A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared With CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis

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This study has been transitioned to CTIS with ID 2024-511967-26-00 check the CTIS register for the current data. Primary Objective: The primary objective is to evaluate the efficacy of daratumumab plus CyBorD compared with CyBorDalone in the...

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

Summary

ID

NL-OMON48611

Source
ToetsingOnline

Brief title
54767414AMY3001/Andromeda

Condition

- Plasma cell neoplasms

Synonym
Amyloid Light Chain Amyloidosis/clonal neoplasm of the plasma cell

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AL Amyloidosis, Newly diagnosed systemic, Subcutaneous Daratumumab

Outcome measures

Primary outcome

The primary endpoint is overall complete hematologic response rate.

Secondary outcome

The secondary efficacy endpoints include:

Major Organ Deterioration Progression-Free Survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from randomization to any one of the following events, whichever comes first:

1. Death

2. Clinical Manifestation of Cardiac Failure: Defined as development of dyspnea at rest (for at least 3 consecutive days) and due solely to amyloidosis cardiac deterioration, or need for cardiac transplant, left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP)

3. Clinical Manifestation of Renal Failure: Defined as the development of end stage renal disease (need for hemodialysis or renal transplant)

4. Development of hematologic PD as per consensus guidelines

From CHR, abnormal free light chain ratio (light chain ratio must double).

Note: the development of a IgG Kappa spike on SPEP/IFE will not be considered disease progression for subjects who have received daratumumab, DIRA testing may be indicated.

From CHR, VGPR or PR, 50% increase in serum M-protein to > 0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present)

Free light chain increase of 50% to > 100 mg/L

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of first documentation of hematologic disease progression, or organ (cardiac, renal, or liver) progression, or death due to any cause, whichever occurs first according to central laboratory results and judged by international consensus guidelines. For those subjects who are still alive and have not yet progressed, the subject*s data will be censored at the last disease assessment.

Organ response rate (OrRR) for kidney, heart, liver is defined as the proportion of baseline organ involved subjects who achieve organ response in each corresponding organ.

Overall survival (OS) is measured from the date of randomization to the date of the subject*s death. 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.

Improvement in fatigue is defined as the change from baseline in the EORTC QLQ-C30

Fatigue scale score, improvement in mental functioning is defined as the change from baseline in the SF-36v2 MCS, and improvement in health-related quality of

life is defined as change from baseline in the EORTC QLQ-C30 Global Health Status scale score.

Time to next treatment (TNT) defined as the time from the date of randomization to the start date of subsequent AL amyloidosis (non-protocol). Death due to PD prior to subsequent therapy is considered as an event. Otherwise, TNT is censored at the date of death or the last date known to be alive.

Hematologic VGPR or better rate is defined as the proportion of subjects who achieve hematologic CR or VGPR.

Time to complete hematologic response (or VGPR or better) is defined as the time between the date of randomization and the first efficacy evaluation at which the subject has met all criteria for hematologic CR (or VGPR or better). For subjects without a hematologic CR (or VGPR or better), data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease assessment.

Duration of complete hematologic response (or VGPR or better) is defined as the time between the date of initial documentation of CHR (or VGPR or better) to the date of first documented evidence of hematologic progressive disease. For subjects who have not progressed, data will be censored at the last disease assessment.

Time to organ response is defined as the time between the date of randomization and the first efficacy evaluation at which the subject has each corresponding organ response. For subjects without organ response, data will be censored either at the date of the corresponding organ progressive disease or,

in the absence of organ progressive disease, at the last disease assessment.

Duration of organ response is defined as the time between the date of initial documentation of each corresponding organ response to the date of first documented evidence of the corresponding organ progressive disease. For subjects who have not had organ progression, data will be censored at the last disease assessment.

Study description

Background summary

refer to question/answer 4
Hypothesis: The primary hypothesis of this study is that daratumumab in combination with CyBorD will improve the
overall complete hematological response rate compared to CyBorD alone, in subjects with newly diagnosed
AL amyloidosis.The primary hypothesis of this study is that daratumumab in combination with CyBorD
will improve the overall complete hematological response rate compared to CyBorD alone, in subjects with
newly diagnosed AL amyloidosis.

