Open-Label, Phase 2 Study to Evaluate the Efficacy and Safety of CUDC-907 in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma, Including Patients with MYC Alterations

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This is a Phase 2, open-label, multicenter trial designed to evaluate the efficacy and safety of CUDC-907 in subjects 18 years and older with RR DLBCL, including those with MYC Alterations.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON46260

Source
ToetsingOnline

Brief title
CUDC-907-201

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Curis, Inc.
Source(s) of monetary or material Support: Curis;Inc.

Intervention

Keyword: Open-Label, Phase 2, Relapsed/Refractory MYC-Altered Diffuse Large B-Cell Lymphoma

Outcome measures

Primary outcome

To evaluate the efficacy of CUDC-907 as measured by the objective response rate (ORR) in Group B subjects with relapsed and/or refractory (RR) diffuse large B-cell lymphoma (DLBCL) with MYC-altered disease by immunohistochemistry (IHC).

Secondary outcome

• To evaluate ORR (central and local determination) in Group B subjects

• To evaluate progression-free survival (PFS), median PFS, and PFS at 6 months (PFS6) in Group B subjects.

• To evaluate overall survival (OS) in Group B subjects.

• To evaluate the disease control rate (DCR) and duration of response (DOR) in Group B subjects.

• To evaluate ORR in Group A and C subjects

• To evaluate the incidence and severity of adverse events (AEs), serious adverse events (SAEs), and other safety parameters in subjects receiving CUDC-907.

• To characterize the pharmacokinetics (PK) of CUDC-907 alone.

Study description

Background summary

see p. 32 of protocol

Study objective

This is a Phase 2, open-label, multicenter trial designed to evaluate the efficacy and safety of CUDC-907 in subjects 18 years and older with RR DLBCL, including those with MYC Alterations.

Study design

Patients with RR DLBCL will be eligible for treatment with CUDC-907 as long as they have tumor tissue available that can be tested for MYC-altered disease. This is defined as MYC translocation by fluorescence in-situ hybridization (FISH), or MYC expression in >= 40% of tumor cells by immunohistochemical (IHC) staining, and/or MYC gene copy number gain by FISH based on central testing of one of the following:
• Fresh tumor tissue obtained from biopsy accessible lesions with low estimated risk for serious complications (less than 2%), or
• Archived tumor tissue (most recent available)

All eligible subjects will receive the following treatment:
• CUDC-907 60 mg (2 × 30 mg capsules) orally (PO) for 5 days on/2 days off (5/2) (21 day cycles).

Based on central testing and review, subjects will be classified into one of the following categories:
(1) Group A: MYC translocation+ by FISH, and/or MYC gene copy number gain by FISH,
(2) Group B: MYC expression in >= 40% of tumor cells by IHC
(3) Groups C: MYC translocation* by FISH, and MYC expression in < 40% of tumor cells, and no MYC gene copy number gain by FISH. Subjects who do not meet criteria for Groups A or B based on central laboratory testing and review will be assigned to Group C.
Subjects receiving CUDC-907 will be assigned to Groups A, B, or C according to their MYC status as described above. Subjects who are both MYC translocation+ and/or MYC gene copy number gain by FISH and have MYC expression in >= 40% of tumor cells by IHC will be classified as MYC IHC+ and assigned to Group B.

Enrollment may continue until the minimum number of subjects are enrolled in Group B.

Subjects in all groups will continue to receive treatment until they meet criteria for treatment discontinuation.

Intervention

Treatment administration:
• CUDC-907 monotherapy:
* CUDC-907 60 mg (2 × 30 mg capsules) orally (PO) for 5 days on/2 days off (5/2) (21-day cycles).

During Treatment:
Subjects will have 4 clinic visits during Cycle 1 (Days 1, 5, 12, and 15) and clinic visits every 3 weeks on Day 1 of every cycle thereafter. For the first 50 subjects enrolled on amendment 4, there will also be a Cycle 1 Day 8 visit.
Subjects who continue past Cycle 13 will have clinic visits every 6 weeks on Day 1 of every other cycle (Cycles 14, 16, 18, etc.).
Safety assessments will be conducted at each clinic visit.
Subjects will have efficacy assessments (CT/MRI) performed during the last week (Day 15-21) of Cycles 2, 4, and 6. If F-fluorodeoxyglucose (FDG) PET/CT is acquired at baseline, follow-up PET/CT imaging at Cycle 4 and at Cycle 10 is required. Scans will be sent for a central radiographic review.
Subjects who continue to receive CUDC-907 after Cycle 6 will have disease response assessments (CT/MRI) performed every 12 weeks ± 1 week (i.e., Cycles 10, 14, 18) until Cycle 18 in the first 12 months with scans collected through the first year, then every 24 weeks ± 2 weeks (i.e., Cycles 26, 34) until progressive disease (PD) or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care).
All currently and newly enrolled subjects will be required to undergo testing for CMV infection status per local standards at Screening (newly enrolled subjects) and on the first day of every other cycle, beginning with Cycle 2 (all subjects). See Section 11.2.12 for more details.
During Post-Treatment Follow-Up
All subjects will have PFS and survival assessments every 12 weeks during the first 6 months, then every 24 weeks until PD or death, or up to 2 years, whichever occurs first. After that, disease assessments may be performed as clinically indicated (i.e., at the discretion of the Investigator or per standard of care). Overall survival may be checked by phone every 3 months and data entered in the eCRF.

