A PHASE II STUDY EVALUATING THE SAFETY AND EFFICACY OF GLOFITAMAB IN COMBINATION WITH RITUXIMAB (R) PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (CHOP) IN CIRCULATING TUMOR (ct)DNA HIGH-RISK PATIENTS WITH UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA

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This study has been transitioned to CTIS with ID 2023-504994-19-00 check the CTIS register for the current data. This Phase II, open-label, multicenter study, will evaluate the safety, efficacy, and pharmacokinetics of glofitamab in combination with...

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

Summary

ID

NL-OMON56027

Source
ToetsingOnline

Brief title
GO43075

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
B-cell lymphoma, lymph node cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman - La Roche

Intervention

Keyword: ctDNA high-risk, Diffuse large B-cell lymfoma, DLBCL, glofitamab

Outcome measures

Primary outcome

Primary objective:

To evaluate the efficacy of glofitamab in combination with R-CHOP in ctDNA

high-risk patients with previously untreated DLBCL

Corresponding endpoint:

EOT CR rate, as determined by the investigator according to the 2014 Lugano

Response Criteria.

Secondary outcome

Secondary objectives:

- To evaluate the efficacy of glofitamab in combination with R-CHOP in ctDNA

high-risk patients with previously untreated DLBCL

- To evaluate the safety of glofitamab in combination with R-CHOP in ctDNA

high-risk participants with DLBCL

- To characterize the serum PK profile of glofitamab in combination with R-CHOP

- To evaluate potential effects of ADAs

Corresponding endpoints:

- ORR at the EOT, as determined by the investigator according to the 2014 Lugano Response Criteria

- PFS, defined as the time from the first study treatment to the first occurrence of disease progression or relapse, as determined by the investigator according to the 2014 Lugano Response Criteria

- OS, defined as the time from the first study treatment to death from any cause

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0

- Tolerability, as assessed by dose modifications, dose intensity, and study

- Serum concentrations of glofitamab at specified timepoints

- Serum trough concentrations of glofitamab at specified timepoints

- Glofitamab PK parameters (e.g., Cmax, AUC), as appropriate

- Relationship between ADA status and efficacy, safety, or PK endpoints

Study description

Background summary

ctDNA high-risk patients are those who fail to achieve at least a 2 log-fold reduction in ctDNA levels between Day 1 of Cycle 1 (pretreatment) and Day 1 of Cycle 2. ctDNA is a novel biomarker that offers the potential for an early, sensitive approach to identifying patients with DLBCL at a higher risk of front-line treatment failure.

In the front-line setting, a subset of patients with DLBCL have poor outcomes following treatment with R-CHOP immunochemotherapy. Despite this, R-CHOP remains the standard-of-care treatment for DLBCL. Efforts to define baseline prognostic scores and develop biomarkers to improve on the International Prognostic Index (IPI) and to guide treatment decisions have so far proved unsuccessful.

In contrast to current baseline prognostic factors, ctDNA has the distinct advantage of permitting dynamic assessments early during a patient*s treatment journey and in so doing, identify newly diagnosed individuals with suboptimal responses to immunochemotherapy who will likely progress in the absence of a change in treatment strategy and therefore may benefit from therapy intensification with glofitamab.

Study objective

This study has been transitioned to CTIS with ID 2023-504994-19-00 check the CTIS register for the current data.

This Phase II, open-label, multicenter study, will evaluate the safety, efficacy, and pharmacokinetics of glofitamab in combination with R-CHOP in individuals with ctDNA high-risk DLBCL in the first-line setting. Specific objectives and corresponding endpoints for the study are outlined in Table 3 of the protocol.

Study design

This is a Phase II, multicenter study evaluating the safety and efficacy of glofitamab in combination with R-CHOP immunochemotherapy in high-risk individuals with untreated DLBCL, as assessed by ctDNA.

ctDNA high-risk patients will enroll in the study prior to Cycle 3 of R-CHOP and commence step-up doses (2.5 mg, 10 mg, and 30 mg) of glofitamab, starting on Day 8 of Cycle 3). For the purposes of this study, individuals who achieve at least a 2-log fold reduction in ctDNA.

For enrollment at Cycle 3, eligible patients will be treated with standard-of-care doses of R-CHOP from Cycle 1. During Cycles 3-6, participants will be treated with R-CHOP in combination with glofitamab and will receive glofitamab monotherapy as consolidation during Cycles 7-10.

Participants will be assessed for radiologic tumor response by PET/CT and CT scans at the end of Cycle 2 (ctDNA screening), following the completion of treatment, and during the study follow-up period.

