Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis

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The primary hypothesis of this study is that the 6-month OS rate of patients with newly diagnosed stage 3B AL amyloidosis will exceed 50% after primary therapy with daratumumab

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

Summary

ID

NL-OMON54540

Source
ToetsingOnline

Brief title
EMN22

Condition

- Plasma cell neoplasms

Synonym
light chain (AL) amyloidosis

Research involving
Human

Sponsors and support

Primary sponsor: Stichting European Myeloma Network
Source(s) of monetary or material Support: European Myeloma Network

Intervention

Keyword: light chain (AL) amyloidosis, Monotherapy

Outcome measures

Primary outcome

The primary objective is to evaluate the overall survival rate at 6 months following treatment with daratumumab in frontline AL patients with stage 3B disease

Secondary outcome

The secondary objectives are:

• To evaluate the overall (ORR), very good partial (VGPR) and complete (CR) hematologic response rates at 3 and 6 months

• To evaluate the Major Organ Deterioration Progression-Free Survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from the start of study treatment (Cycle 1 Day 1) to any one of the following events (whichever occurs first)

* Death

* Clinical manifestation of cardiac failure:

o Defined as development of dyspnea at rest (for at least 3 consecutive days and solely due to amyloidosis cardiac deterioration) that requires hospitalization for management, or need for cardiac transplant, or left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP).

* Clinical manifestation of renal failure:

o Defined as the development of end stage renal disease (need for hemodialysis or renal transplant)

* Development of hematologic PD as per consensus guidelines (two consecutive assessments are required, see section 9.2.1)

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

o From CHR/VGPR/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)

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

• To evaluate PFS based on all-cause mortality and progression of disease (PD, including hematologic PD and organ (heart and kidney) PD according to consensus guidelines)

• To evaluate the organ response rate (OrRR)

o Heart

o Kidney

o Liver

• To evaluate treatment effects on patient-reported outcomes (PROs) such as the Short Form-36 Health Survey (SF-36), European Quality of Life-5 Dimensions Questionnaire (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

• To characterize time to and duration of response

• To assess the safety and tolerability of daratumumab in patients with stage 3B AL amyloidosis

Study description

Background summary

AL amyloidosis is a rare disease with a poor prognosis. The median survival of untreated patients is 13 months from diagnosis. The therapeutic options for AL amyloidosis should include eradication of plasma cells that produce the toxic protein deposits leading to organ failure. These plasma cells express CD38 and could be targeted by antibodies such as daratumumab that binds and eliminates CD38 expressing cells.
Based on the available safety data from single-agent daratumumab studies (GEN501 & SIRIUS), and from combination studies of daratumumab with lenalidomide or bortezomib or pomalidomide, the expected safety profile of daratumumab in this combination therapy study is considered manageable. In addition, the safety run-in phase of this study will provide information on the safety of daratumumab in the stage 3B AL patient population.
In summary, there is a strong rationale for evaluating daratumumab in AL:
• There is a medical need for new treatments for stage 3B AL since no specific standard of care therapy in frontline or relapsed setting exist
• There is high morbidity and mortality in stage 3B AL subjects and the current treatment options are inadequate
• Preclinical data suggest that malignant plasma cells in AL express CD38 and therefore can be targeted by daratumumab
• There is substantial evidence that daratumumab may be efficacious and with a manageable safety profile in patients with AL

Study objective

The primary hypothesis of this study is that the 6-month OS rate of patients with newly diagnosed stage 3B AL amyloidosis will exceed 50% after primary therapy with daratumumab

Study design

This is an open-label, multicenter, Phase 2 study in subjects with newly diagnosed stage 3B light chain (AL) amyloidosis. Approximately 40 subjects will receive primary therapy with daratumumab. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase

Intervention

Yes

Study burden and risks

Participants in this study should return to hospital day care every week the first 8 weeks for IV/SC administration of Daratumumab. As soon as the amended version of the protocol (protocol amd #1) is in force subjects that will start will receive Daratumumab subcutaneously.

Adverse effects of daratumumab can lead to airway infection and changes in the blood findings. Infusion related reactions may also occur.

These risks will be monitored extensively and compared to the fact that there is currently no effective treatment for 3B light-chain amyloidosis

Riscs of Daratumumab are managed by staggered dosing. Subjects will also receive pre-medication to lower the risk of known side effects. A DSMB is implemented who will evaluate safety after the first 6 subjects have completed one full cycle.
The reason for administering pre-infusion medications is to avoid infusion related reactions (IRR). Signs and symptoms of IRRs may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms are having trouble breathing (wheezing), runny nose, fever, chest discomfort, itching of the skin, low blood pressure or high blood pressure and fluid in the lungs (pulmonary edema).The IRR are mostly seen during infusion 1, in some patients also in 2 but not anymore afterwards
With the current pre medication around 25% of patients will experience an IRR during infusion 1.
The following medications to reduce the risk of known side effects of daratumumab are depicted in the study protocol, section 6.2.3.1:
• Dexamethasone 20 mg IV or PO, Paracetamol (acetaminophen) 650 to 1000 mg PO or IV
• An antihistamine (diphenhydramine 25 to 50 mg, or equivalent) either given IV or PO
• Montelukast (leukotriene inhibitor): Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional on Cycle 1 Day 1 and can be administered up to 24 hours before the IV/SC infusion as per investigator*s discretion. If necessary, oral pre-infusion medications may be administered at the subject*s home on the day of the daratumumab treatment, provided they are taken within 3 hours prior to the administration of daratumumab IV/SC infusion.*

