LOTIS-5, an Ongoing, Phase 3, Randomized Study of Loncastuximab Tesirine With Rituximab (Lonca-R) Versus Immunochemotherapy in Patients With R/R DLBCL

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TPS7097

Product

Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is an ADC comprising a humanized **anti-CD19** antibody conjugated to a PBD dimer cytotoxin that is indicated for R/R DLBCL

Rituximab (R) is an **anti-CD20** monoclonal antibody that is a part of standard frontline and subsequent DLBCL immunotherapy

Patients

Adults with **R/R DLBCL** who have received ≥1 line of prior systemic therapy

Trial

LOTIS-5 (NCT04384484) is a **phase 3**, randomized, open-label, two-part, multicenter study evaluating the antitumor activity and safety of **Lonca-R compared with R-GemOx** in patients with R/R DLBCL

Current Status

Enrollment in the randomized part of LOTIS-5 began in January 2022

As of April 2024, **294 patients are enrolled** across sites in North America, South America, Europe, and Asia

ADC, antibody–drug conjugate; DLBCL, diffuse large B-cell lymphoma; PBD, pyrrolobenzodiazepine; R/R, relapsed or refractory; R-GemOx; rituximab + gemcitabine + oxaliplatin.

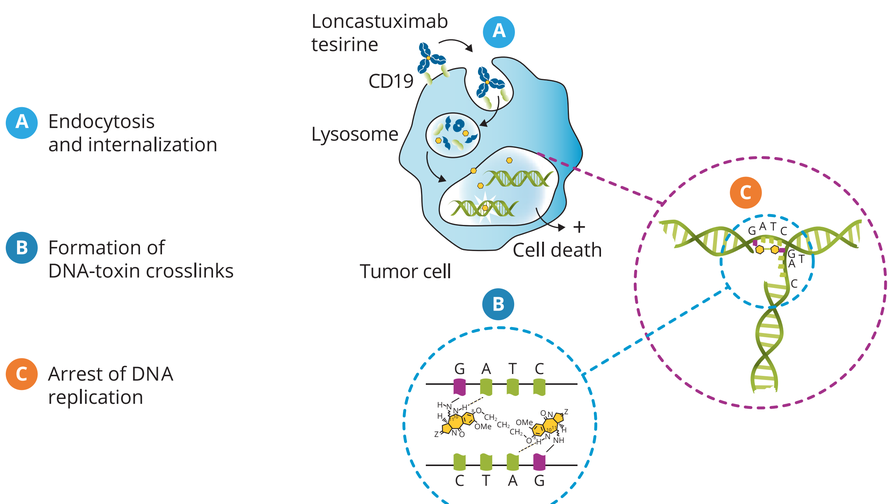
KEY MESSAGE

- This phase 3, randomized, open-label, two-part, multicenter trial-in-progress (LOTIS-5; NCT04384484) evaluates loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) in combination with rituximab (R) versus standard immunochemotherapy in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL)

INTRODUCTION

- Patients with R/R DLBCL typically have poor outcomes following standard treatment[1]
- Lonca, an antibody–drug conjugate (ADC) comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, received accelerated US and conditional EU approval for R/R DLBCL after ≥2 lines of systemic therapy based on data from the phase 2 LOTIS-2 study[2-4]
  - Lonca is internalized by cells expressing CD19; the linker is cleaved, and the PBD dimer causes interstrand DNA crosslinks that lead to cell death (**Figure 1**)[5,6]

Figure 1. Mechanism of action of Lonca



- Rituximab, an anti-CD20 monoclonal antibody, is part of standard frontline and subsequent DLBCL immunotherapy[7,8]
- Preclinical evidence suggests that R + anti-CD19 ADC therapy may result in prolonged tumor control[9]

OBJECTIVE

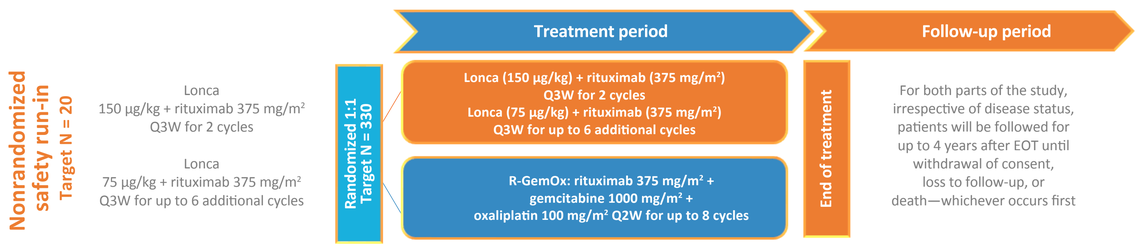
- To evaluate the efficacy of the Lonca-R combination compared with R + gemcitabine + oxaliplatin (R-GemOx) in patients with R/R DLBCL

