# A Phase 2, Open-Label Study of Loncastuximab Tesirine in Combination With Rituximab (Lonca-R) in Previously Untreated Unfit/Frail Patients With Diffuse Large B-cell Lymphoma (DLBCL) (LOTIS-9)

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## INTRODUCTION

- Rituximab (R) in combination with chemotherapy (R-CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]) is the standard first-line therapy for patients with diffuse large B-cell lymphoma (DLBCL).[1]
- Aging unfit or frail patients who may not tolerate R-CHOP represent an increasing unmet need.[2]
  - There are limited treatments for patients who are frail and/or ineligible for anthracycline-based therapy.[1]
- There is also significant heterogeneity in how fitness for therapy is assessed.
- The simplified geriatric assessment (sGA) is a validated objective tool to assess fitness status and predict overall survival (OS) of patients with DLBCL.[3]
  - The sGA includes three distinct categories (fit, unfit, and frail) and is based on age, activities of daily living (ADL), instrumental activities of daily living (IADL), and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[3]

**Table 1:** The Simplified Geriatric Assessment

| Criteria | Fit | Unfit | | Frail |
|---|---|---|---|---|
| ADL | ≥5[a] | <5[a] | 6[a] | <6[a] |
| IADL | ≥6[a] | <6[a] | 8 | <8[a] |
| CIRS-G | 0 score = 3-4, ≤8 score = 2 | ≥1 score = 3-4, >8 score = 2 | 0 score = 3-4, <5 score = 2 | ≥1 score = 3-4, ≥5 score = 2 |
| Age, years | <80 | <80 | ≥80 | ≥80 |

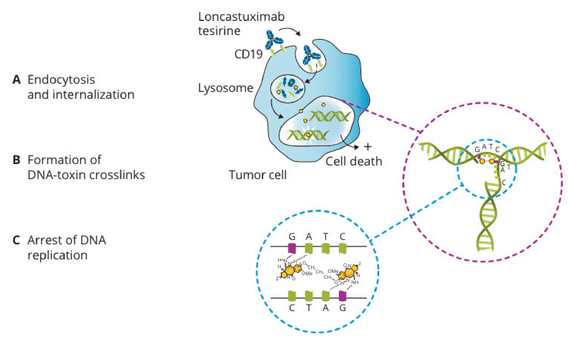
[a]Number of residual functions.
ADL, activities of daily living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; IADL, instrumental activities of daily living.

- Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca) is an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin,[4] which induces cell death via DNA damage.[4,5]
- Lonca is approved as a monotherapy in relapsed or refractory (R/R) DLBCL after ≥2 systemic treatments, based on data from the pivotal phase 2 LOTIS-2 trial.[4]
- The addition of R to Lonca is expected to produce improvements in outcomes and could potentially result in prolonged tumor control.
- The safety and efficacy of Lonca-R versus immunochemotherapy are being studied in patients with R/R DLBCL in an ongoing, separate study (LOTIS-5; NCT04384484).[6]
- The efficacy and safety of this combination in untreated unfit/frail patients have not been established.

## OBJECTIVE

To determine the safety and efficacy of loncastuximab tesirine (Lonca) in combination with rituximab (Lonca-R) in previously untreated unfit/frail patients (LOTIS-9; NCT05144009).