Study burden and risks

As with any investigational new drug or research study procedure, there are risks and discomforts. The risks and
discomforts of CUDC-907 are described in the Patient Information and Informed Consent Form in section 7.

The risks and discomforts of rituximab are mentioned in annex 2 of the Patient Information and Informed Consent Form, as well as other risks associated with study procedures and pregnancy.

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

1. Age >= 18 years.
2. At least 2 but no more than 4 prior lines of therapy for the treatment of de novo DLBCL and ineligible for (or failed) autologous or allogeneic stem cell transplant (salvage therapy, conditioning therapy and maintenance with transplant will be considered one prior treatment). NOTE: For follicular lymphoma transformed to DLBCL (t FL/DLBCL), single-agent non-cytotoxic therapy will not be considered as a line of therapy.
3. Histopathologically confirmed diagnosis of one of the following:

• RR DLBCL per the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tumors (Swerdlow et al, 2008)
• High grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 rearrangements, or DLBCL, not otherwise specified (NOS), per the 2016 revision of the WHO classification of lymphoid neoplasms (Swerdlow et al, 2016).
• Diagnosis of t-FL/DLBCL is allowed. However, other B-cell lymphomas including other transformed indolent lymphomas/DLBCL per the 2008 WHO classification, HGBL, NOS per the 2016 WHO classification, and Burkitt lymphoma are not eligible.
4. Confirmed availability of viable tissue (defined as most recent available archival tumor tissue, or fresh tumor samples) for central laboratory FISH and IHC testing and review prior to study dosing. Previously decalcified samples are not appropriate for FISH testing. Therefore bone marrow samples are not acceptable. For subjects who enter the study with unconfirmed MYC-altered disease, fresh tumor samples are preferred.
NOTE: To facilitate early testing of MYC status, a separate informed consent form (ICF) specific for MYC testing will be available to be signed prior to sample testing and the signing of the main ICF.
5. CT scan showing at least 1 or more clearly demarcated lymph node(s) with a long axis > 1.5 cm and short axis > 1.0 cm or 1 clearly demarcated extranodal lesion(s) with a long axis > 1.0 cm and short axis > 1.0 cm. All lesions must have a maximum diameter of < 10 cm. Baseline FDG-PET scans, if used, must demonstrate positive lesions compatible with CT-defined anatomical tumor sites.
6. Presence of RR disease per Revised Response Criteria for Malignant Lymphoma (Cheson et al, 2007).
• Relapsed disease is defined by DLBCL confirmed by excisional/incisional biopsy (preferred) or fine needle aspiration (FNA) or core needle biopsy (CNB) after a complete response (CR) or unconfirmed complete response (CRu).
o For relapse during prior treatment, biopsy/FNA reconfirmation of the lymphoma is recommended but not mandatory.
• Refractory disease is defined by (a) PD during prior treatment, (b) stable disease (SD) after >= 3 cycles of prior treatment, or (c) partial response (PR) after >= 6 cycles of prior treatment, or for stage II disease, >= 3 cycles of treatment and definitive involved field radiotherapy.
o For sustained PR after prior treatment, confirmation biopsy for DLBCL is preferred. An FNA may be acceptable, but if inappropriate (e.g., due to biopsy inaccessibility), the Sponsor may determine eligibility following review of imaging results and disease history.
For SD or PD after prior treatment, reconfirmation of DLBCL by biopsy (preferred) or FNA is recommended but not mandatory.
7. Eastern Cooperative Oncology Group (ECOG) performance status of <= 1.
8. Recovery to Grade 1 or baseline of any toxicity due to prior anticancer therapies (excluding alopecia).
9. Absolute neutrophil count >= 1,000/µL; platelets >= 75,000/µL; creatinine <= 1.5 × upper limit of normal (ULN) or calculated creatinine clearance >= 50 mL/minute as determined by Cockcroft-Gault (using actual body weight) or by 24-hour urine collection measurements of creatinine; aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) <= 2.5 × ULN; total bilirubin <= 1.5 × ULN or <= 3 ULN for patients with documented Gilbert*s syndrome. Platelet transfusions and administration of granulocyte colony-stimulating factors to help patients meet eligibility criteria are not allowed within 1 week prior to screening CBC

or Cycle 1, Day 1 treatment.
10. Women of childbearing potential must have a negative serum or urine pregnancy test (not applicable after bilateral oophorectomy and/or hysterectomy).
11. Men and women of childbearing potential and their partners must agree to use adequate birth control throughout their participation in the study and for 30 days following the last study treatment. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence. Acceptable methods of contraception are described in Table 3.
12. In the Investigator*s judgement, able to provide written informed consent and follow protocol requirements.

