A Phase 3 Randomized Study of Loncastuximab Tesirine Combined with Rituximab Versus Immunochemotherapy in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (LOTIS-5)

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This study has been transitioned to CTIS with ID 2023-503916-33-00 check the CTIS register for the current data. Primary Objective• Evaluate the efficacy of loncastuximab tesirine combined with rituximab compared to standard immunochemotherapy…

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

Summary

ID

NL-OMON53841

Source
ToetsingOnline

Brief title
Loncastuximab Tesirine in Combination with Rituximab

Condition

- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's B-cell

Synonym
non-Hodgkin Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: ADC Therapeutics SA
Source(s) of monetary or material Support: ADC Therapeutics SA

Intervention

Keyword: ADCT-402-311, B-cell lymphoma (DLBCL), Loncastuximab Tesirine Combined with Rituximab Versus Immunochemotherapy, Phase 3

Outcome measures

Primary outcome

Progression-free survival (PFS) defined as the time between randomization and

the first documentation of recurrence or progression by independent central

review, or death from any cause

Secondary outcome

• Overall survival (OS) defined as the time between randomization and death

from any cause

• Overall response rate (ORR) by independent central review according to the

2014 Lugano classification. Overall response rate is defined as the

proportion of patients with a best overall response (BOR) of complete response

(CR) or partial response (PR)

• CR rate by independent central review defined as the proportion of patients

with a BOR of CR

• Duration of Response (DOR) defined as the time from first documentation of response to recurrence or progression by independent central review, or death from any cause

• Frequency and severity of adverse events (AEs)

• Changes from baseline of safety laboratory variables, vital signs, physical examinations, eastern cooperative oncology group (ECOG) performance status, and electrocardiograms (ECGs)

• Concentrations and PK parameters of loncastuximab tesirine pyrrolobenzodiazepine (PBD)-conjugated antibody, total antibody and SG3199 unconjugated warhead

• Anti-drug antibody (ADA) titers to loncastuximab tesirine after treatment with loncastuximab tesirine

• Changes in patient-reported outcomes (PROs) (e.g., symptoms, functions, and overall health status) from baseline as evaluated by EORTC QLQ-30, Lymphoma subscale (LymS) of FACT-Lym, GP5 item of FACT-Lym, and EQ-5D-5L

Study description

Background summary

A Phase 3 Randomized Study of Loncastuximab Tesirine Combined with Rituximab Versus Immunochemotherapy in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (LOTIS-5)

Study objective

This study has been transitioned to CTIS with ID 2023-503916-33-00 check the CTIS register for the current data.

Primary Objective
• Evaluate the efficacy of loncastuximab tesirine combined with rituximab compared to standard immunochemotherapy

Secondary Objectives
• Further evaluate the efficacy of loncastuximab tesirine combined with rituximab compared to standard immunochemotherapy.
• Characterize the safety profile of loncastuximab tesirine combined with rituximab
• Characterize the pharmacokinetic (PK) profile of loncastuximab tesirine combined with rituximab
• Evaluate the immunogenicity of loncastuximab tesirine combined with rituximab
• Evaluate the impact of loncastuximab tesirine combined with rituximab treatment on treatment-related and disease-related symptoms, patient-reported functions, and overall health status

Exploratory Objectives
• Characterize the exposure-response relationship between loncastuximab tesirine exposure and measures of efficacy
• Explore correlations between clinical activity and tumor and/or blood biomarkers, including pharmacogenetic markers

Study design

This is a Phase 3, randomized, open-label, 2-part, 2-arm, multicenter study of loncastuximab tesirine combined with rituximab versus immunochemotherapy in patients with relapsed or refractory DLBCL. A 2-part design will be used to conduct the study: Part 1 will be a non-randomized safety run-in period with loncastuximab tesirine + rituximab (Lonca-R) to characterize the safety of Lonca-R combination therapy and Part 2 will be a randomized study evaluating efficacy and safety of Lonca-R versus standard immunochemotherapy.

This study will enroll a total of ~350 patients: 20 patients will be enrolled in the safety run-in and 330 patients in the randomized part. The first 20 patients will be non-randomly assigned to receive Lonca R as part of a safety run in. Toxicity of Lonca-R will be compared with historical safety data from loncastuximab tesirine monotherapy studies after the last enrolled patient in

the safety run-in has completed the first cycle of study treatment. The randomized part of study will be initiated after last patient in the safety run-in completes the first treatment cycle and it is observed that there is no significant increase in toxicity of Lonca-R as compared to historical safety data of loncastuximab tesirine monotherapy, then subsequent patients will be randomly assigned (1:1 ratio) to receive either Lonca-R or rituximab/gemcitabine/oxaliplatin [R-GemOx].
The randomized part will enroll approximately 330 patients. Randomization will be stratified based on number of prior treatment regimens and response to most recent line of therapy. Enrollment to individual strata may be limited to target approximately 50% of the patients enrolled have only one previous line of therapy. For Part 2 of the study, an interim analysis will be performed at 1/3 information level, for analyzing (PFS). The final analysis of the primary endpoint of PFS for Part 2 of the study will be conducted after 262 PFS events occur (approximately 6 months after enrolment is completed).

For OS, one interim analysis at the time of final PFS analysis will be performed. It is expected that approximately 150 OS events will occur (approximately 6 months after enrolment is completed). The final analysis for OS will be performed when 233 deaths have occurred (approximately 18 months after enrolment is completed).

