Multicenter, Single-arm, Phase 2 Study to Determine the Efficacy for the Combination of Daratumumab (DARA) Plus Durvalumab (DURVA) (D2) in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) who have Progressed on DARA While on a DARA-containing Regimen as the Most Recent Multiple Myeloma Therapy. *Fusion MM-005*

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Primary: · To determine the efficacy of DARA plus durvalumab (DURVA) in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.Secondary:· Determine the safety of DARA plus DURVA in subjects...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON45465

Source
ToetsingOnline

Brief title
'FUSION MM-005'
MEDI4736-MM-005
0451/0234

Condition

- Plasma cell neoplasms

Synonym
Relapsed and Refractory Multiple Myeloma; Kahler's disease (relapsing and not responding to treatment)

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene International II Sàrl

Intervention

Keyword: Daratumumab, Durvalumab, Efficacy, Relapsed and Refractory Multiple Myeloma

Outcome measures

Primary outcome

- Overall response rate (ORR): Tumor response (partial response [PR] or

better), and the rate of progressive disease (PD) according to the

International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar,

2011).

Secondary outcome

Secondary:

- Safety: Type, frequency, seriousness and severity of adverse events (AEs),

and relationship of AEs to study treatment

- Time-to-response (TTR): Time from treatment initiation to the first

documentation of response (PR or greater)

- Duration of response (DOR): Time from the first documentation of response

(PR or greater) to the first documentation of PD or death, whichever is earlier, based on the investigator assessments according to the IMWG Uniform Response Criteria.

- Progression-free survival (PFS): Time from treatment initiation to the first documentation of PD or death from any cause during study, whichever occurs earlier

- Overall survival (OS): Time from treatment initiation to death due to any cause

- Pharmacokinetic (PK) parameters: Typical serum/plasma PK parameters for DURVA and DARA, such as maximum observed concentration (Cmax), area under the concentration-time curve (AUC), time to maximum concentration (Tmax), terminal elimination half-life (t1/2), clearance (CL/F), and volume of distribution (Vz/F)

Exploratory:

- Immunogenicity: The number of subjects who develop anti-drug antibodies against DURVA and/or DARA

- Biomarker: Gene expression signatures from bone marrow aspirates at DARA relapse and specified time points after DURVA and DARA combination therapy

- Biomarker: Evaluation of the tumor microenvironment at DARA relapse and with DURVA and DARA therapy at the protein, ribonucleic acid (RNA), and deoxyribonucleic acid (DNA) level. Biomarkers of interest include expression of PD-L1, CD38, CD55, and CD59 as well as immune cell subsets and activation markers

- Biomarker: The host immune activation status in peripheral blood at DARA relapse and at specified time points during DURVA and DARA treatment.

- Pharmacodynamic (Pd) biomarkers: Individual soluble factors and immune cell subset levels in peripheral blood at baseline and at specified time points during treatment

- Clinical Outcome: Evaluate minimal residual disease (MRD) negativity and its association with key clinical outcomes.

- Biomarker: Genetic mutations and cytogenetic abnormalities in bone marrow at baseline

Study description

Background summary

Multiple myeloma (MM) is a rare and incurable progressive neoplastic disease that accounts for 10% of all hematological malignancies. It has been estimated that 63,700 incident cases and 79,410 deaths from MM occurred globally in 2013 (GBD, 2015).
Despite the progress in treatment options for MM, the disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. Multiple myeloma remains incurable using conventional treatments, with an overall 5-year relative survival rate of 48.5% (Howlader, 2016). New therapies are needed to treat RRMM patients.

The importance of the immune system in cancer development and progression has been recognized during the past decade (Hanahan, 2000). Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines (Shields, 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity.

Daratumumab (DARA) is a human IgG1k monoclonal antibody that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a

variety of hematological malignancies including multiple myeloma. DARA acts through multiple immune effector-mediated mechanisms, including CDC, ADCC, and antibody-dependent cellular phagocytosis. In addition to direct targeting of CD38+ myeloma cells, recently published data suggests an immune stimulating/modulatory role of DARA.

The mechanism of resistance to DARA remains to be fully explained, but immune escape by upregulation of PD-L1 signaling through PD-1 is hypothesized to contribute to resistance. A recent study showed that PD-L1 expression positively correlates with increased proliferative potential of tumor cells and resistance to therapies in MM (Tamura, 2013). Durvalumab (MEDI4736; DURVA) is a human immunoglobulin (Ig) G1 kappa monoclonal antibody (mAb) directed against human programmed death ligand-1 (PD-L1) protein. Combination treatment of anti-PD-L1 mAb, like DURVA, with other anti-MM therapies that modulate MM-host immune responses, like DARA will potentially enhance both host anti-MM immunity and clinical response and warrant further exploration in the relapsed/refractory population being considered in this study.

