A Phase 1/2, Open-Label, Dose-Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma

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This study has been transitioned to CTIS with ID 2023-504802-12-00 check the CTIS register for the current data. Dose Escalation Objectives:Primary:* Determine maximum tolerated dose (MTD) and RP2DSecondary:* Establish tolerability of epcoritamab*...

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

Summary

ID

NL-OMON54761

Source
ToetsingOnline

Brief title
GCT3013-01

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
B-cell Lymphoma, Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Genmab

Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: B-cell lymphoma, epcoritamab, First-in-human, Open-label

Outcome measures

Primary outcome

Dose escalation:

Primary:

* Dose limiting toxicity

* Adverse events

Dose expansion:

* Overall response rate (ORR) determined by Lugano criteria as assessed by independent review committee (IRC)

Optimization

Rate of >= Grade 2 CRS events and all grade CRS events from first dose of epcoritamab through 7 days following administration of the second full dose of epcoritamab

Secondary outcome

Dose escalation:

Secondary:

* Cytokine measures

* Laboratory parameters (biochemistry, hematology including immunophenotyping for absolute T-cell and B-cell counts as well as T-cell activation and exhaustion markers)

* PK parameters (clearance, volume of distribution and area-under-the-concentration-time curve (AUC0-Clast and AUC0-*), maximum concentration (Cmax), time of Cmax (Tmax), pre dose values, and half-life)

* Immunogenicity of epcoritamab

* Anti-lymphoma activity, i.e. resolution of constitutional symptoms, reduction in tumor size, objective and best response (ORR, CR and PR)

* Duration of response

* Progression free survival

* Time to next anti-lymphoma therapy (TTNT)

* Overall survival (OS)

Expansion Efficacy End Points per IRC and Optimization Efficacy End Points per investigator:

- Duration of response (DOR) determined by Lugano criteria

- Complete response (CR) rate determined by Lugano criteria

- Duration of CR (DoCR) by Lugano criteria

- Progression-free survival (PFS) determined by Lugano criteria

- Time to response (TTR) determined by Lugano criteria

- Objective and best response rate determined by Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC)

- PFS determined by LYRIC

- DOR determined by LYRIC

- DoCR determined by LYRIC

- TTR determined by LYRIC

- Overall survival (OS)

- Time to next (anti-lymphoma) therapy (TTNT)

- Rate of MRD negativity

- Safety (i.e., adverse events, laboratory parameters [biochemistry, hematology including immunophenotyping for absolute T-cell and B-cell counts as well as T-cell activation and exhaustion markers], hospitalizations, and cytokine measures)

- PK parameters (clearance, volume of distribution, Cmax, Tmax, trough concentrations, and half-life) and incidence of ADAs to GEN3013

- Changes in lymphoma symptoms as measured by the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

- Rate of >= Grade 2 CRS events and all grade CRS events following first full dose

- Rate of >= Grade 2 CRS events and all grade CRS events overall

Study description

Background summary

There is an unmet medical need for new efficacious therapies for the population of patients with B-cell malignancies whose disease is no longer responsive to standard therapies.

The purpose of the dose escalation part of this trial is to establish the maximum tolerated dose of epcoritamab and the recommended phase 2 dose (RP2D) of epcoritamab in patients with relapsed, progressive or refractory B-cell lymphoma.

The purpose of the expansion part of this trial is to evaluate the efficacy and safety of epcoritamab at the RP2D in patients with the following B-cell non-Hodgkin lymphomas (B-NHL) with limited therapeutic options:
* Aggressive relapsed or refractory B-NHL (aNHL cohort) including:
o Diffuse large B-cell lymphoma (DLBCL)
o High grade B-cell lymphoma (HGBCL)
o Primary mediastinal B-cell lymphoma (PMBCL)
o Follicular lymphoma (FL) grade 3B
* Indolent relapsed or refractory B-NHL (iNHL cohort) including:
o FL grade 1-3A
o Marginal zone lymphoma (MZL)
o Small lymphocytic lymphoma (SLL)
* Mantle cell lymphoma (MCL)

Epcoritamab is a bispecific antibody recognizing the T-cell antigen CD3 and the B-cell antigen CD20; the mechanism of action is engagement of T-cells as effector cells to induce killing of CD20-expressing B-cells and tumor cells. CD20 is a clinically validated target for treatment of B-cell malignancies. Since the resistance of B-cell malignancies to CD20-targeting monocloncal antibodies is not due to the loss of CD20 expression or CD20 mutation, epcoritamab aims to target CD20 with a different mechanism of action.

