and tumor associated angiogenesis and DNA repair. Importantly, in vitro studies in MM cel lines resistant to dexamethasone, bortezomib and melphalan have shown
Clinical and preclinical data support that melflufen provides peptidase potentiated alkylating metabolites to tumor cells such as MM and thereby exerts a higher anti-tumor activity compared with equimolar administration of melphalan but with a similar safety profile.
Pomalidomide is indicated for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.
Although the incorporation of novel agents such as PIs and IMiDs, including retreatment, sequential and combination therapy approaches, has significantly improved outcomes in addition to autologous stem-cell transplant (ASCT), for those that are eligible, myeloma is not yet curable and additional treatment options are needed.

Study objective

Primary Objective*
* To compare the PFS of melflufen plus dexamethasone (Arm A) versus pomalidomide plus dexamethasone (Arm B) as assessed by the Independent Review Committee (IRC) according to the International Myeloma Working Group Uniform Response Criteria (IMWG-URC) (Rajkumar et al. 2011, Appendix C).
Key Secondary Objectives*
* To assess and compare the overall response rate (ORR), i.e., proportion of patients with >= PR (stringent complete response [sCR], complete response [CR], very good partial response [VGPR] and partial response [PR]) as best response in Arm A versus Arm B.
* To assess and compare duration of response (DOR) in patients with >= PR (sCR, CR, VGPR, PR) as best response in Arm A versus Arm B
* To assess and compare overall survival (OS) in Arm A versus Arm B
* To assess and compare the safety and tolerability in Arm A and Arm B
Other Secondary Objectives*
* To assess and compare clinical benefit rate (CBR) (i.e proportion of patients with, >= MR) as best response in Arm A versus Arm B
* To assess and compare time to response (TTR) in patients with a PR or better in Arm A versus Arm B
* To assess and compare time to progression (TTP) in Arm A versus Arm B*
* To assess and compare the duration of clinical benefit (i.e., >= MR) in Arm A versus Arm B.

* To assess and compare best response during the study in Arm A versus Arm B.
* To assess and compare investigator assessment of primary and secondary endpoints in Arm A versus Arm B.
* To assess and compare the primary and secondary endpoints in various subgroups of Arm A and Arm B.
* To evaluate the melphalan pharmacokinetic (PK) parameters during treatment with melflufen, the impact of covariates on this relationship and the inter-occasion variability in melphalan exposure (Arm A)
* All tumor response and progression-depended objectives are as assessed by the IRC according to the IMWG-URC (Rajkumar et al. 2011,
Appendix C) unless otherwise specified.
Exploratory Objective
* To evaluate the relationship between melphalan exposure and effect on safety and efficacy variables (Arm A)
* To assess minimal residual disease (MRD) in patients that achieve a CR (Arm A and Arm B).
With this amendment comes an additional Exploratory Objective added to further evaluate the effect of melflufen on patients reported outcomes of functional status and well-being. Value and change from baseline in each scale of the EORTC QLQC30, each scale of the MY20, each dimension of the EQ-5D, and the visual analog scale (VAS) of the EQ-5D.

Study design

This is a randomized, controlled, open-label, Phase 3 multicenter study which will enroll patients with RRMM following 2-4 lines of prior therapy (Appendix D) and who are refractory to both the last line of therapy and to lenalidomide (>=10 mg) administered within 18 months prior to randomization as demonstrated by disease progression on or within 60 days of completion of the last dose of lenalidomide.
Patients will be randomized to either one of two arms.Arm A is the experimental Arm and Arm B is the control Arm.
Arm A:
Melflufen 40 mg on Day 1 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.
Arm B:
Pomalidomide 4 mg daily on Days 1 to 21 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of each 28-day cycle.
Patients >= 75 years of age will have a reduced dose of dexamethasone of 20 mg on Days 1, 8, 15 and 22 for both Arm A and Arm B.
Patients may receive treatment until there is documented disease progression, unacceptable toxicity or the patient/treating physician
determines it is not in the patient*s best interest to continue.
Dose modifications and delays in therapy may be implemented based on patient tolerability as detailed in the protocol Section 7.8. In the event of
a cycle delay, unrelated to dexamethasone toxicity, it is recommended to continue dexamethasone weekly.