Exclusion criteria

1. Known primary mediastinal, ocular, epidural, testicular or breast DLBCL.
2. Patients with prior brain metastases are permitted, but must have completed treatment and have no evidence of active CNS disease (clear cerebrospinal fluid [CSF]) for at least 4 weeks prior to the first dose of CUDC-907. Intrathecal chemoprophylaxis to prevent the emergence or recurrence of lymphoma in the CNS is permitted on study and may be administered per institutional guidelines.
3. Known allergy or hypersensitivity to phosphatidylinositol 3 kinase (PI3K) inhibitors or any component of the formulations used in this study.
4. Cytotoxic anticancer therapy (e.g., alkylating agents, anti-metabolites, purine analogues) or any other systemic anticancer therapy within 2 weeks of study entry.
5. Radiotherapy delivered to non-target lesions within one week prior to starting study treatment, or delivered to target lesions that will be followed on the study (NOTE: prior sites of radiation will be recorded).
6. Treatment with experimental therapy within 5 terminal half-lives (t1/2) or 4 weeks prior to enrollment, whichever is longer.
7. Current or planned glucocorticoid therapy, with the following exceptions:
• Doses <= 10 mg/day prednisolone or equivalent is allowed, provided that the steroid dose has been stable or tapering for at least 14 days prior to the first dose of CUDC-907.
• Inhaled, intranasal, intraarticular, and topical steroids are permitted.
8. Graft versus host disease following transplant within 100 days prior to study treatment.
9. Major surgery, other than diagnostic surgery, occurring 4 weeks prior to study treatment.
10. Diabetes mellitus that is not controlled with medication.
11. Serious infection requiring intravenous antibiotic therapy within 14 days prior to study treatment.
12. Uncontrolled or severe cardiovascular disease, including myocardial infarction, unstable angina, or atrial fibrillation (AFib) within 6 months prior to study treatment, New York Heart Association (NYHA) Class II or greater congestive heart failure, serious arrhythmias requiring medication for treatment, clinically significant pericardial disease, cardiac amyloidosis, or QTc with Fridericia*s (QTcF) correction that is unmeasurable or >= 480 msec on screening ECG. (Note: for QTcF >= 480 sec on the screening ECG, the ECG may be repeated twice at least 24 hours apart; the mean QTcF from the three screening ECGs must be < 480 msec in order to meet eligibility for trial participation).

13. Gastrointestinal disease or disorder that could interfere with the swallowing, oral absorption, or tolerance of CUDC-907. This includes uncontrolled diarrhea (> 1 watery stool/day), major abdominal surgery, significant bowel obstruction and/or gastrointestinal diseases that could alter the assessment of pharmacokinetics or safety, including but not limited to: irritable bowel syndrome, ulcerative colitis, Crohn*s disease and hemorrhagic coloproctitis.
14. History of other invasive malignancy, unless adequately treated with curative intent and with no known active disease present within 1 year prior to the first dose of study drug, provided it is deemed to be at low risk for recurrence by the treating physician.
• These conditions include but are not limited to non-melanoma skin cancer, carcinoma in situ, (including superficial bladder cancer), cervical intraepithelial neoplasia and organ-confined prostate cancer.
15. Known infection with human immunodeficiency virus (HIV).
16. Known active or chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
• Regardless of hepatitis B surface antigen (HBsAg) status, if hepatitis B core antibody (HBcAb) is positive, then HB DNA testing will be performed and if positive the patient will be excluded.
• Regardless of hepatitis RNA level, patients who are positive for hepatitis C antibody (anti HCV) will be permitted to enroll provided that they meet all eligibility criteria and are without evidence of cirrhosis. Patients diagnosed with HCV < 6 months prior to enrollment will be considered to have acute HCV and excluded unless viral load is undetectable.
17. Pregnant or breast-feeding women.
18. Unstable or clinically significant concurrent medical condition that would, in the opinion of the Investigator, jeopardize patient safety and/or compliance with the protocol.
19. Active cytomegalovirus (CMV) infection as defined per local standards by CMV PCR, presence of CMV antigenemia, or evidence of any invasive CMV end organ disease (e.g., CMV colitis), or any prior history of CMV organ infection.

Study design

Design

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

Recruitment

NL
Recruitment status: Will not start

Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	CUDC-907 mesylate
Generic name:	CUDC-907 mesylate

Ethics review

Approved WMO Date:	14-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2017

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
EudraCT	EUCTR2014-004509-34-NL
ClinicalTrials.gov	NCT02674750
CCMO	NL58248.078.16