# 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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ABCL-272

## INTRODUCTION

- Rituximab (R) in combination with chemotherapy (R-CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]) is the standard first-line therapy for patients with 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[3]
- 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 >64 years 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 |

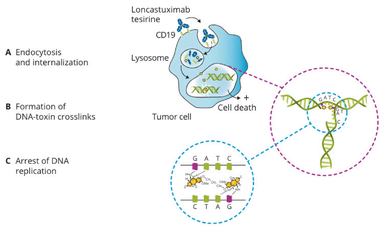
[a]Number of residual functions.
ADL, activities of daily living; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; IADL, instrumental activities of daily living.

- Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca), an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, 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]
- As the PBD component of Lonca produces cell death via DNA damage in a similar fashion to many cytotoxic chemotherapy agents,[5] the addition of R is expected to produce similar 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

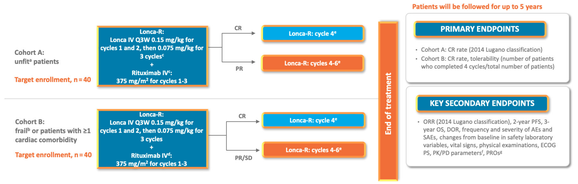



## METHODS

### 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
  - Fitness (Cohort A) and frailty (Cohort B) will be assessed using the sGA
  - Lonca-R treatment:
    - R (IV; 375 mg/m$^2$) on day 1 of cycles 1-4
    - Lonca 150 µg/kg IV on day 2 of cycle 1 and day 1 of cycle 2, and Lonca 75 µg/kg IV on day 1 of cycles 3 and 4
  - 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




[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 <5 scores of 2 based on the 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
  - Cohort A: CR
  - Cohort B: CR and tolerability
    - Tolerability is defined by the percentage of patients completing a total of 4 cycles of therapy
- Secondary endpoints
  - 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
  - Immunogenicity of Lonca-R
- Exploratory endpoints
  - Correlations between blood and tumor tissue measures and selected clinical activity
  - Relation between blood/tissue biomarkers and selected clinical endpoints

### ELIGIBILITY CRITERIA

- Key inclusion and exclusion criteria are shown in Table 2

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

**Key inclusion criteria (both cohorts)**

- Pathologic diagnosis of stage I-IV DLBCL[a]
- ECOG performance status 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[b]

**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 CNS 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 NMSC, nonmetastatic prostate cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast

[a]As defined by the 2016 WHO classification, including patients with DLBCL transformed from indolent lymphoma, HGBCL, or grade 3b FL.
[b]Absolute neutrophil count ≥ 1.0 × 10$^9$/L (and off of growth factors for at least 72 hours); platelet count ≥75 × 10$^9$/L without transfusion in the past 7 days; alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase ≤2.5 × the 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 BOR of CR according to the 2014 Lugano Classification criteria.

## STUDY STATUS

- The study opened for recruitment in April 2022

## 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)

### Acknowledgments & Study Funding

The authors would like to thank all participating patients and their families, all study coinvestigators, and the research coordinators. Medical writing support was provided by CiTRUS Health Group, funded by ADC Therapeutics SA.

### Disclosures

**Westin:** Consultant/advisor for Kite Pharma, Bristol Myers Squibb, Novartis, MorphoSys, AstraZeneca, Genentech, ADC Therapeutics, Janssen, and Merk. **Burke:** Consultant for AbbVie, Adaptive Biotechnologies, AstraZeneca, BeiGene, Bristol Myers Squibb, Epizyme, Kura, Kymera, MorphoSys, Nurix, Roche/Genentech, Seagen, TG Therapeutics, Verastem, and X4 Pharmaceuticals; speaker's bureau for BeiGene and Seagen; research funding from MorphoSys. **Chapman:** Consultant for ADC Therapeutics and Roche. **Kilavuz:** Employee with stock ownership at ADC Therapeutics. **Xu:** Employee with stock ownership at ADC Therapeutics. **Shmuely:** Employee with stock ownership at ADC Therapeutics. **Radford:** Consultant/advisor for ADC Therapeutics, Bristol Myers Squibb, Kite Pharma, Novartis, Takeda; speaker for ADC Therapeutics, Seagen, Takeda; stock ownership (spouse) in ADC Therapeutics and AstraZeneca; honoraria for expert testimony from ADC Therapeutics and Takeda; research funding from Takeda.

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Poster presented at the Tenth Annual Meeting of the Society of Hematologic Oncology (SOHO 2022). September 28-October 1, 2022, Houston, TX, USA | Previously accepted for publication only at the EHA 2022 Hybrid Congress