A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy

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This study has been transitioned to CTIS with ID 2023-507312-13-00 check the CTIS register for the current data. Primary ObjectiveThe primary objective is to determine if the addition of daratumumab to VELCADE (bortezomib),Revlimid (lenalidomide),...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON52950

Source
ToetsingOnline

Brief title
54767414MMY3019

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)
- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Opdrachtgever

Intervention

Keyword: Daratumumab, Multiple Myeloma, Newly diagnosed

Outcome measures

Primary outcome

The primary endpoint of this study is:

Overall MRD negativity rate, which is defined as the proportion of subjects who have achieved MRD negative status (at 10-5) by bone marrow aspirate after randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy. Subjects who have achieved MRD negative status on or after PD or after the switch to subsequent anti-myeloma therapy before PD, will not be considered MRD negative in the primary endpoint analysis.

Secondary outcome

Secondary efficacy endpoints are:

* PFS defined as the duration from the date of randomization to either progressive disease (PD) or death, whichever comes first. Disease progression will be determined according to the International Myeloma Working Group (IMWG) criteria

For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

* MRD negativity rate at 1 year.

* Durable MRD negativity rate is defined as the proportion of subjects who have achieved MRD negative status (at 10-5) at 2 bone marrow aspirate examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.

* Overall response rate is defined as the proportion of subjects who achieve PR or better responses prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria, during or after the study treatment.

* VGPR or better rate is defined as the proportion of subjects achieving VGPR and CR (including sCR) prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria during or after the study treatment.

* CR or better rate is defined as the proportion of subjects achieving CR or sCR prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria during or after the study treatment.

* Progression-free survival on the next line of therapy is defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. Subjects who are still alive and not yet progressed on the next line of treatment will be censored on the last date of followup.

* Overall survival is measured from the date of randomization to the date of the subject*s death due to any cause. If the subject is alive or the vital status is unknown, then the subject*s data will be censored at the date the subject was last known to be alive.

* Medical Resource utilization

* Time to response is defined as the time between the randomization and the first efficacy evaluation at which the subject meets all criteria for PR or better.

* Duration of response is calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of PD, as defined in the IMWG evaluation before the start of any subsequent anti-myeloma

therapy.

* Clinical efficacy (i.e., overall MRD negativity rate and PFS) of D-VRd in high-risk molecular subgroups compared with VRd alone.

* Change in health-related quality of life (HRQoL), symptoms, and functioning using 2 European Organization for Research and Treatment of Cancer (EORTC) questionnaires and utility and visual analog scale of the EuroQol Five Dimension Questionnaire (EQ-5D-5L).

* Pharmacokinetic concentrations of daratumumab.

* Incidence of anti-daratumumab antibodies.

* Prevalence and incidence of anti-rHuPH20 antibodies.

Study description

Background summary

Daratumumab has multiple mechanisms of action, including the direct targeting of tumor cells by selectively binding to cluster of differentiation 38 (CD38) molecules, immune mediated activity
with antibody-dependent cellular cytotoxicity, antibody dependent cellular phagocytosis and
complement-dependent cytotoxicity, decreased immunosuppression and CD38 enzymatic
inhibition. CD38 is highly expressed on myeloma cells but is expressed at relatively low levels
on normal lymphoid and myeloid cells and in some tissues of non-hematopoietic

origin, making it a relevant target for the treatment of multiple myeloma.

Multiple myeloma is characterized by uncontrolled and progressive proliferation of a plasma cell clone. Patients with multiple myeloma produce a monoclonal protein (paraprotein) comprising monoclonal protein (M-protein) and free light chain (FLC), which is an immunoglobulin (Ig) or a fragment of one that has lost its function. The proliferation of myeloma cells causes displacement of the normal bone marrow. Normal Ig levels are compromised, leading to susceptibility to infections. Hypercalcemia, renal insufficiency or failure, and neurological complications are frequently reported signs and symptoms of the disease.

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors. Newly diagnosed patients with multiple myeloma are typically categorized into 2 subpopulations usually defined by their age and suitability for intensive treatment. Younger patients (ie, <65 years of age) typically receive an induction regimen followed by treatment with high-dose chemotherapy and autologous stem cell transplantation (ASCT), followed by consolidation therapy and maintenance treatment. For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered standards of care.