**Figure 1.** Mechanism of action of loncastuximab tesirine

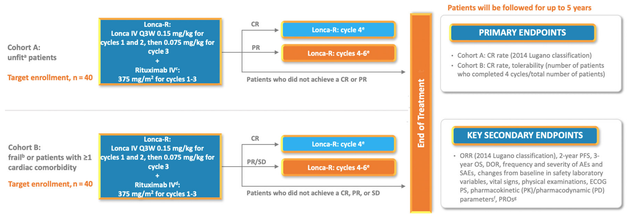



## METHODS

### STUDY DESIGN

- This is a phase 2, open-label, response-adapted study of Lonca-R in previously untreated unfit (Cohort A) or frail (Cohort B) patients with DLBCL[7].
  - Patients will be enrolled into Cohort A and Cohort B based on sGA criteria for fitness and frailty, respectively.
  - Lonca-R treatment includes the following:
    - R (IV; 375 mg/m$^2$) on day 1 of cycles 1-3; and
    - Lonca 0.15 mg/kg IV on day 2 of cycle 1 and day 1 of cycle 2, and Lonca 0.075 mg/kg IV on day 1 of cycle 3.
  - Patients will receive 3 Lonca-R cycles.
    - Patients who achieve complete response (CR) or partial response (PR) after 3 cycles will continue to receive 1 or 3 additional cycles of Lonca-R, respectively.
    - Patients in Cohort A who do not achieve a CR or PR will discontinue treatment on the study.
    - Patients in Cohort B who achieve stable disease and derive clinical benefit, as determined by the treating physician, may continue to receive an additional 3 cycles of Lonca-R.
- All patients will be followed every 12 weeks for 1 year, then every 24 weeks for up to 3 years, and then annually for up to 5 years .
- Each cohort will enroll 40 patients.

**Figure 2.** Study design




AE, adverse event; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PRO, patient reported outcome; Q3W, every 3 weeks; SAE, serious adverse event; SD, stable disease. [a]Defined by the sGA as ≥80 years of age; an ADL score of 6; an IADL score of 8; and for CIRS-G, no score of 3-4 and no 5 scores of 2 based on the Fondazione Italiana Linfoma (FIL) tool. [b]Defined by the sGA as ≥80 years of age; and/or an ADL score of <6; and/or an IADL score of <8; and/or CIRS-G, ≥1 score of 3-4 and/or ≥5 scores of 2 based on the FIL tool. [c]1 cycle is 3 weeks (21 days). [d]A subcutaneous formulation of rituximab may be used at a flat dose of 1400 mg, starting from cycle 2. [e]Doses as per cycle 3. [f]Concentrations and PK parameters of Lonca-PBD-conjugated antibody, total antibody, and SG3199 unconjugated warhead, frequency of confirmed positive antidrug antibody responses, their associated titers, and, if applicable, neutralizing activity to Lonca after treatment with Lonca in combination with rituximab. [g]Changes in PROs (eg, symptoms, functions, and overall health status) from baseline as evaluated by FACT-Lym.

### OUTCOMES

- Primary endpoints include the following:
  - Cohort A: CR ; and
  - Cohort B: CR and tolerability.
    - Tolerability is defined by the percentage of patients completing a total of 4 cycles of therapy.
- Secondary endpoints include the following:
  - Overall response rate (ORR, 2014 Lugano Classification);
  - Progression-free survival (PFS) at 2 years;
  - Duration of response (DOR);
  - Overall survival (OS) at 3 years;
  - Frequency and severity of adverse events (AEs) and serious AEs;
  - Changes from baseline in laboratory variables, vital signs, physical examinations, and Eastern Cooperative Oncology Group (ECOG) performance status;
  - Health-related quality of life;
  - Pharmacokinetic parameters and confirmed positive antidrug antibody (ADA) responses; and
  - Immunogenicity of Lonca-R.
- Exploratory endpoints include the following:
  - Correlations between blood and tumor tissue measures and selected clinical activity; and
  - Relation between blood/tissue biomarkers and selected clinical endpoints.

**Table 2.** LOTIS-9 key eligibility criteria

**Key inclusion criteria (both cohorts)**

- Pathologic diagnosis of stages I-IV DLBCL, as defined by the 2016 WHO classification to include patients with DLBCL transformed from indolent lymphoma, high-grade B-cell lymphoma (HGBCL), or grade 3b follicular lymphoma (FL)
- ECOG performance status (PS) of 0-2 or ECOG PS 3 if a decline in status is deemed related to lymphoma and potentially reversible
- Measurable disease (2014 Lugano Classification)
- No prior therapy for DLBCL, HGBCL, or grade 3b FL, with the exception of ≤14 days of corticosteroids for symptom management
- No clinically significant third space fluid accumulation (ie, ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
- Adequate organ function defined by screening laboratory values[a]

**Inclusion criteria specific for Cohort A**

Unfit as defined by the sGA (includes all of the following):

- Aged ≥ 80 years
- ADL score of 6
- IADL score of 8
- CIRS-G: no score of 3-4 and < 5 scores of 2

**Inclusion criteria specific for Cohort B**

Frail as defined by the sGA:

- Aged ≥ 80 years
- ADL score of < 6 and/or
- IADL score of < 8 and/or
- CIRS-G ≥ 1 score of 3-4 and/or ≥ 5 scores of 2