A Schedule of Events for the study is outlined in protocol Section 8.1.

Patients with good tolerability will no longer require weekly CBC assessments. Good tolerability is defined as no dose modifications, dose delays or need of supportive therapy (growth factors, blood or platelet transfusions) in the two preceding cycles. If a patient fulfils all criteria CBC assessments may be excluded Day 8 and Day 22.

Intervention

Treatment will be given in an outpatient treatment setting in cycles. Each cycle is 28 days.
Arm A: Melflufen 40 mg will be administered as a 30-minutes intravenous infusion on Day 1 of every 28-day cycle via acceptable central catheter
Arm B: Pomalidomide capsules 4 mg administered orally Days 1 to 21 in each 28-day cycle.
Arm A and B:
Dexamethasone tablets for 40 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient < 75 years of age.
OR
Dexamethasone tablets for 20 mg administered orally on Days 1, 8, 15 and 22 of each 28-day cycle for patient >= 75 years of age.
Oral dexamethasone may be substituted with intravenous dexamethasone at the investigators discretion (USA only). In the event of cycle delays, it is recommended that dexamethasone continue weekly.
Dose modifications and delays may be implemented based on patient tolerance as detailed in the protocol.

Study burden and risks

Patients may experience drug-related side effect. For full list of side effects please refer to Appendix D of the main patient information sheet and infomed consent from.
In addition to side effects patients may experience discomforts and risks associated with the study procedures such as blood drawing, bone marrow sampling, imaging.

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

1. Male or female, age 18 years or older
2. A prior diagnosis of multiple myeloma with documented disease progression requiring further treatment at time of screening
3. Measurable disease defined as any of the following:
* Serum monoclonal protein >= 0.5 g/dL by protein electrophoresis.
* >= 200 mg/24 hours of monoclonal protein in the urine on 24-hour electrophoresis
* Serum free light chain >= 10 mg/dL AND abnormal serum kappa to lambda free light chain ratio
4. Received 2-4 prior lines of therapy (Appendix D), including lenalidomide and a PI, either sequential or in the same line, and is refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide (>= 10 mg) administered within 18 months prior to randomization. Refractory to lenalidomide is defined as progression while on lenalidomide therapy or within 60 days of last dose, following at least 2 cycles of lenalidomide with at least 14 doses of lenalidomide per cycle.
5. Life expectancy of >= 6 months.
6. Eastern Cooperative Oncology Group (ECOG) performance status <= 2. (Patients with lower performance status based solely on bone pain secondary to multiple myeloma may be eligible following consultation and approval of the medical

monitor) (Appendix A)
7. Females of child bearing potential (FCBP)* must have a medically supervised negative serum or urine pregnancy test with a sensitivity according to local Risk Evaluation and Mitigation Strategy* (REMS) or pomalidomide pregnancy prevention plan (PPP) completed within 10 to 14 days prior to planned start of treatment. All FCBP must agree to either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking treatment and as appropriate based on the treatment assignment (See Section 7.7.1). FCBP must also agree to ongoing pregnancy testing. Men must agree to use a condom during sexual contact with a FCBP even if they have had a vasectomy from the time of starting study treatment through 3 months after the last dose of melflufen (Arm A) or 28 days after the last dose of pomalidomide (Arm B). All patients enrolled in Canada and the USA must be willing to comply with all requirements of the Canadian or USA pomalidomide REMS program. All patients enrolled outside of Canada and the USA must be willing to comply with all the requirements of the pomalidomide PPP (Appendix J). (Willingness, to comply with the REMS or PPP, must be documented prior to knowledge of randomization but is only required if randomized to Arm B).
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent.
9. 12-lead Electrocardiogram (ECG) with QT interval calculated by Fridericia Formula (QTcF) interval of <= 470 msec (Appendix H).
10. The following laboratory results must be met during screening and also immediately before study drug administration on Cycle 1 Day 1:
* Absolute neutrophil count (ANC) >= 1,000 cells/mm3 (1.0 x 109/L) (Growth factors cannot be used within 10 days prior to first drug administration)
* Platelet count >= 75,000 cells/mm3 (75 x 109/L) (without transfusions during the 10 days prior to first drug administration)
* Hemoglobin >= 8.0 g/dl (red blood cell (RBC) transfusions are permitted)
* Total Bilirubin <= 1.5 x upper limit of normal (ULN), or patients diagnosed with Gilberts syndrome that have been reviewed and approved by the medical monitor.
* Aspartate transaminase (AST/SGOT) and alanine transaminase (ALT/SGPT) <= 3.0 x ULN.
* Renal function: Estimated creatinine clearance by Cockcroft-Gault formula >= 45 mL/min. (Appendix G).
11. Must be able to take antithrombotic prophylaxis (see Section 7.7.1).
12. Must have, or be willing to have an acceptable central catheter. (Port a cath, peripherally inserted central catheter [PICC] line, or central venous catheter) (Willingness must be documented prior to randomization but insertion only required if randomized to Arm A).
*(FCBP) is any sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing

potential) for at least 24 consecutive months.

Exclusion criteria

1. Primary refractory disease (i.e. never responded (>= MR) to any prior therapy)
2. Evidence of mucosal or internal bleeding or platelet transfusion refractory (platelet count fails to increase by > 10,000 after a transfusion of an appropriate dose of platelets)
3. Any medical conditions that, in the Investigator*s opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study. Examples of such conditions are:
a significant history of cardiovascular disease (e.g., myocardial infarction, significant conduction system abnormalities, uncontrolled hypertension, >= grade 3 thromboembolic event in the last 6 months),
4. Prior exposure to pomalidomide
5. Known intolerance to IMiDs. (>= Grade 3 hypersensitivity reaction or at the investigators discretion)
6. Known active infection requiring parenteral or oral anti-infective treatment within 14 days of randomization.
7. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cel carcinoma, squamous cell skin cancer, carcinoma in-situ of the
cervix or breast or very low and low risk prostate cancer in active surveillance.
8. Pregnant or breast-feeding females
9. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation
10. Known human immunodeficiency virus or active hepatitis C viral infection
11. Active hepatitis B viral infection (defined as HBsAg+).
* Patients with prior hepatitis B vaccine are permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-).
* Non-active hepatitis B (HBsAg-, Anti-HBs+, Anti-HBc+) may be enrolled at the discretion of the investigator after consideration of risk of reactivation.
12. Concurrent symptomatic amyloidosis or plasma cell leukemia.
13. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes)
14. Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to randomization. The use of live vaccines within 30 days before randomization. IMiDs, PIs or corticosteroids within 2 weeks prior to randomization. Other investigational therapies and monoclonal antibodies within 4 weeks of randomization. Prednisone up to but no more than 10 mg orally q.d. or its equivalent for symptom management of comorbid conditions is permitted but dose should be stable for at least 7 days prior to randomization

15. Residual side effects to previous therapy > grade 1 prior to randomization (Alopecia any grade and/or neuropathy grade 2 without pain are permitted)
16. Prior peripheral stem cell transplant within 12 weeks of randomization
17. Prior allogeneic stem cell transplantation with active graft-versushost-disease).
18. Prior major surgical procedure or radiation therapy within 4 weeks of the randomization (this does not include limited course of radiation used for management of bone pain within 7 days of randomization).
19. Known intolerance to steroid therapy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	09-05-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fortecortin
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Imnovid
Generic name:	pomalidomide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	melflufen
Generic name:	melflufen
Product type:	Medicine
Brand name:	Pomalyst
Generic name:	pomalidomide

Ethics review

Approved WMO Date:	13-04-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-06-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	12-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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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)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-12-2020
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Approved WMO Date:	25-04-2022
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	EUCTR2016-003517-95-NL
CCMO	NL60178.078.17

Study results

Date completed: 05-06-2022

Results posted: 20-09-2023

First publication
12-09-2023