While the treatment of newly diagnosed patients with multiple myeloma continues to improve, patients still are not cured. The most active combination to date is the VRd regimen described above. Due to prior results from studies with daratumumab in combination with either bortezomib or lenalidomide in the relapsed/refractory setting, and bortezomib in the frontline setting, it is expected that the addition of daratumumab with VRd is anticipated to improve the response rates and the depth of response and may lead to improved long-term outcomes in newly diagnosed patients with multiple myeloma.

Study objective

This study has been transitioned to CTIS with ID 2023-507312-13-00 check the CTIS register for the current data.

Primary Objective
The primary objective is to determine if the addition of daratumumab to VELCADE (bortezomib),Revlimid (lenalidomide), and dexamethasone (VRd) will improve overall minimal residual disease (MRD) negativity rate compared with VRd alone.

Secondary Objectives
Key secondary objectives are:
* To determine if the addition of daratumumab to VRd will improve clinical outcome as measured by:
* Progression-Free Survival (PFS)
* Durability of MRD negativity
* Rate of complete response (CR) or better
* To assess the safety profile of daratumumab + VRd (D-VRd)

Study design

This is a randomized, open-label, multicenter, Phase 3 study evaluating subjects with newly diagnosed multiple myeloma and for whom transplant is not planned. Approximately 360 subjects (180/arm) will be randomized 1:1. Subjects in Arm A will receive VRd alone for eight 21-day cycles followed by lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity. Subjects in Arm B will receive D-VRd for eight 21-day cycles followed by daratumumab, lenalidomide, and dexamethasone (DRd) therapy until disease progression or unacceptable toxicity. Subjects will be stratified at randomization by International Staging System (ISS) Stage and age/transplant eligibility.

Intervention

Daratumumab 1800 mg SC will be administered to subjects in Arm B once every week for Cycles 1 to 2, then every 3 weeks for Cycles 3-8. For Cycle 9 and beyond, subjects will receive daratumumab 1800 mg SC once every 4 weeks until documented disease progression or unacceptable toxicity.

Study burden and risks

For a detailed overview of all assessments done during the study, please see the "Time and events schedule" in the protocol.

Contacts

Public
Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL
Scientific
Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:1.Newly diagnosed and not considered candidate for high-dose chemotherapy with stem cell transplantation due to:*Being age >=65years,or*age 18-65years with presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with SCT or who refuse high-dose chemotherapy with SCT as initial treatment2.Diagnosis of multiple myeloma as documented per International Myeloma Working Group Criteria:Monoclonal plasma cells in the bone marrow >=10% or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the calcium,renal,anemia,bone(CRAB)criteria or biomarkers of malignancy criteria:CRAB criteria:1.Hypercalcemia:serum calcium >;0.25mmol/L (>1mg/dL) higher than upper limit of normal (ULN) or >;2.75mmol/L (>11mg/dL)2.Renal

insufficiency:creatinine clearance <40mL/min or serum creatinine >177 µmol/L (>2mg/dL)3.Anemia:hemoglobin >2g/dL below the lower limit of normal or hemoglobin <10g/dL4.Bone lesions:one or more osteolytic lesions on skeletal radiography,computed tomography (CT),or positron emission tomography (PET)-CTBiomarkers of Malignancy:a.Clonal bone marrow plasma cell percentage >=60%b.Involved: uninvolved serum free light chain (FLC)ratio>=100c. >1 focal lesion on magnetic resonance imaging (MRI) studies3.Must have measurable disease,as assessed by central laboratory,defined by any of the following:- IgG,IgA,IgM,IgD,or IgE multiple myeloma:Serum monoclonal paraprotein (M-protein) level >=1.0g/dL or urine M-protein level >=200mg/24 hours;or- Light chain multiple myeloma without measurable disease in serum or urine:Serum Ig FLC >=10mg/dL and abnormal serum Ig kappa lambda FLC ratio4.Eastern cooperative oncology group(ECOG) performance status score of 0,1 or25.Clinical laboratory values meeting the following criteria during the Screening Phase:a.hemoglobin >=7.5g/dL (>=5 mmol/L) (without prior RBC transfusion within 7days before the laboratory test;recombinant human erythropoietin use is permitted)b.absolute neutrophil count (ANC) >= 1.0x10^9/L (granulocyte colony stimulating factor [G-CSF] use is permitted)c.platelet count >= 70x10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells;otherwise platelet count >50×10^9/L (transfusions are not permitted within 7days)d.aspartate aminotransferase (AST)<=2.5xULNe.alanine aminotransferase (ALT)<=2.5xULNf.total bilirubin <=1.5xULN,except in subjects with congenital bilirubinemia,such as Gilbert syndrome (direct bilirubin <=2.0 x ULN)g.Estimated creatinine clearance (CrCl) >=30 mL/min.Creatinine clearance can be calculated using the Cockcroft-Gault (Appendix8),or eGFR (MDRD;Appendix9);or CKD-epi formula or for subjects with over- or underweight, CrCl may be measured from a 24-hours urine collection using the formula provided in Appendix 8h.If Cockcroft-Gault formula is used and body mass index (BMI) is >or = 30 kg/m² then adjusted body weight should be used in calculation (Appendix 8 section 10.8)corrected serum calcium <=13.5 mg/dL (<=3.4 mM/L);or free ionized calcium <=6.5 mg/dL (<=1.6 mM/L)6.Female subjects of reproductive childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously during the Treatment Period,during any dose interruptions,and for 3months after the last dose of any component of the treatment regimen.Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug.This birth control method must include one highly effective form of contraception (tubal ligation,intrauterine device,hormonal [birth control pills,injections,hormonal patches,vaginal rings or implants]or partner*s vasectomy)and one additional effective contraceptive method (male latex or synthetic condom,diaphragm,or cervical cap).Contraception must begin 4weeks prior to dosing.Reliable contraception is indicated even where there has been a history of infertility,unless due to hysterectomy or bilateral oophorectomy7.A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening,first within 10to14 days prior to dosing and the second within 24hours prior to dosing.For requirements during the Treatment Phase8.A woman must agree not to donate eggs (ova, oocytes)for

