Phase 3 Study Comparing Daratumumab, Bortezomib and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects With Relapsed or Refractory Multiple Myeloma

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Primary ObjectiveThe primary objective is to compare the efficacy of daratumumab when combined with VELCADE (bortezomib) and dexamethasone (DVd) to that of VELCADE and dexamethasone (Vd), in terms of progression-free survival (PFS) in subjects with...

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

Summary

ID

NL-OMON50435

Source
ToetsingOnline

Brief title
Daratumumab + Bortezomib + Dexamethasone for RRMM patients, CASTOR

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Multiple Myeloma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Daratumumab, Refractory Multiple Myeloma, Relapsed Multiple Myeloma, VELCADE

Outcome measures

Primary outcome

Percentage of participants with progression-free survival (PFS)

Secondary outcome

Time to disease progression (TTP)

Percentage of Participants With Overall Response

Duration of response

Time to Response

Percentage of participants with a very good partial response (VGPR) or better

Percentage of participants with Minimal Residual Disease (MRD)

Percentage of participants with overall survival (OS)

Study description

Background summary

Multiple myeloma is a malignant disorder of the plasma cells characterized by uncontrolled and progressive proliferation of a plasma cell clone. The proliferating multiple myeloma cells displace the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs (Kyle 2003).19 Patients with multiple myeloma produce a monoclonal protein, also called paraprotein (comprising

monoclonal protein [M-protein] and free-light chain), which is an immunoglobulin (Ig) or a fragment of one that has lost its function (Palumbo 2011, Kyle 2009).27,20 Normal immunoglobulin levels are compromised, leading to susceptibility to infections. Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen (Palumbo 2011).27 Multiple myeloma is recognized as a source of significant morbidity and mortality. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the European Union (EU) and United States (US), and 30,000 patients per year die due to multiple myeloma (ACS 2012, Ferlay 2010).1,13
Treatment choices for multiple myeloma vary with the aggressiveness of the disease and related prognostic factors (Palumbo 2011).27 Newly diagnosed patients in good physical health with active disease will generally receive high-dose chemotherapy with autologous stem cell transplantation (ASCT) (Attal 1996, Child 2003).2,6 Eligibility for ASCT is established primarily by age and comorbidities (Harousseau 2009).14 For patients in whom transplantation is not an option, treatment traditionally consists of systemic chemotherapy, with adjunctive use of radiation or surgery in selected cases associated with extramedullary disease (Palumbo 2009a, Smith 2005, NCCN 2013).28,38 ,23
The therapeutic landscape of multiple myeloma has changed markedly in the past decade with the introduction of the novel immunomodulatory agents thalidomide and lenalidomide, as well as the first-in-class proteasome inhibitor (PI), VELCADE® (bortezomib). New approaches to therapy that incorporate these agents have produced significantly higher response rates and improved duration of both progression-free survival (PFS) and overall survival (OS) in the context of randomized, controlled studies. Collectively, novel therapies for multiple myeloma have been associated with substantial improvements in patient outcome (Kumar 2012).21
There is ample evidence to support the efficacy and safety of VELCADE in the treatment of patients with relapsed or refractory multiple myeloma. VELCADE is approved by the FDA and European Regulatory Authorities for this indication. The regulatory approval is based, in part, on data presented in Richardson 2003.34 In this trial, the investigators treated 202 patients with relapsed myeloma that was refractory to their most recent line of therapy. Patients received up to 8 cycles of treatment with VELCADE given at a dose of twice weekly for 2 concurrent weeks, followed by a 1-week rest. Dexamethasone was added for patients who had an insufficient response to VELCADE alone. Overall, the response rate was 35% in this heavily pretreated population with a median overall survival of 16 months. In the APEX trial, patients who had 1 to 3 prior myeloma therapies were randomized to either VELCADE or high-dose dexamethasone as a salvage strategy. Patients in the VELCADE cohort had higher response rates (defined as partial response (PR) or better), (38% vs 18%), longer time to progression (189 days vs 106 days), and an improved overall survival (OS) (80% vs 66% at 1 year) than those randomized to high-dose dexamethasone (Richardson 2005).35 Updated data from this trial confirmed the OS benefit at a median follow-up of 22 months (29.8 months for Vd vs 23.7 months for dexamethasone) (Richardson 2007).36 Furthermore, overall response was improved after the longer interval of follow-up (43% of patients responding to treatment with Vd

at a median follow-up of 22 months vs 38% initially reported).
Although significant progress has been made in the management of multiple myeloma, it remains an incurable malignancy. Relapsed and refractory disease constitutes a specific unmet medical need. Patients with relapsed and refractory disease are defined as those who, having achieved minor response or better, relapse and then progress while on salvage therapy, or experience progression within 60 days of their last therapy.

