An Open Label, Phase 2 Study to Evaluate Efficacy and Safety of Daratumumab in Relapsed or Refractory Mantle Cell Lymphoma, Diffuse Large B-Cell Lymphoma, and Follicular Lymphoma

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The purpose of this study is to see if Daratumumab is useful for treating patients with relapsed or refractory Mantle Cell Lymphoma (MCL), Diffuse Large B-Cell Lymphoma (DLBCL), or Follicular Lymphoma (FL). Another purpose of the study is to see if...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON43938

Source
ToetsingOnline

Brief title
CARINA

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Non Hodgkin lymphoma; lymphoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Daratumumab, Diffuse Large B-Cell Lymphoma, Follicular Lymphoma, Mantle Cell Lymphoma

Outcome measures

Primary outcome

Disease evaluations will be performed every 8 weeks (±7 days) in the first 6 months (Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1), followed by every 16 weeks (±7 days) for the next 6 months (Cycle 11 Day 1, Cycle 15 Day 1), and thereafter every 24 weeks (±14 days). These assessments will be conducted until disease progression, withdrawal of consent from study participation, or the end of study. The determination of disease status will be assessed by the investigator based on the Revised Criteria for Response Assessment (Cheson 2014). Identical methodology should be used for disease assessment at screening and throughout the course of the study. Radiological and PET scans should be performed and collected according to instructions from the independent imaging laboratory. A central review of the response assessments may be performed if deemed necessary. The major efficacy endpoint, ORR, is defined as the proportion of subjects who achieve CR or PR.

Secondary efficacy endpoints are:

* Duration of response (DoR) will be duration from the date of the initial documentation of a response to the date of first documented evidence of PD (or relapse for subjects who experience CR). For those subjects who are still without progression/relapse, DoR will be censored at the last adequate tumor assessment.

* PFS is defined as the duration from the date of the first daratumumab dose to the date of progression/relapse or death, whichever comes first. For those subjects who are still alive without progression/relapse, PFS will be censored at the last adequate tumor assessment.

* Overall survival (OS) is defined as the duration from the date of the first daratumumab dose to the date of death. For those subjects who are still alive without progression/relapse, OS will be censored at the last date known to be alive.

* Time to response is defined as the duration from the date of the first dose of daratumumab to the earliest date that a response (CR/PR) is first documented. For non-responders, it will be censored at the date of progressive disease/relapse or the date of the last adequate disease assessment, whichever comes first.

Secondary outcome

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

For all subjects, pharmacokinetic samples to determine serum concentration of

daratumumab will be obtained according to Time and Events Schedule. At specified timepoints, venous blood samples (5 mL per sample) will be collected to determine serum concentration of daratumumab and the serum will be divided into 3 aliquots (1 aliquot for pharmacokinetic analysis, 1 aliquot for antibodies to daratumumab analysis [when appropriate], and 1 aliquot as a backup).

BIOMARKER EVALUATIONS

During screening, subjects will be required to provide tumor samples (archived sample mandatory, additional fresh biopsy should be obtained whenever possible) for assessment of CD38 expression based on central IHC methodology. Fresh tumor samples can be either lymph node excision or core needle biopsy; fine needle aspirates are not acceptable. In addition to evaluating CD38 expression, fresh or archived biopsy samples may be evaluated in all subjects to identify markers predictive of response to daratumumab or prognostic markers for disease progression. Paraffin-embedded, formalin-fixed tumor tissue may also be subjected to DNA (eg, somatic mutations) and RNA analysis (eg, GEP, qRT-PCR, or RNA-seq) to determine if specific mutations or transcriptomic profiles (translocations, deletions, inversions, genes involved in B-cell signaling pathways, CD38 signaling pathways, or others) are associated with daratumumab response. Comparison of CD38 IHC results may be made to transcriptomic data. In addition to CD38, CD59 expression will be measured by IHC in a designated laboratory as an exploratory biomarker. CD59 is a complement inhibitory protein and can contribute to

resistance to complement dependent cytotoxicity, which may be important for daratumumab response. Whole blood samples will be utilized for immunophenotyping, (performed by flow cytometry or mass cytometry/time-of-flight mass spectrometry which includes analysis of natural killer cells, T cells, and B cells as well as other potential immune cell subpopulations. Plasma samples may be analyzed for proteins associated with disease progression or daratumumab response, including complement proteins, sCD38, proteins indicative of infusion reaction (IL-1, IL-6, TNF*, IFN*, tryptase), and exploratory proteomics.

SAFETY EVALUATIONS

Safety will be measured by adverse events, laboratory test results, ECGs, vital sign measurements, physical examination findings, and assessment of ECOG performance status score.