the purposes of assisted reproduction during the study and for a period of 3months after receiving the last dose of any component of the treatment regimen9.Male subjects of reproductive potential who are sexually active with females of reproductive potential must always use a latex or synthetic condom during the study and for 3months after discontinuing study treatment (even after a successful vasectomy)10.Male subjects of reproductive potential must not donate sperm during the study or for 3months after the last dose of study treatmentPlease refer to Protocol for completed list of inclusion criteria

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:1. Frailty index of >=2 according to Myeloma Geriatric Assessment score.2. Prior therapy for multiple myeloma other than a short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day, total of 160 mg dexamethasone or equivalent).3. Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomization (exceptions are adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other noninvasive lesion that in the opinion of the investigator, with concurrence with the sponsor*s medical monitor, is considered cured with minimal risk of recurrence within 3 years).4. Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.5. Focal Radiation therapy within 14 days of randomization with the exception of palliative radiotherapy for symptomatic pain management. Radiotherapy within 14 days prior to randomization on measurable extramedullary plasmacytima is not permitted even in the setting of palliation for symptomatic management 6. Plasmapheresis within 28 days of randomization.7. Clinical signs of meningeal involvement of multiple myeloma.8. Chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted. (FEV1 testing is required for subjects suspected of having COPD).9. Moderate or severe persistent asthma within the past 2 years,
uncontrolled asthma of any classification. (Subjects who have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).10. Subject is:
a. Known to be seropositive for human immunodeficiency virus (HIV).
b. seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to total 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.
c. Known to be seropositive for hepatitis C virus (HCV; anti-HCV antibody positive or HCV-RNA quantitation positive), except in the setting of a sustained virologic response (SVR), defined as aviremia at least 12 weeks after completion of antiviral therapy.11. Concurrent medical or psychiatric condition or disease (such as but
not limited to, systemic amyloidosis, POEMS, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard if enrolled in the study.12. Has clinically significant cardiac disease, including:
* Myocardial infarction within 6 months before signing the informed consent form (ICF), or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV; Appendix 18)
* Uncontrolled cardiac arrhythmia or clinically significant electrocardiogram (ECG) abnormalities
* Screening 12-lead ECG showing a baseline QT interval as corrected by Frederica's formula (QTcF) >470 msec.13. Received a strong CYP3A4 inducer within 5 half-lives prior to
Randomization14. Allergy, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients, or sensitivity to mammalian-derived products or lenalidomide.ehandelingskuur. Seksuele onthou

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:	Recruiting
Start date (anticipated):	26-04-2019
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Darzalex
Generic name:	Daratumumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-11-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	31-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	18-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2023-507312-13-00

Register	ID
EudraCT	EUCTR2018-001545-13-NL
ClinicalTrials.gov	NCT03652064
CCMO	NL67804.056.18