Study objective

Primary Objective
The primary objective is to compare the efficacy of daratumumab when combined with VELCADE (bortezomib) and dexamethasone (DVd) to that of VELCADE and dexamethasone (Vd), in terms of progression-free survival (PFS) in subjects with relapsed or refractory multiple myeloma.
Major Secondary Objectives
The major secondary objectives are as follows:
* To evaluate clinical outcomes including time to disease progression (TTP), overall response rate (ORR), and overall survival (OS).
* To evaluate the proportion of subjects with a response of very good partial response (VGPR) or better.
* To evaluate duration of and time to response.
* To assess the safety and tolerability of daratumumab when administered in combination with Vd.
* To assess Minimal Residual Disease (MRD) in subjects who achieve >=VGPR.
Other secondary objectives are as follows:
* To assess the pharmacokinetics of daratumumab in combination with Vd.
* To assess the immunogenicity of daratumumab.
* To evaluate treatment effects on patient reported outcomes (PROs) including the EuroQol-5 Dimensions (EQ-5D-5L) and EORTC QLQ-C30.
* To evaluate clinical efficacy of DVd in high risk molecular subgroups (del17p, t(4;14), t(14;20), UAMS-70).
Exploratory Objectives
The exploratory objective is as follows:
* To explore biomarkers predictive of response to daratumumab and potential mechanisms of treatment resistance.

Study design

This is a multicenter, Phase 3, randomized, open-label, active-controlled study comparing daratumumab, VELCADE, and dexamethasone (DVd) with VELCADE and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma. Approximately 480 subjects will be randomized in a 1:1 ratio to receive either DVd or Vd. Randomization will be stratified by International Staging System (ISS), number of prior lines (1 vs. 2 or 3 vs. >3), and prior VELCADE (no vs. yes). Within each stratum, subjects will be randomized using an equal

allocation ratio of 1:1. Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. Subjects will be treated until disease progression, unacceptable toxicity, or other reasons as listed in Section 10.2.

Intervention

Daratumumab Drug: Daratumumab will be administered as an IV infusion at a dose of 16 mg/kg weekly for the first 3 cycles, on Day 1 of Cycles 4-9, and then every 4 weeks thereafter.

VELCADE (Bortezomib) Drug: VELCADE will be administered at a dose of 1.3 mg/m2 subcutaneously (SC) on Days 1, 4, 8 and 11 of each 21-day cycle. Eight VELCADE treatment cycles are to be administered.

Dexamethasone Drug: Dexamethasone will be administered orally at 20 mg on Days 1, 2, 4, 5, 8, 9, 11 and 12 of the first 8 VELCADE treatment

Study burden and risks

See "Time and events schedule" in the protocol.

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

- Must have had documented multiple myeloma
- Must have received at least 1 prior line of therapy for multiple myeloma
- Must have documented evidence of progressive disease based on investigator*s determination of response by the International Myeloma Working Group criteria on or after their last regimen
- Must have an Eastern Cooperative Oncology Group Performance Status score of 0, 1, or 2
- Must have achieved a response (partial response or better) to at least 1 prior regimen

Exclusion criteria

- Has received daratumumab or other anti-CD38 therapies previously
- Is refractory to VELCADE or another Proteasome Inhibitor (PI), like ixazomib and carfilzomib (had progression of disease while receiving VELCADE therapy or within 60 days of ending VELCADE therapy (or another PI therapy, like ixazomib and carfilzomib)
- Is intolerant to VELCADE (ie, discontinued due to any adverse event while on VELCADE treatment)
- Has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization
- Has a history of malignancy (other than multiple myeloma) within 3 years before the date of randomization
- Has any concurrent medical condition or disease (eg, active systemic infection) that is likely to interfere with study procedures

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):	23-09-2014
Enrollment:	24
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	15-07-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	30-09-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-06-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	06-04-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	04-05-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	24-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-04-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-04-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-04-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2014-000255-85-NL
CCMO	NL49687.091.14