A phase 1B multicenter, open-label study to determine the recommended dose and regimen of Durvalumab (MEDI4736) either as monotherapy or in combination with Pomalidomide (POM) with or without low-dose Dexamethasone (DEX) in subjects with relapsed and refractory multiple myeloma (RRMM)

Published: 06-11-2015
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Primary ObjectiveThe primary objective of the study is to determine the recommended dose and regimen ofdurvalumab either as monotherapy or in combination with POM +/- dex in subjects with RRMM.Secondary ObjectivesThe secondary objectives are to:*...

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

Summary

ID

NL-OMON53145

Source
ToetsingOnline

Brief title
MEDI4736-MM-001

Condition

- Plasma cell neoplasms

Synonym
Multiple myeloma - bone marrow cancer

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Onderzoek wordt gefinancierd door Celgene Corporation

Intervention

Keyword: durvalumab, multiple myeloma, phase 1, pomalidomide

Outcome measures

Primary outcome

The primary objective of the study is to determine the recommended dose and

regimen of durvalumab either as monotherapy or in combination with POM +/- dex

in subjects with RRMM.

Secondary outcome

The secondary objectives are to:

* Evaluate the safety and preliminary efficacy of durvalumab monotherapy and in

combination with POM +/- dex in subjects with RRMM

* Evaluate the PK of durvalumab and POM with or without dex in subjects with

RRMM

The exploratory objectives are to:

* Determine the immunogenicity of durvalumab as monotherapy and when given in

combination with POM +/- dex in subjects with RRMM

* Establish PK/Pd relationship, explore Pd, mechanistic, and predictive

biomarkers of durvalumab and POM as single agents and when given in

combination in subjects with RRMM

* Evaluate minimal residual disease (MRD) and its correlation to clinical

outcome measures

* Evaluate additional measures of efficacy of durvalumab monotherapy and in

combination with POM +/- dex in subjects with RRMM

Study description

Background summary

Durvalumab has been studied primarily in subjects with solid tumors and a limited number of
subjects with MDS but not MM. While pharmacokinetics (PK) and safety of durvalumab as
monotherapy and in combination have been characterized in more than 500 subjects, the
paraprotein present in myeloma may alter the PK and pharmacodynamics (Pd) of durvalumab
and higher doses may be required. The combination with POM and dexamethasone (dex) has
not been previously studied. While the starting dose of 1500 mg once every 4 weeks (Q4W) is
justified based on PK and Pd data and the expectation is that there will not be synergistic
toxicity, dose de-escalation may be considered. As dex may interfere with the immune-mediated
efficacy of durvalumab but has shown efficacy when added with POM, this study aims to
generate PK/Pd, safety, biomarker, and preliminary efficacy data with and without the use of
dex.
Durvalumab (MEDI4736) is a human immunoglobulin G1 kappa monoclonal antibody targeted
against PD-L1. The proposed mechanism of action for durvalumab involves immune system
activation leading to T-cell activation and proliferation, inhibition of human tumor growth via a
T-cell-dependent mechanism, and immune mediated killing

Pomalidomide has shown efficacy in combination with dexamethasone for RRMM patients who
have failed prior lenalidomide and bortezomib, a proteasome inhibitor (San Miguel, 2013;
Richardson, 2014). Based on the current information on IMiDs, the combination of durvalumab
+ POM + dex warrants further investigation in RRMM patients who have already had prior
lenalidomide and proteasome inhibitor therapy.

Study objective

Primary Objective
The primary objective of the study is to determine the recommended dose and regimen of
durvalumab either as monotherapy or in combination with POM +/- dex in subjects with RRMM.
Secondary Objectives
The secondary objectives are to:
* Evaluate the safety and preliminary efficacy of durvalumab monotherapy and in combination with POM +/- dex in subjects with RRMM
* Evaluate the PK of durvalumab and POM with or without dex in subjects with RRMM
Exploratory Objectives
The exploratory objectives are to:
* Determine the immunogenicity of durvalumab as monotherapy and when given in combination with POM +/- dex in subjects with RRMM
* Establish PK/Pd relationship, explore Pd, mechanistic, and predictive biomarkers of
durvalumab and POM as single agents and when given in combination in subjects with RRMM
* Evaluate minimal residual disease (MRD) and its correlation to clinical outcome
measures
* Evaluate additional measures of efficacy of durvalumab monotherapy and in combination with POM +/- dex in subjects with RRMM