Study objective

Primary:

· To determine the efficacy of DARA plus durvalumab (DURVA) in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.

Secondary:

· Determine the safety of DARA plus DURVA in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.

· Further evaluate the efficacy of the combination of DARA plus DURVA in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment. Key efficacy measures include time-to-response [TTR], duration of response [DOR], progression-free survival [PFS], and overall survival [OS].

· Evaluate the pharmacokinetics (PK) of DARA and DURVA in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.

Exploratory:

· Determine the immunogenicity of the combination of DARA plus DURVA in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.

· Evaluate the dynamic changes in the microenvironment of the tumor and in peripheral immune cell subsets in subjects prior to DURVA treatment and while on DURVA/DARA combination therapy to investigate whether DURVA can restore the immune defects associated with DARA resistance.

· Explore the pharmacodynamics (Pd), mechanistic, and predictive biomarkers of DARA and DURVA when given in combination to subjects with RRMM.

· Evaluate minimal residual disease (MRD) negativity and its correlation to key clinical outcome measures.

Study design

This is a single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of the combination regimen of DARA plus DURVA (D2) in subjects with relapsed and refractory multiple myeloma after failure of prior therapies containing a PI, immunomodulatory drug and DARA.

The study will consist of the following consecutive phases: Screening, Treatment, and Follow-up. The Screening Phase may not exceed a 28-day window prior to start of study treatment (Cycle 1 Day 1). Subjects may continue on study treatment until PD or unacceptable toxicity. All subjects will have an End of Treatment (EOT) visit within 7 days after discontinuation of all study treatment. Subjects are to return to the study site 28 (+3) days after the EOT visit and 90 (+3) days after the last dose of DURVA or DARA, whichever is later, for safety follow-up visits.

The study will be conducted in 2 parts: Part 1 and Part 2.
Part 1 has a selected 2-stage design, where a limited number of subjects will be enrolled in Stage 1 to ensure a sufficient efficacy signal is seen prior to enrolling additional subjects in Stage 2. If data are available and the safety profile of DARA plus DURVA has been evaluated as tolerable, enrollment in Part 1 Stage 1 will not be paused. Part 2 will consist of an expansion phase and will be initiated once Part 1 has been completed and if a sufficient efficacy signal has been determined by the Sponsor at the end of Part 1, Stage 2.

Up to approximately 120 subjects with RRMM will be enrolled worldwide.
- Part 1, Stage 1: Up to 18 subjects
- Part 1, Stage 2: Up to 32 subjects
- Part 2, Expansion: Up to 70 subjects

Intervention

Subjects will receive intravenous (IV) DARA at 16 mg/kg on the same dosing schedule (weekly [QW], every 2 weeks [Q2W], or every 4 weeks [Q4W] of each 28-day treatment cycle) received during their last prior therapy containing

DARA at the time of DARA progression. Dosing schedules, for the administration of DARA, may be adjusted during the course of the study, as detailed in Section 7.2, provided that the subject has a response of stable disease (SD) or better. Subjects will also receive IV DURVA at 1500 mg on Day 2 (Cycle 1) and on Day 1 (Cycles * 2) of each 28-day treatment cycle.

Study burden and risks

Refer to SIS/ICF Appendix D: 'Risks and Side Effects'.

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 received at least 3 prior anti-myeloma regimens including a PI and an immunomodulatory agent or is double-refractory to a PI and an immunomodulatory agent. ;* Induction, bone marrow transplant with or without maintenance therapy is considered one regimen.;* Refractory is defined as disease that is nonresponsive on therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy. ;* For subjects who received more than 1 regimen containing a PI their disease must be refractory to the most recent PI containing regimen.;* For subjects who received more than 1 regimen containing a immunomodulatory agent their disease must be refractory to the most recent immunomodulatory agent containing regimen.;2. All subjects must have failed DARA either as a single agent or in combination on last MM therapy. Failure is defined as PD on DARA either as a single agent or in combination.;3. Subject has measurable disease defined as:;a. M-protein (serum protein electrophoresis (sPEP) or urine protein electrophoresis (uPEP): sPEP * 0.5 g/dL or uPEP * 200 mg/24 hours) and/or ;b. Light chain MM without measurable disease in the serum or the urine: serum immunoglobulin free light chain *10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio;4. Subject achieved a response (minimal response [MR] or better) to at least 1 prior treatment regimen.;5. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 2 or less.;6. Subject*s toxicities resulting from previous therapy (including peripheral neuropathy) have resolved or stabilized to * Grade 1.;7. Subject is at least 18 years of age at the time of signing the informed consent form (ICF). ;8. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted. ;9. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.;10. Females of childbearing potential (FCBP) must:;a. Have 2 negative pregnancy tests as verified by the investigator prior to starting study treatment. This applies even if the subject practices true abstinence from heterosexual contact.;i. Negative serum pregnancy test at screening ;ii. Negative serum or urine pregnancy test (investigator*s discretion) within 72 hours prior to starting study treatment (Cycle 1, Day 1), and before beginning each subsequent cycle of treatment, and after end of study treatment. ;Note: Pregnancy testing does not need to be repeated prior to Cycle 1 if the serum pregnancy test for screening was performed within 72 hours of the first dose of study treatment.;b. Either practice true abstinence 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 (eg, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; true abstinence; or vasectomized partner), 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. Agree to abstain from breastfeeding during study participation and for at least 90 days after the last dose of DARA or DURVA, whichever is later.;d. Refrain from egg cell donation for at least 90 days after the final dose of DURVA or DARA, whichever is later.;11. Male subjects must:;a. Either practice true abstinence (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 DURVA or DARA, whichever is later.