Study description

Background summary

Daratumumab is a human IgG1* monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. CD38 is also expressed in subtypes of non-Hodgkin*s lymphoma (NHL), warranting further investigation of daratumumab in NHL.This multicentric international open label study will evaluate daratumumab separately in three relapsed or refractory NHL subtypes that are CD38 positive: mantle cell lymphoma (MCL), diffuse large B cell lymphoma (DLBCL), and follicular lymphoma (FL).

Study objective

The purpose of this study is to see if Daratumumab is useful for treating patients with relapsed or refractory Mantle Cell Lymphoma (MCL), Diffuse Large B-Cell Lymphoma (DLBCL), or Follicular Lymphoma (FL). Another purpose of the study is to see if certain patients respond to Daratumumab treatment better than others. The safety of Daratumumab will also be studied.

There are two main objectives:
* To assess overall response rate (ORR, including complete response (CR) and partial response (PR)),
of daratumumab in subjects with CD38+ disease in each NHL subtype.
* To evaluate association between ORR and CD38 expression level in order to determine a threshold
for CD38 expression level in each NHL subtype, above which daratumumab activity is enhanced.

Study design

There are 2 stages in this study. The 1st stage is to determine if Daratumumab may work for lymphoma. If there is possibility that Daratumumab may work, then the study will proceed to stage 2. If not, the study will end for that cancer type. For example, 20 subjects with MCL are enrolled in Stage 1. If the results from these 20 subjects indicate that Daratumumab may work, the study will continue to Stage 2 and an additional 80 new patients will join the study. The same plan applies to the other groups. Each type of cancer is studied separately.

Number of subjects per group and per stage:
MCL: Stage 1: 20 subjects // Stage 2: 80 subjects
DLBCL: Stage 1: 15 subjects // Stage 2: 40 subjects
FL: Stage 1: 15 subjects // Stage 2: 40 subjects

You will participate in only 1 of the 2 stages of the study. The treatment for stage 1 and stage is the same.
Patients will have daratumumab administered in thehospital. Patients will receive Daratumumab weekly for 2 months, then every 2 weeks for 4 months, and then once monthly thereafter.

Intervention

All cycles will be 28 days. Daratumumab (16 mg/kg) will be administered by IV infusion to subjects once every week for 8 weeks;
then once every other week for 16 weeks; thereafter once every 4 weeks until documented progression, unacceptable toxicity, or study end.

Study burden and risks

The risks of the treatment and the procedures for this trial are all listed in the ICF.
Al efforts have been made to decrease the risks and inconveniencies for this trial to an absolute minimum.

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

Key eligibility criteria include the following: subjects who are *18 years of age, have histologically
confirmed diagnosis of MCL, DLBCL, or FL and measurable disease, centrally determined expression
levels of CD38, and an ECOG performance status score of 0 or 1. Key criteria for each NHL subtype:

MCL:
* pathologically verified diagnosis of MCL based on local pathology report, AND
* relapsed or refractory disease after at least 2 prior lines of therapy, including at least one cycle of BTK inhibitor therapy and documented PD during or after BTK inhibitor treatment or subjects who could not tolerate BTK inhibitor (ie, discontinued BTK inhibitor due to AEs)
DLBCL:
* pathologically confirmed diagnosis of non-transformed DLBCL, AND
* relapsed or refractory disease; for those subjects who have not received HDT/ASCT are not eligible for HDT/ASCT due to comorbidities
FL:
* pathologically confirmed diagnosis of FL of Grade 1, 2, or 3a according to World Health Organization criteria without pathological evidence of transformation, AND
* relapsed disease after at least two prior systemic therapies including one anti-CD20 containing
combination regimen

Exclusion criteria

Known central nervous system lymphoma - Prior anti-tumor therapy including (all times measured prior to start of study drug): nitrosoureas within 6 weeks chemotherapy within 3 weeks therapeutic antibodies within 4 study drug): nitrosoureas within 6 weeks, chemotherapy within 3 weeks, therapeutic antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 2 weeks, investigational agents within 3 weeks, unless antibody this should be within 4 weeks - Daratumumab or other anti-CD38 therapies - Participant has a history of malignancy (other than NHL) within 3 years before the screening period (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, non-muscle invasive bladder cancer (papillary neoplasms of low malignant potential and primary noninvasive tumors), or malignancy that in the opinion of the investigator, with concurrence with the sponsor's
medical monitor, is considered cured with minimal risk of recurrence within 2 years).

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-09-2015
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Daratumumab
Generic name:	Daratumumab

Ethics review

Approved WMO Date:	12-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-08-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-01-2016
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-01-2017
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
EudraCT	EUCTR2014-005299-26-NL
ClinicalTrials.gov	NCT02413489
CCMO	NL53338.041.15