Study objective

This study has been transitioned to CTIS with ID 2024-511967-26-00 check the CTIS register for the current data.

Primary Objective: The primary objective is to evaluate the efficacy of daratumumab plus CyBorD compared with CyBorD
alone in the treatment of newly diagnosed AL amyloidosis patients.

Secondary Objectives:
To evaluate the clinically observable endpoints for major organ deterioration (MOD-PFS) following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
To evaluate the following efficacy measures following treatment with daratumumab in combination with CyBorD compared with CyBorD alone:
* Progression-free survival (PFS)
* Organ response rate (OrRR)

* Overall survival (OS)
* Time and duration of response
# To evaluate fatigue, mental functioning, and health-related quality of life following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
# To assess the safety and tolerability of daratumumab when administered in combination with CyBorD
# To assess the pharmacokinetics of daratumumab and the immunogenicity of daratumumab and rHuPh20
# To explore minimal residual disease status in amyloidosis patients as a surrogate for PFS and OS or as a biomarker for relapse

Exploratory Objectives
To evaluate biomarkers of response following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
To evaluate physical functioning, symptom improvement, functional improvement and health utility following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
To evaluate diastolic function following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
To explore the pharmacokinetic/pharmacodynamic relationship of daratumumab, such as exposure response relationship for efficacy/safety endpoints and/or disease-related or mechanism-based biomarkers

Study design

This is a randomized, open-label, active-controlled, multicenter Phase 3 study in subjects with newly
diagnosed amyloid light chain amyloidosis. Approximately 360 subjects will be stratified by cardiac stage
(Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or
List B), and renal function (CrCl >=60 mL/min or CrCl <60 mL/min) and then assigned to receive either
CyBorD or CyBorD in combination with daratumumab. Subject participation will include a Screening
Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.
Given the potential safety concern with regards to the use of IV daratumumab in the amyloidosis population
(ie, volume overload), this study will utilize the daratumumab SC co-formulation. Although the risk of
volume overload is predicted to be lower with SC daratumumab than with IV infusion, patients with newly
diagnosed AL amyloidosis may still develop adverse events attributable to hypervolemia (for example,
dyspnea, peripheral edema, etc) secondary to amyloid-induced cardiac or renal

insufficiency. Additionally,
daratumumab has not been co-administered with CyBorD. Therefore, prior to the start of the randomized
portion of the study, a safety run-in will be conducted. Dosing of these subjects will be staggered so that no
subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety
evaluation will be performed by the sponsor (and external academic hematologists) after at least 10 subjects
have received at least 1 cycle of treatment. If no safety signal is observed, particularly in regard to volume
overload, the randomized portion of the study will begin.
In the randomized portion of the study, subjects randomized to Treatment Arm A will receive study
treatment with CyBorD. All treatment cycles are 4 weeks (28 days) in length. CyBorD will be administered
for a maximum of 6 cycles (24 weeks).
Subjects randomized to Treatment Arm B will receive CyBorD plus daratumumab at a fixed dose of
1800 mg. A maximum of 6 cycles (24 weeks) of CyBorD plus daratumumab will be administered. After
Cycle 6, subjects may receive daratumumab monotherapy on Day 1 of subsequent 28-day cycles until
disease progression, start of subsequent therapy, or a maximum of 2 years from the start of the study.

Intervention

Daratumumab 1800 mg will be administered subcutaneously through a syringe by a manual push over
approximately 5 minutes. Daratumumab will be administered weekly for the first 8 weeks (2 cycles), then
every 2 weeks for 4 cycles (Cycles 3-6), and then every 4 weeks until progression of disease or subsequent
therapy for a maximum of 2 years from the start of the study.
Subjects will receive 300 mg/m2 cyclophosphamide (maximum weekly dose 500 mg) as an oral or IV
weekly dose and 1.3 mg/m2 bortezomib as an SC injection weekly (Days 1, 8, 15, 22) in every 28-day cycle
for a maximum of 6 cycles.
Dexamethasone will be administered at a total dose of 40 mg weekly (ie, Days 1, 8, 15, 22). On days of
daratumumab dosing, subjects in Treatment Arm B will receive 20 mg on the day of daratumumab dosing
as premedication and 20 mg on the day after daratumumab dosing. On weeks that daratumumab is not
administered, or for subjects randomized to Treatment Arm A, dexamethasone is

to be given 40 mg weekly
on a single day or divided into 2 days.