*or*

- Aged ≥ 65 - < 80 with at least one of the following cardiac comorbidities that make anthracycline-containing regimens inadvisable as determined by the investigator
  - Left ventricular ejection fraction (LVEF) ≥ 30 to < 50%
  - History of myocardial infarction within 6 months prior to screening
  - Ischemic heart disease
  - History of stroke within 12 months prior to screening

**Exclusion criteria**

- Previous therapy for DLBCL, HGBCL, or grade 3b FL or previous treatment with Lonca or R for any indication
- Known hypersensitivity to or positive serum ADA to a CD19 antibody and/or hypersensitivity to Lonca or R
- Clinically significant third space fluid accumulation
- Lymphoma with active central nervous system involvement
- Major surgery, radiotherapy, chemotherapy, or other antineoplastic therapy within 14 days before the start of the study drug
- Use of any other experimental medication within 14 days before the start of the study drug
- Congenital long QT syndrome or a corrected QTcF interval of > 480 ms at screening
- Active second primary malignancy other than nonmelanoma skin cancer, nonmetastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast

[a]Absolute neutrophil count ≥1.0 × 103/μL (and off of growth factors for at least 72 hours); platelet count ≥75 × 103/μL without transfusion in the past 7 days; alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transferase ≤2.5 × ULN; total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin of up to ≤3 × ULN); and calculated creatinine clearance >30 mL/min by the Cockcroft-Gault equation.

### STUDY ASSESSMENTS

- Study assessments are shown in Table 3.
- Screening visits should occur within 4 weeks of day 1 of cycle 1.
- Imaging will be performed at screening (baseline), before cycle 4, and at the end of cycle 6 (as applicable) and then every 12 (±2) weeks up to 1 year, every 24 weeks up to 2 years, and annually to 5 years.
- All safety assessments on dosing days will be performed before study drug administration; additional assessments may be performed as clinically indicated.

**Table 3.** Study assessments

| Safety | Efficacy |
|---|---|
| • Physical examination<br>• ECOG PS<br>• Height and weight<br>• Vital signs<br>• Pregnancy test, if applicable<br>• Safety laboratories (hematology, chemistry, urinalysis)<br>• AEs/SAEs, grading per Common Terminology Criteria for Adverse Events, version 5.0 | Primary: CR[a]<br>Secondary: ORR, PFS, OS, DOR<br>Disease assessment<br>• Imaging<br>• Clinical examination<br>**PK, PD, and immunogenicity**<br>• PK of Lonca-conjugated antibody, total antibody, and unconjugated SG3199 warhead in serum<br>• ADA in whole blood<br>• Blood biomarkers, cfDNA, gDNA<br>• Tumor tissue biomarkers |

[a]Defined as the proportion of patients with a best overall response of CR according to the 2014 Lugano Classification criteria.

## STUDY STATUS

- 9 patients (5 in Cohort A [unfit], 4 in Cohort B [frail]) were enrolled as of November 7, 2022.
- The study is currently enrolling patients in the United States and will be available to centers in additional countries, including Spain, Italy, and Israel, in the coming months.

## KEY MESSAGE

The safety and efficacy of Lonca-R in unfit or frail patients with untreated DLBCL, high-grade B-cell lymphoma, or grade 3b follicular lymphoma is being evaluated in the phase 2, open-label, LOTIS-9 clinical trial (NCT05144009).

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### References

1. NCCN 2022 guidelines: B-cell lymphoma. Version 3.2022. Accessed August 10, 2022. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
2. Morrison V, et al. *J Geriatric Onc.* 2020;11:41-54.
3. Merli F, et al. *J Clin Oncol.* 2021;39:1214-1222.
4. Caimi et al. *Lancet Oncol.* 2021;22:790-800.
5. Zammarchi F, et al. *Blood.* 2018;131(10):1094-1105.
6. ADCT Therapeutics SA. ClinicalTrials.gov registration number: NCT04384484. Accessed July 22, 2022. https://clinicaltrials.gov/ct2/show/NCT04384484
7. Wang Y. Protocol ADCT-402-203 Amendment 3. Épalinges, CH: ADCT Therapeutics SA. 2022. EudraCT Number: 2021-005312-57.

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