Epcoritamab efficiently induced killing of various B-cell lymphoma cell lines in vitro. Moreover, epcoritamab induced potent anti-tumor activity in vivo, in lymphoma xenograft models in mice with a human immune system or with human effector cells. In cynomolgus monkeys, epcoritamab induced dose-dependent B-cell depletion in both peripheral blood and lymphoid organs, with time to recovery related to the treatment dose.

Study objective

This study has been transitioned to CTIS with ID 2023-504802-12-00 check the CTIS register for the current data.

Dose Escalation Objectives:

Primary:
* Determine maximum tolerated dose (MTD) and RP2D

Secondary:
* Establish tolerability of epcoritamab
* Establish pharmacokinetic (PK) profile after single and multiple doses
* Evaluate immunogenicity
* Evaluate anti-lymphoma activity

Exploratory:
* To evaluate biomarkers predictive of clinical response to epcoritamab
* To evaluate pharmacodynamic markers linked to the mechanism of action of epcoritamab

Dose expansion objectives:

Primary:
* To evaluate clinical efficacy as determined by Lugano criteria

Secondary:
* To further evaluate clinical efficacy as determined by Lugano criteria
*To evaluate the clinical efficacy as determined by LYRIC
* To further evaluate clinical efficacy
* To evaluate MRD status as a clinical efficacy endpoint
* To evaluate safety and tolerability of epcoritamab
* To evaluate the PK and immunogenicity of epcoritamab
* To evaluate patient-reported outcomes (PROs) related to lymphoma symptoms

Exploratory:
* To evaluate biomarkers predictive of clinical response to epcoritamab
* To evaluate pharmacodynamic markers linked to the mechanism of action of epcoritamab
* To evaluate PROs related to well-being and general health status

Optimization part
Primary
*Determine whether an alternative priming/intermediate dose regimen may reduce CRS risk

Secondary
*To evaluate safety and tolerability of alternative priming/intermediate dosing regimens
*Establish PK and pharmacodynamic profile after single and multiple doses
*Evaluate immunogenicity
*Evaluate clinical efficacy as determined by Lugano criteria
*To evaluate MRD status as a clinical efficacy endpoint

Exploratory
To evaluate pharmacodynamic markers linked to the mechanism of action of

epcoritamab

Study design

This is an open label, phase 1/2 trial in patients with relapsed, progressive and/or refractory mature B-cell lymphoma. The dose escalation part will determine the MTD and RP2D. The expansion part will be conducted in 2 stages. In Stage 1, patients with DLBCL, FL grades 1-3A and R/R MCL will be enrolled and response data will be collected. Following an interim futility analysis, additional patients with DLBCL, FL grades 1-3A and R/R MCL may be enrolled for Stage 2 in order to reach the sample size required for statistical analysis. In addition, patients with other aNHL or iNHL subtypes as described above may be enrolled in Stage 2.

A separate optimization part will explore alternative priming/intermediate dose levels to reduce the incidence and severity of CRS in patients with DLBCL, FL grades 1-3A, and MCL.

Intervention

Epcoritamab will be administered as a subcutaneous (SC) injection in cycles of 4 weeks, i.e. 28 days.
The dose-levels will be determined by the starting dose and the escalation steps taken in the trial.
A minimum anticipated biologic effect level (MABEL)-derived SC starting (priming) dose of 4.0 µg (microgram) flat. The priming dose for the first patient will be followed with a subsequent dose that will be as a maximum 12.8 µg (microgram) flat dose.

In the optimization part, dose levels will be determined by the starting dose and escalation steps.