Study burden and risks

Burden (both arm A and B): Hospital visits on a more frequent schedule than standard, including additional assessments.
Risks (arm B): Adverse Events observed mostly related to the IV administration of daratumumab are fever, fatigue, infusion-related reactions, diarrhea, cough, headache, infection of the nose, sinuses and/or throat, nausea, swelling of hands, feet or limbs, low white blood cell, platelets and/or red blood cell counts and muscle spasms (refer to the patient information sheet for a complete overview).
Adverse Events for daratumumab administered SC appear to be similar to those reported in studies of daratumumab administered IV either alone or in combination with other drugs, but with a lower incidence of infusion/injection-related reactions (IRRs). In approximately 1 in 4 patients with daratumumab administered SC an infusion-related reaction occurred. Administration of daratumumab in the abdominal SC tissue was associated with injection site erythema and hardening of the skin. This was observed in approximately 30 to 40% of subjects.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

18 years of age or older.
Histopathological diagnosis of amyloidosis based on detection by IHC and polarizing light microscopy of green bi-refringent material in congo red stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance, if required
Measurable disease of amyloid light chain amyloidosis as defined by at least ONE of the following:
* serum M- protein >=0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation (IFE) performed at a central laboratory),
* serum free light chain >=5.0 mg/dL with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) >=5mg/ dL.
# One or more organs impacted by AL amyloidosis according to consensus guidelines
# Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2
# Laboratory values as defined by the protocol

Exclusion criteria

Prior therapy for AL amyloidosis or multiple myeloma including medications that target CD38, with the exception of 160 mg dexamethasone (or equivalent corticosteroid) maximum exposure prior to randomization
Previous or current diagnosis of symptomatic multiple myeloma, including the presence of lytic bone disease, plasmacytomas, >=60% plasma cells in the bone marrow, or hypercalcemia
Evidence of significant cardiovascular conditions as specified below:
a. NT-ProBNP >8500 ng/L
b. New York Heart Association (NYHA) classification IIIB or IV heart failure
c. Heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (eg prior myocardial infarction with documented history of cardiac enzyme elevation and ECG changes) or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy
d. Inpatient admission to a hospital for unstable angina or myocardial infarction within the last 6 months prior to first dose or percutaneous cardiac intervention with recent stent within 6 months or coronary artery bypass

grafting within 6 months
e. For subjects with congestive heart failure, cardiovascular-related hospitalizations within 4 weeks prior to randomization
f. Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular (AV) nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ICD is indicated but not placed (Subjects who do have a pacemaker/ICD are allowed on study)
g. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia*s formula (QTcF) >500 msec. Subjects who have a pacemaker may be included regardless of calculated QTc interval.
h. Supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of >20 mmHg despite medical management (eg, midodrine, fludrocortisones) in the absence of volume depletion
Planned stem cell transplant during the first 6 cycles of protocol therapy are excluded. Stem cell collection during the first 6 cycles of protocol therapy is permitted
Any form of non-AL amyloidosis, including wild type or mutated (ATTR) amyloidosis.
History of malignancy (other than AL amyloidosis) within 3 years before the date of
randomization (see exceptions in the protocol).
Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in
1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal
Moderate or severe persistent asthma within the past 2 years, or currently has uncontrolled asthma of any classification.
Known to be seropositive for HIV, known to be seropositive for Hep B or known to be seropositive for Hep C
Grade 2 sensory or Grade 1 painful peripheral neuropathy
#Subjects who are taking CYP3A4 inducers must discontinue their use at least 5 half-lives prior to the first dose of study treatment.

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):	30-07-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	29-11-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	09-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-03-2019
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:	28-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2022

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2024
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	CTIS2024-511967-26-00
EudraCT	EUCTR2016-001737-27-NL
ClinicalTrials.gov	NCT03201965
CCMO	NL63074.056.17