Intervention

Glofitamab will be administered on a step-up dosing schedule, starting on Day 8 of Cycle 3 (2.5 mg), Day 15 of Cycle 3 (10 mg), followed by 30 mg on Day 8 of Cycles 4-6 and Day 1 of Cycles 7-10, with each cycle being 21 days in length (i.e., every 3 weeks).

Tocilizumab will be administered as a rescue IMP when necessary to participants who experience a CRS event.

Rituximab (375 mg/m2) will be administered intravenously to participants every 21 days along with CHOP. A locally approved standard-of-care biosimilar rituximab is permitted.

CHOP Chemotherapy:
CHOP chemotherapy consists of IV cyclophosphamide, IV doxorubicin, vincristine administered by IV push, and oral prednisone or prednisolone. Standard CHOP will be administered for six 21-day cycles (including Cycles 1 and 2 during ctDNA screening) as follows:

• Cyclophosphamide: 750 mg/m2 administered intravenously on Day 1
• Doxorubicin: 50 mg/m2 administered intravenously or according to institutional guidelines on Day 1
• Vincristine: 1.4 mg/m2 administered by IV push on Day 1 at a recommended cap of 2 mg
• Prednisone/prednisolone: 100 mg/day orally on Days 1-5 (prednisone on Day 1 may be administered intravenously, with the remaining doses on Days 2-5 to be administered orally)

Study burden and risks

The general burden for the patient includes taking blood samples, taking tumor samples (possibly), undergoing scans and administering research products (intravenously), which can lead to various side effects.

See the Subject Information and Investigator's Brochure for more information on the risks of the IMPs, non-IMPs, and investigation procedures.

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

• Age 18 years or older at the time of signing Informed Consent Form
• Previously untreated patients with CD20-positive DLBCL, including one of the following diagnoses made according to the 2016 World Health Organization (WHO) classification of lymphoid neoplasms
o DLBCL, not otherwise specified, including GCB and ABC/non-GCB types as well as double-expressor lymphoma (coexpression of MYC and BCL2)
o High-grade B-cell lymphoma (HGBCL) with MYC and BCL2 and/or BCL6 translocations
o Patients with de novo transformed follicular lymphoma
• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2
• International Prognostic Index (IPI): 1-5
• Life expectancy of at least 6 months

• Adequate biomarker blood samples prior to initiation of R-CHOP on Day 1 of Cycle 1 and on Day 1 of Cycle 2 submitted for screening for determination of ctDNA status
• At least one bi-dimensionally fluorodeoxyglucose (FDG)-avid measurable lymphoma lesion on positron emission tomography/computed tomography (PET/CT) scan
• Left ventricular ejection fraction (LVEF) of at least 50%, as determined on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram (ECHO)
• Negative HIV test at screening, with the following exception: Patients with a positive HIV test at screening are eligible provided that, prior to enrollment, they are stable on anti-retroviral therapy for at least 4 weeks, have a CD4 count ³ 200/µL, have an undetectable viral load, and have not had a history of an AIDS-defining opportunistic infection within the past 12 months.
• Adequate hematopoietic function
• Contraception use

Additional Inclusion Criterion for ctDNA High-Risk Participants
• Plasma sample evaluated to be ctDNA high risk using the experimental AOA*NHL Test,, defined as <2-log fold reduction in ctDNA levels between Day 1 of Cycle 1 and Day 1 of Cycle 2 by central laboratory assessment

Exclusion criteria

• Current diagnosis of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma (gray-zone lymphoma), primary mediastinal (thymic) large B-cell lymphoma, T-cell/histiocyte-rich large B*cell lymphoma, Burkitt lymphoma, central nervous system (CNS) lymphoma (primary or secondary involvement), primary effusion DLBCL, and primary cutaneous DLBCL
• Contraindication to any of the individual components of R-CHOP, including prior receipt of anthracyclines, history of severe allergic or anaphylactic reactions to murine monoclonal antibodies, or known sensitivity or allergy to murine products
• Prior treatment for indolent lymphoma
• Prior solid organ or allogeneic stem cell transplant
• Prior therapy for DLBCL and high-grade B-cell lymphoma (HGBCL) with the exception of palliative, short-term treatment with corticosteroids
• Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 months after the final dose of R-CHOP, 3 months after the final dose of tocilizumab (if applicable), or 2 months after the final dose of glofitamab
• An exclusion criterion of a positive SARS-CoV-2 test within 7 days prior to enrollment (including rapid antigen test) has been added

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):	26-10-2022
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ACTEMRA, RoActemra
Generic name:	tocilizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	glofitamab
Generic name:	RO7082859

Ethics review

Approved WMO

Date:	12-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	24-10-2021

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-11-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	01-12-2023
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	CTIS2023-504994-19-00
EudraCT	EUCTR2021-001647-28-NL
ClinicalTrials.gov	NCT04980222
CCMO	NL78443.056.21