Intervention

There are 2 treatment groups:

Lonca-R:
Cyclus 1 and 2; loncastuximab tesirine 150 µg/kg + rituximab 375 mg/m2 Q3W
Cyclus 3 - 8; loncastuximab tesirine 75 µg/kg + rituximab 375 mg/m2 Q3W

R-GemOx:
Cyclus 1 - 8; rituximab 375 mg/m 2 + gemcitabine 1000 mg/m 2 + oxaliplatin 100 mg/m 2 Q2W for up to 8 cycles

An interim analysis for Part 2 of the study will be performed when 88 events are observed, for analyzing PFS and safety. The final analysis of the primary endpoint of PFS for Part 2 of the study will be conducted when 262 events occur.

Study burden and risks

See ICF Section 6 Appendix D

Contacts

Public
ADC Therapeutics SA

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CH
Scientific
ADC Therapeutics SA

Route de la Corniche, 3B NA
Epalinges 1066
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female patient aged 18 years or older
2. Pathologic diagnosis of DLBCL, as defined by the 2016 World Health Organization classification (including patients with DLBCL transformed from indolent lymphoma), or high-grade B cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
3. Relapsed (disease that has recurred following a response) or refractory (disease that failed to respond to prior therapy) disease following at least one multi-agent systemic treatment regimen
4. Not considered by the investigator to be a candidate for stem cell transplantation based on performance status, advanced age, and/or significant medical comorbidities such as organ dysfunction
5. Measurable disease as defined by the 2014 Lugano Classification as assessed

by positron-emission tomography (PET) - computed tomography (CT) or by CT or magnetic resonance imaging (MRI) if tumor is not fluorodeoxyglucose (FDG)-avid on screening PET-CT
6. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block (or minimum 10 freshly cut unstained slides if block is not available)
Note: Any biopsy since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred.
7. ECOG performance status 0-2
8. Adequate organ function as defined by screening laboratory values within the following parameters:
a. Absolute neutrophil count >=1000/µL (off growth factors at least 72 hours)
b. Platelet count >=100000/µL without transfusion within the past 2 weeks
c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) <=2.5 × the upper limit of normal (ULN)
d. Total bilirubin <=1.5 × ULN (patients with known Gilbert*s syndrome may have a total bilirubin up to <=3 × ULN)
e. Calculated creatinine clearance >=30 mL/min by the Cockcroft and Gault equation
Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.
9. Negative beta-human chorionic gonadotropin (β-hCG) pregnancy test within 7 days prior to start of study drug (Cycle 1 Day 1) for women of childbearing potential
10. Women of childbearing potential must agree to use a highly effective method of contraception from the time of giving informed consent until at least 12 months after the last dose of study treatment. Men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of giving informed consent until at least 7 months after the patient receives his last dose of study treatment.

Exclusion criteria

1. Previous treatment with loncastuximab tesirine
2. Previous treatment with R-GemOx
3. Known history of hypersensitivity to a CD19 antibody, loncastuximab tesirine (including SG3249) or any of its excipients, or history of or positive serum human ADA or positive serum human ADA to a CD19 antibody
4. Pathologic diagnosis of Burkitt lymphoma
5. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor*s medical monitor and Investigator agree and document should not be exclusionary
6. Autologous transplant within 30 days prior to start of study drug (Cycle 1 Day 1)
7. Allogeneic transplant within 60 days prior to start of study drug (Cycle 1

Day 1)
8. Active graft-versus-host disease
9. Post-transplantation lymphoproliferative disorders
10. Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other central nervous system (CNS) autoimmune disease
11. Human immunodeficiency virus (HIV) seropositive with any of the following:
a. CD4+ T-cell (CD4+) counts <350 cells/µL
b. Acquired immunodeficiency syndrome-defining opportunistic infection within 12 months prior to screening
c. Not on anti-retroviral therapy, or on anti-retroviral therapy for <4 weeks at the time of screening
d. HIV viral load >=400 copies/mL
12. Serologic evidence of chronic hepatitis B virus (HBV) infection and unable or unwilling to receive standard prophylactic antiviral therapy or with detectable HBV viral load
13. Serologic evidence of hepatitis C virus (HCV) infection without completion of curative treatment or with detectable HCV viral load
14. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
15. Lymphoma with active CNS involvement, including leptomeningeal disease
16. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
17. Breastfeeding or pregnant
18. Uncontrolled hypertension (blood pressure >=160/100 mm Hg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, severe chronic pulmonary disease, or other serious medical condition which is likely to significantly impair the patient*s ability to tolerate the study treatment
19. Major surgery within 4 weeks prior to start of study drug (Cycle 1 Day 1); radiotherapy, chemotherapy or other antineoplastic therapy within 14 days prior to start of study drug (Cycle 1 Day 1), except shorter if approved by the Sponsor
20. Use of any other experimental medication within 14 days or 5 half-lives prior to start of study drug (Cycle 1 Day 1)
21. Received live vaccine within 4 weeks of Cycle 1 Day 1
22. Failure to recover to <=Grade 1 (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) from acute non hematologic toxicity (except alopecia) due to previous therapy prior to screening
23. Congenital long QT syndrome or a corrected QTcF interval of >=480 ms at screening (unless secondary to pacemaker or bundle branch block)
24. Any other significant medical illness, abnormality, or condition that would, in the Investigator*s judgment, make the patient inappropriate for study participation or put the patient at risk
25. Known history of hypersensitivity to oxaliplatin or other platinum-based

drugs, or gemcitabine, or rituximab, or any of their excipients

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):	23-05-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dexamethasone-ratiopharm
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Loncastuximab Tesirine
Product type:	Medicine

Brand name:	Oxali-Bendalis
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Truxima
Generic name:	Rituximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-05-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-08-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	21-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2023-503916-33-00
EudraCT	EUCTR2020-000241-14-NL
ClinicalTrials.gov	NCT04384484
CCMO	NL80797.028.22