Study burden and risks

* For full details, see the study schedules on pages 50-65 of the study protocol.
* Participation in this study will last approximately 12 months and include approximately 28 (part 1)/ 31 (part 2) visits to the study site. The study visits will take approximately 2 - 6 hours on average each, with the exception of C1, 2, 3 and 4 in the dose escalation phase and C3 in the dose expansion phase (see additional remark section).
* During the screening, the patient is presented with an informed consent form. This is reviewed and if the patient wishes to take part it is signed by the patient and examiner. Medical history of the patient is reviewed with the patient.
* In the study patients will get physical examinations including temperature,

blood pressure, heart rate, respiratory rate and oxygen level in blood and measurement of height and body weight.
* Blood and urine tests will be performed as well as neurological exams. Drawing blood may be painful or cause some bruising.
* Subjects will be tested for hepatitis B, C and cytomegalovirus and also for HIV if this was not done before.
* ECGs will be done and CT, PET or MRI scans. Where needed a lumbar puncture will be done.
* Women of childbearing potential will have a pregnancy test done.
* A sample of a previously taken tumor biopsy will be obtained if possible at screening or an optional fresh biopsy may be taken. 2 fresh core tumor biopsies at start of Cycle 2 (±1 week) are mandatory for all patients with accessible tumors, where it is considered feasible without a high risk of complications for the patient based on the discretion of the investigator. Additionally, where feasible, a biopsy should be collected at the end of treatment visit. Risks of tumor biopsy include pain, small chance of bruising. The biopsy procedure is usually performed while under local anesthesia.
* patients in the dose expansion part might have bone marrow biopsy and/or aspirate if clinically indicated. This will be performed while under local anesthesia. In addition, patients in the dose expansion phase will get questionnaires to complete and lymph node examinations
* The patient will be questioned during visits regarding (adverse events) side effects and the medication use.
* Patients will receive an unregistered drug, epcoritamab (DuoBody-CD3xCD20).The injections of the study drug under the skin may cause local reactions like swelling, redness, warmth and itching.
* Possible side effects of the study drug that are already known are described in the Patient Information and Investigator's Brochure.
*Subjects in the Optimization with DLBCL or FL do not need to stay in the hopstital, but do need to remain in close proximity of the hospital (withint 30 minutes travel distance) for 24 hours after the first full dose of epcoritamab.

Contacts

Public
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Scientific
Genmab

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patient must be 18 years of age or older (for expansion: In countries where the legal age is 21 years of age; only patients 21 years of age or older are eligible)
2. Documented CD20+ mature non-Hodgkin B-cell lymphoma according to WHO classification
3. Relapsed, progressive and/or refractory disease (Cheson et al., 2007) following treatment with an anti-CD20 monoclonal antibody
4. Patients must have received at least 2 prior lines of therapy
5. Patients must have measurable disease by imaging
6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2. For MCL: ECOG PS less than 2 required for participation.
7. For the optimization part, patients must have R/R DLBCL, or FL grades 1-3A, or MCL (according to cohort).

Exclusion criteria

1. Primary central nervous system (CNS) lymphoma or known CNS involvement by lymphoma
2. AST, and/or ALT greater than 3 x upper limit of normal
3. Total bilirubin greater than 1.5 x upper limit of normal
4. Creatinine clearance lower than 45 mL/min
5. Known clinically significant cardiac disease, including:
a. Onset of unstable angina pectoris within 6 months of signing ICF
b. Acute myocardial infarction within 6 months of signing ICF

c. Congestive heart failure (grade III or IV as classified by the New York Heart Association and/or known decrease ejection fraction of lower than 45%
6. Ongoing active bacterial, viral, fungal, mycobacterial, parasitic, or other infection requiring systemic treatment (excluding prophylactic treatment) at the time of enrolment or within the previous 2 weeks prior to the first dose of epcoritamab, including COVID-19 infection.
7. Eligible for curative salvage therapy with high dose therapy followed by stem cell rescue
8. Active hepatitis B (DNA PCR-positive) or hepatitis C (RNA PCR positive infection). Subjects with evidence of prior HBV but who are PCR negative are permitted in the trial but should receive prophylactic antiviral therapy.
9. Known human immunodeficiency virus (HIV) infection.
10. Exposed to live or live attenuated vaccine within 4 weeks prior to signing ICF
11. Prior treatment with chimeric antigen receptor T-cell (CAR-T) therapy within 30 days prior to first GEN3013 administration
12. Autologous HSCT within 100 days prior to first GEN3013 administration, or any prior allogeneic HSCT or solid organ transplantation
13. Contraindication to all uric acid lowering agents

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-07-2018
Enrollment:	61
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DuoBody-CD3xCD20
Generic name:	Epcoritamab (GEN3013)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-05-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-04-2020
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-08-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	05-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

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	CTIS2023-504802-12-00
EudraCT	EUCTR2017-001748-36-NL
CCMO	NL64317.078.17