Exclusion criteria

1. Subject has had prior exposure to anti-CTLA-4, anti-PD-1, anti-PD-L1 mAbs, or cancer vaccines;2. Subject has received ASCT within 12 weeks before the date of randomization.;3. History of organ or allogeneic stem cell transplantation;4. Subject received any of the following within the last 14 days of initiating study treatment:;a. Plasmapheresis;b. Major surgery;c. Radiation therapy other than local therapy for myeloma associated bone lesions;d. Use of any systemic anti-myeloma drug therapy (except for DARA either alone or in combination with other agents given with it);5. Subject received prior treatment with a monoclonal antibody within 5 half-lives of initiating study treatment, other than DARA.;6. Subject is receiving concurrent chemotherapy or biologic or hormonal therapy for cancer treatment.;7. Subject has any of the following laboratory abnormalities:;a. ANC < 1,000/µL;b. Platelet count: < 75,000/µL (it is not permissible to transfuse a subject to reach this level);c. Hemoglobin < 8 g/dL (< 4.9 mmol/L)(it is not permissible to transfuse a subject to reach this level);d. Creatinine clearance (CrCl) < 45 mL/min (calculated using the Cockcroft-Gault formula or directly calculated from the 24-hour urine collection method);e. Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L);f. AST or ALT > 2.5 × ULN;g. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert*s syndrome ;8. Subject has clinical evidence of CNS or pulmonary leukostasis, disseminated intravascular coagulation, or CNS MM;9. Subject has known COPD with a FEV1 50% of predicted normal. Note that forced expiratory testing (FEV1)is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal. ;10. Subject has known moderate or severe persistent asthma within the past 2 years or uncontrolled asthma of any classification. Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.;11. Subject has plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome, or amyloidosis;12. Subject has nonsecretory MM;13. Subject has known allergy or hypersensitivity to study drug formulations;14. Subject has active or prior documented autoimmune or inflammatory disorders 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*s disease) stable on hormone replacement.;c. Psoriasis not requiring systemic treatment.;15. Subject has history of primary immunodeficiency;16. Subject is positive for HIV-1, chronic or active hepatitis B or active hepatitis A or C.;17. Subject has received live, attenuated vaccine within 30 days prior to the first dose of DURVA.;18. Subject is currently using or has used immunosuppressive medication within 14 days prior to the first study dose of study treatment. The following are exceptions to this criterion:;a. Intranasal, topical, inhaled, or local steroid injections (eg, intra-articular injection).;b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.;c. Steroids as premedication for hypersensitivity reactions (eg, infusion-related reactions, computed tomography [CT] scan premedication).;19. Subject has any one of the following:;a. Clinically significant abnormal ECG finding at screening;b. Congestive heart failure (NYHA 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 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 noninvasive malignancies:;a. Basal cell carcinoma of the skin;b. Squamous cell carcinoma of the skin;c.

Carcinoma in situ of the cervix;d. Carcinoma in situ of the breast;e. Incidental histologic finding of prostate cancer (T1a or T1b using the TNM clinical staging system) or prostate cancer that is curative;21. Subject is a female who is pregnant, nursing, or breastfeeding, or who intends to become pregnant during the participation in the study. ;22. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study;23. 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;24. Subject has any condition that confounds the ability to interpret data from the study

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	daratumumab
Generic name:	DARZALEX
Product type:	Medicine
Brand name:	Durvalumab
Generic name:	NA

Ethics review

Approved WMO Date:	14-03-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-06-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-08-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2016-003801-32-NL
Other	IND number: 127058, US NCT number: NCT03000452, WHO Universal Trial Number (UTN): U1111-1191-1405
CCMO	NL60506.028.17