METHODS

Study Design

- This is a phase 3, randomized, open-label, two-part, two-arm, multicenter study of Lonca-R in patients with R/R DLBCL (NCT04384484)
  - Part 1 was a nonrandomized safety run-in with Lonca-R (now complete)
  - Part 2 is a randomized efficacy and safety evaluation of Lonca-R vs R-GemOx; approximately 330 patients will be randomized 1:1 to receive Lonca-R or R-GemOx
- Dosing regimens are shown in **Figure 2**. In the Lonca-R group, Lonca and R are administered intravenously (IV) on day 1 of each 21-day cycle; in the R-GemOx group, R, Gem, and Ox are administered IV on day 1 of each 14-day cycle

Figure 2. Study design



EOT, end of treatment; Lonca, loncastuximab tesirine; Q2W, every 2 weeks; Q3W, every 3 weeks; R-GemOx, R + gemcitabine + oxaliplatin.

Outcomes

- The primary endpoint is progression-free survival by independent central review (**Table 1**)

Table 1. Study outcomes and endpoints

Primary objective	Primary endpoint
• Evaluate efficacy of Lonca-R versus R-GemOx	• PFS[a] (by independent central review)
Secondary objectives	**Secondary endpoints**
• Further efficacy evaluation • Characterize safety profile of Lonca-R • Characterize PK of Lonca-R • Evaluate immunogenicity of Lonca-R • Evaluate impact of Lonca-R on PROs and overall health status	• OS, ORR, CRR, and DoR • Frequency and severity of AEs and laboratory values • PK parameters for Lonca total Ab, PBD-conjugated Ab, and free SG3199 • ADA titers to Lonca • Changes in PROs from baseline

[a]Defined as the time between randomization and the first documentation of recurrence, progression, or death from any cause.
Ab, antibody; ADA, antidrug antibody; AE, adverse event; CRR, complete response rate; DoR, duration of response; Lonca-R, loncastuximab tesirine + rituximab; ORR, overall response rate; OS, overall survival; PBD, pyrrolobenzodiazepine; PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcome; R-GemOx, rituximab + gemcitabine + oxaliplatin.

Eligibility Criteria

- Key inclusion and exclusion criteria are shown in **Table 2**

Table 2. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Adults with a pathologic diagnosis of R/R DLBCL (including DLBCL transformed from indolent lymphoma) or HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements • R/R disease following ≥1 multiagent systemic treatment regimen • Measurable disease (2014 Lugano Classification) • Not a candidate for SCT based on performance status, advanced age, and/or significant medical comorbidities (as considered by the investigator) • ECOG performance status of 0-2 • Adequate organ function	• Previous treatment with Lonca or R-GemOx • Autologous SCT within 30 days before the start of the study drug • Allogeneic SCT within 60 days prior to the start of the study drug • Lymphoma with active CNS involvement, including leptomeningeal disease • Serologic evidence of chronic HBV infection and unable or unwilling to receive standard prophylactic antiviral therapy or with detectable HBV viral load • Serologic evidence of HCV infection without completion of curative treatment or with detectable HCV viral load • Clinically significant third-space fluid accumulation (ie, ascites requiring drainage or pleural effusion either requiring drainage or associated with shortness of breath) • Major surgery within 28 days or radiotherapy, chemotherapy, or other antineoplastic therapy within 14 days prior to the start of the study drug unless approved by the sponsor

CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HGBCL, high-grade B-cell lymphoma; Lonca, loncastuximab tesirine; R-GemOx, rituximab + gemcitabine + oxaliplatin; R/R, relapsed/refractory; SCT, stem cell transplant.