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Men or women 18 years of age or older., 2. Diagnosis of amyloidosis, AL type, based on:, a. Histopathological diagnosis of amyloidosis based on detection by immunohistochemistry and polarizing light microscopy of green bi-refringent material in Congo Red stained tissue specimens (excluding bone marrow) or characteristic electron microscopy appearance, AND, b. Measurable disease of amyloid light chain amyloidosis as defined by at least ONE of the following: , - serum monoclonal protein >=0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation performed at local lab), - serum free light chain (FLC) >=2.0 mg/dL (20 mg/L) with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) >=2mg/dL (20 mg/L). Serum FLCs will be measured using the Freelite assay at a central laboratory., - Note: Measurable disease by Urine Bence-Jones Proteinuria is not sufficient for study enrolment. , AND, c. Cardiac involvement by AL amyloidosis according to consensus guidelines (See ATTACHMENT 3), 3. Mayo Stage 3B disease, defined as both A. increased cardiac troponin (hsTnT >54 pg/ml) AND B. increased NT-proBNP >= 8500 pg/ml, 4. For subjects with congestive heart failure, symptoms should be optimally managed and clinically stable with no cardiovascular-related hospitalizations within 2 weeks prior to Cycle 1 Day 1, as assessed by the Principal Investigator. [See also exclusion criteria 3], 5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1,2 or 3 (ATTACHMENT 1), 6. Subject must have pre-treatment clinical laboratory values meeting the following criteria during the Screening Phase:, a. Absolute neutrophil count >=1.0 × 109/L;, b. Hemoglobin level >=8.0 g/dL (>=5 mmol/L), c. Platelet count >=75 × 109/L; platelet transfusions are NOT acceptable, d. Alanine aminotransferase level (ALT) <=2.5 x

ULN;, e. Aspartate aminotransferase (AST) <=2.5 x ULN, f. Total bilirubin level <=1.5 × ULN, except for subjects with history of Gilbert Syndrome, in which case direct bilirubin <= 2 × ULN, g. Estimated Glomerular Filtration Rate (eGFR) >=20 mL/min; Please note that the eGFR is measured by using the CKD-EPI equation , 7. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse (if this is the preferred and usual lifestyle of the subject) or to use 2 methods of reliable birth control simultaneously. This includes 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 prior to dosing and continue for 3 months after discontinuation of daratumumab. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy., 8. During the study and for 3 months after receiving the last dose of daratumumab, female subjects must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction., 9. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, e.g. either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during and up to 3 months after discontinuation of daratumumab. All men must not donate sperm during the study and for 3 months after discontinuation of daratumumab., 10. Female subjects of childbearing potential must have a negative serum or urine pregnancy tests within 14 days prior to Cycle 1 Day 1. For requirements during the Treatment Phase, please see the Time and Events Schedule., 11. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of the procedures required for the study and are willing to participate in the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

Exclusion criteria

1.Prior therapy for AL amyloidosis or multiple myeloma with the exception of 160 mg dexamethasone (or equivalent steroid) maximum exposure prior to Cycle 1 Day 1., 2.Previous or current diagnosis of symptomatic multiple myeloma including the presence of lytic bone disease, plasmacytomas, >= 60% plasma cells in the bone marrow, and/or hypercalcemia., 3.Evidence of significant cardiovascular conditions as specified below:, a. New York Heart Association (NYHA) classification of heart failure, stages IIIB or IV , b. Heart failure that in the opinion of the investigator due to ischemic heart disease or uncorrected valvular disease, and not due to AL amyloid cardiomyopathy., c. Hospitalization for unstable angina or myocardial infarction or percutaneous

cardiac intervention with recent stent or coronary artery bypass grafting, all within the last 6 months prior to the first dose , d. 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 will not be placed (subjects who do have a pacemaker/ICD are allowed in the study), e. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia*s formula (QTcF) >500 msec. Subjects who have pacemaker may be included regardless of calculated QTc interval., f. Supine systolic blood pressure <90 mmHg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of >20 mmHg despite medical management in the absence of volume depletion, 4. Subjects planning to undergo a 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., 5. Diagnosed or treated for malignancy other than AL, except:, a. Malignancy treated with curative intent and with no known active disease present for >=24 months before Cycle 1 Day 1, b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, c. Adequately treated carcinoma in situ (e.g. cervical, breast) with no evidence of disease, 6. Subject has known 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, 7. Subject has known moderate or severe persistent asthma within the past 2 years or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study)., 8. Subject is known to be seropositive for human immunodeficiency virus (HIV). HIV positive subjects who are stable on highly active antiretroviral therapy (HAART) with no opportunistic infections within the last 6 months are eligible. , 9. Subjects known: a. To be 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 hepatitis B core antigen [antiH-Bc] 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. , b. To be seropositive for hepatitis C, 10. Subject has any concurrent medical condition or disease that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study., 11. Any form of non-AL amyloidosis, including wild type or mutated (ATTR) amyloidosis. , 12. Subject has known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, or their excipients, or known sensitivity to mammalian-derived products., 13. Subject is known or suspected of not being able to comply with the study protocol or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject or that could prevent, limit, or confound the protocol-specified assessments., 14. Subject is a woman who is

pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 3 months following discontinuation of daratumumab., 15. Subject has received an investigational drug or used an invasive investigational medical device within 4 weeks prior to Cycle 1 Day 1, 16. Subject has had major surgery within 2 weeks prior to Cycle 1, Day 1, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-10-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Daratumumab SC
Generic name:	Daratumumab co-formulated with recombinant human hyaluronidase (rHuPH20)
Product type:	Medicine
Brand name:	Darzalex
Generic name:	Daratumumab
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Velcade
Generic name:	Bortezomib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-07-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-07-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-08-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-04-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
Other	Clinicaltrials.gov.uk
EudraCT	EUCTR2018-004333-33-NL
CCMO	NL68619.041.19