Study design

This is a multicenter, open-label, Phase 1b study to determine the recommended dose and regimen of durvalumab either as monotherapy or in combination with POM with or without low dose dex in subjects with RRMM. The study will consist of a dose-finding portion as well as a parallel dose-expansion portion to determine the optimal dose and regimen. See Figure 1: Overall Study Design.
Dose-finding
The dose-finding portion of the study will use a modified Rolling 6 design

(Skolnik, 2008). Subjects will be randomized in parallel to 1 of 3 treatment arms.
• Treatment Arm A: durvalumab monotherapy
• Treatment Arm B: durvalumab + POM
• Treatment Arm C: durvalumab + POM + dex

Expansion
All expansion decisions will be determined by the DRT after review of all safety, and if applicable PK/Pd, and/or biomarker, and/or preliminary efficacy data.

Intervention

The dose of durvalumab will depend on the cohort (Cohort -1: 750 mg; Cohort 1: 1500 mg; Cohort 2: 2250 mg; Cohort 3: 3000 mg). Additional/or and intermediate dose levels may be added as deemed appropriate by the Dose Review Team (DRT). The DRT consists of the Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives as appropriate and site investigator and/or designees who have enrolled subjects to the study. The DRT members are responsible for all dose level decisions.
Initially up to 6 evaluable subjects will be enrolled in the Dose-finding Cohort 1 (durvalumab 1500 mg) of each treatment arm. Enrollment of up to 6 evaluable subjects into the Dose-finding Cohorts -1, 2, or 3 for each treatment arm will be based on the Rolling 6 design, and only occur after review of safety, and if applicable, PK/Pd, and/or biomarker, and/or preliminary efficacy data by the DRT from prior cohorts.
The starting dose level of POM will be 4 mg for all cohorts.
The starting dose level of dex will be 40 mg/day (<= 75 years old) or 20 mg/day (> 75 years old) for all cohorts

Arm A expansion:
Once the data from the Dose-finding Cohort(s) for Arm A are obtained and reviewed, up to 12 additional subjects (a total of 18) may be enrolled into an Expansion Cohort for Arm A.
Arm B and C expansion:
• If the Dose-finding Cohort 1 (durvalumab 1500 mg) does not exceed the maximum tolerated dose (MTD), safety, PK/Pd, and efficacy will be further evaluated in an Expansion of Cohort 1 dose level with up to 24 additional subjects (a total of 30) enrolled into each Arm.
• If applicable, after data from the Arm B and Arm C Dose-finding Cohort 2 (durvalumab 2250 mg) and/or Cohort 3 (durvalumab 3000 mg) are obtained and reviewed, up to 24 additional subjects (a total of 30) may be enrolled into any one of the following: Arm B Cohort 2 or Arm B Cohort 3 or Arm C Cohort 2 or Arm C Cohort 3.

Study burden and risks

The patients will have to come to the outpatient clinic more often for the study and have to undergo a number of additional procedures, including extra blood tests, ECGs, X-rays, bone marrow biopsies and bone marrow aspirates. The study medication can cause side effects, but the patients are monitored regularly (refer to section E2, E4 and E6)

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. Subject is >= 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other

protocol requirements.
4. Subject has documented diagnosis of multiple myeloma and have measurable disease by serum protein electrophoresis (sPEP) or urine protein electrophoresis (uPEP): sPEP >= 0.5 g/dL or uPEP >= 200 mg/24 hours (except for subjects in the EMP sub-group).
5. Subject had at least 2 prior anti-myeloma regimens.
(Note: Induction, bone marrow transplant with or without maintenance therapy is considered one regimen.)
6. Subject achieved at least a stable disease (SD) for at least 1 cycle of treatment to at least 1 prior anti-myeloma regimen before developing PD.
7. Subject had documented PD during or within 60 days after the last anti-myeloma regimen.
8. Subject received prior treatment with a lenalidomide-containing regimen for at least 2 consecutive cycles.
9. Subject received prior treatment with a proteasome inhibitor-containing regimen for at least 2 consecutive cycles.
10. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.
11. Females of childbearing potential (FCBP) must:
a. Have 2 negative pregnancy tests as verified by the investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence from heterosexual contact.
b. Either practice true abstinence2 from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting study treatment, during the study therapy (including dose interruptions), and for at least 90 days after discontinuation of study treatment.
c. Refrain from egg cell donation for at least 90 days after the final dose of durvalumab
12. Male subjects must:
a. Either practice true abstinence2 (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 90 days following study treatment discontinuation, even if he has undergone a successful vasectomy.
b. Refrain from sperm donation for at least 90 days after the final dose of durvalumab
For subjects who will be in the Arm C extramedullarly plasmacytoma subgroup, the following includsion criterium will also apply:
13. Subject has radiologically measurable EMP disease (soft tissue of bone related) that is amenable to biopsy and subject agrees and consents to additional biopsy procedures as described in the protocol. These subjects do not need to have measurable disease by sPEP and/or uPEP.