Study Assessments

- Study assessments are shown in **Table 3**. Time-to-event endpoints will be assessed for the intent-to-treat population using a stratified log-rank test, and an interim futility analysis will be conducted after one-third of the expected progression-free survival events have occurred

Table 3. Study assessments

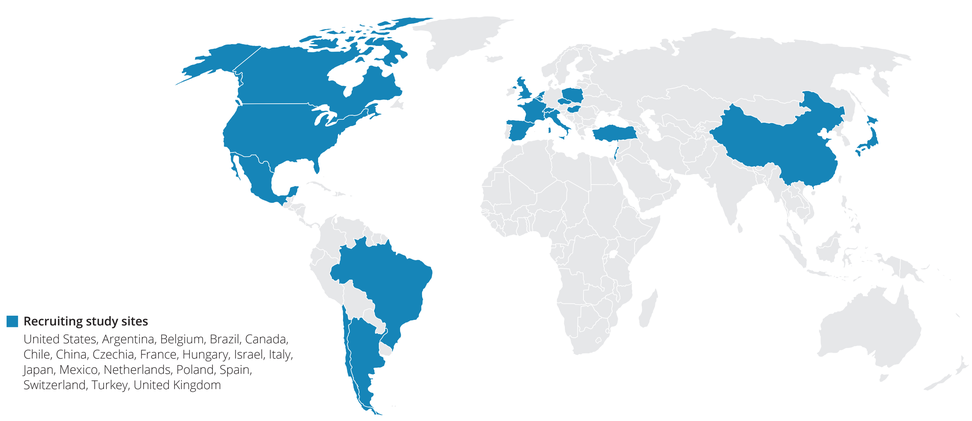
Efficacy	Safety
Disease assessments • Imaging (PET-CT)[a,b] • Clinical examination for lymphoma	• AEs graded to CTCAE v5.0 • ECOG performance status • Clinical laboratory tests[c] • Physical examination • Pregnancy test (if applicable) • Vital signs • Height and weight • 12-lead ECG
PK and Immunogenicity	**Symptoms, PROs, and Overall Health**
• PK of Lonca	• EORTC QLQ-C30 • EQ-5D-5L • LymS subscale of FACT-Lym • GP5 item of FACT-Lym

[a]Imaging will be performed at baseline and at 6 and 12 weeks after cycle 1, day 1, and then every 12 weeks until the end of treatment. During the follow-up period, imaging will be performed every 12 weeks until 1 year after the end of treatment and then every 6 months until 4 years after the end of treatment for patients who discontinued treatment for reasons other than disease progression or initiation of other anticancer therapy. [b]Contrast-enhanced CT (or MRI) is permitted instead of PET-CT if patients have a disease that is not FDG-avid. [c]Hematology, chemistry, coagulation, and urinalysis.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; FDG, ^{18}F-fluorodeoxyglucose; GP5, "I am bothered by side effects of treatment"; Lonca, loncastuximab tesirine; LymS, lymphoma subscale; MRI, magnetic resonance imaging; PET-CT, positron emission tomography and computerized tomography; PK, pharmacokinetic; PRO, patient-reported outcome.

Study Status

- The randomized part of LOTIS-5 began in January 2022; the estimated primary completion date is September 2025
- Enrollment continues; as of April 23, 2024, 294 patients are enrolled in the randomized part of the study across sites in North America, South America, Europe, and Asia (**Figure 3**)

Figure 3. Recruiting sites in the LOTIS-5 study



Recruiting study sites
United States, Argentina, Belgium, Brazil, Canada, Chile, China, Czechia, France, Hungary, Israel, Italy, Japan, Mexico, Netherlands, Poland, Spain, Switzerland, Turkey, United Kingdom

Acknowledgments

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Disclosures

MT Kwiatek: no disclosures. **C Carlo-Stella:** served in a consultant or advisory role for ADC Therapeutics, Celgene/Bristol Myers Squibb, Karyopharm, Merck Sharp & Dohme, Novartis, Roche, Sanofi, and Scenic Biotech. **A Urban:** employee and a current equity holder at ADC Therapeutics SA. **A Niewiarowski:** employee and a current equity holder at ADC Therapeutics SA. **L Wang:** employee and a current equity holder at ADC Therapeutics SA. **M Hamadani:** received research support/funding/consultancy from AbbVie, ADC Therapeutics, Allovir, Bristol Myers Squibb, Caribou, CRISPR, Genmab, Kite, and Omeros; served on speaker's bureaus for ADC Therapeutics, AstraZeneca, BeiGene, CRISPR, DMC Inc., Kite, Myeloid Therapeutics, and Sanofi Genzyme.

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