Exclusion criteria

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
3. Subject has any condition that confounds the ability to interpret data from the study
4. Subject has non-secretory or oligosecretory multiple myeloma (uitzondering voor patienten in de EMP sub-groep.
5. Subject has any of the following laboratory abnormalities:
a. Absolute neutrophil count (ANC) < 1,000/µL
b. Platelet count: < 75,000/µL
c. Hemoglobin < 8 g/dL (< 4.9 mmol/L)
d. Creatinine Clearance (CrCL) < 45 mL/min
e. Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)
f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × ULN
g. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert*s syndrome
6. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for >= 5 years with the exception of the following non-invasive malignancies:
• Basal cell carcinoma of the skin
• Squamous cell carcinoma of the skin
• Carcinoma in situ of the cervix
• Carcinoma in situ of the breast
• Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative
7. Subject had prior treatment with POM but did not achieve at least a SD with the POM-containing regimen
8. Subject had prior exposure to immunotherapy, including, but not limited to, other anti-CTLA-4,anti-PD-1, anti-PD-L1 mAbs, cell-based therapies, or cancer vaccines
9. Subject has history of organ or allogeneic stem cell transplantation
10. Subject has or had clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS multiple myeloma
11. Subject has history of anaphylaxis or hypersensitivity to thalidomide, lenalidomide, POM, or dex
12. Subject had rash >= Grade 3 during prior thalidomide, lenalidomide, or POM therapy
13. Subject has incidence of gastrointestinal disease that may significantly

alter the absorption of POM
14. Subject has known or suspected hypersensitivity to the excipients contained in the formulation of durvalumab, POM, or dex
15. Subject has received any of the following within the last 14 days of initiating study treatment:
a. Plasmapheresis
b. Major surgery (as defined by the investigator)
c. Radiation therapy other than local therapy for myeloma associated bone lesions
d. Use of any systemic anti-myeloma drug therapy
16. Subject has received prior treatment with a monoclonal antibody within 5 half-lives of initiating study treatment
17. Subject has used any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment
18. Subject has peripheral neuropathy >= Grade 2
19. Subject has any one of the following:
a. Clinically significant abnormal electrocardiogram (ECG) finding at screening
b. Congestive heart failure (New York Heart Association Class III or IV)
c. Myocardial infarction within 12 months prior to starting study treatment
d. Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
20. Subject has current or prior use of immunosuppressive medication within 14 days prior to the first dose of study treatment. The following are exceptions to this criterion:
a. Intranasal, inhaled, topical, or local steroid injections (eg, intra-articular injection)
b. Systemic corticosteroids at physiologic doses that do not exceed 10 mg/day of prednisone or equivalent
c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)
21. Subject has active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn*s disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener*s syndrome [granulomatosis with polyangiitis]; myasthenia gravis; Graves* disease; rheumatoid arthritis; hypophysitis, uveitis; etc) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
a. Subjects with vitiligo or alopecia
b. Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
c. Subjects with psoriasis not requiring systemic treatment
22. Subject has history of primary immunodeficiency
23. Subject is positive for human immunodeficiency virus (HIV), chronic or active hepatitis B or active hepatitis A or C.
24. Subject has received live, attenuated vaccine within 30 days prior to the

first dose of durvalumab (NOTE: Subjects, if enrolled, should not receive live vaccine during the study and 30 days after the last dose of durvalumab)
25. Subject is unable or unwilling to undergo protocol required thromboembolism prophylaxis
26. Subject is a female who is pregnant, nursing, or breastfeeding, or who intends to become pregnant during the participation in the study.
27. Subject is a current smoker

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imnovid
Generic name:	Pomalidomide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	NA
Generic name:	Durvalumab

Ethics review

Approved WMO Date:	06-11-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-01-2017

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-04-2022
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-03-2023
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	EUCTR2015-003066-93-NL
ClinicalTrials.gov	NCT02616640
CCMO	NL54990.078.15