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

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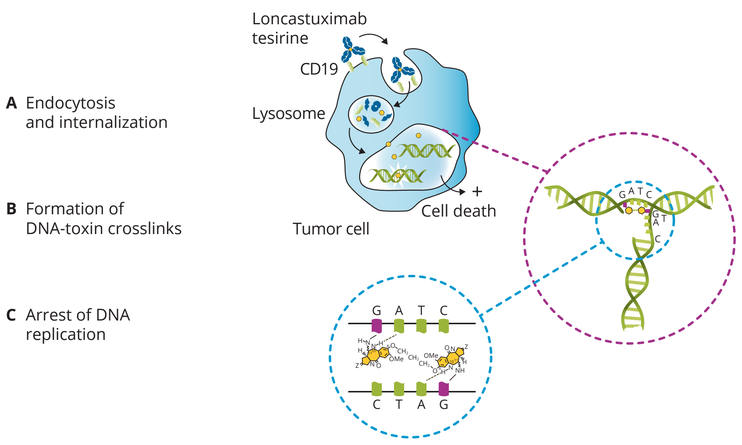
INTRODUCTION

- Patients with refractory or relapsed diffuse large B-cell lymphoma (DLBCL) typically have poor outcomes following standard treatment.[1]
- Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca), an antibody-drug conjugate (ADC) comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, is approved in relapsed/refractory (R/R) DLBCL based on data from the phase 2 LOTIS-2 trial.[2,3]
- 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**).[4,5]
- Rituximab (R) is part of standard immunochemotherapy for DLBCL, both as frontline therapy and in subsequent treatments.[6,7]
- Preclinical evidence suggests that the addition of rituximab to anti-CD19 ADC therapy may result in prolonged tumor control.[8]
- LOTIS-5 aims to evaluate Lonca + R (Lonca-R) vs. standard immunochemotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in patients with R/R DLBCL.

Figure 1. Mechanism of action of loncastuximab tesirine



OBJECTIVE

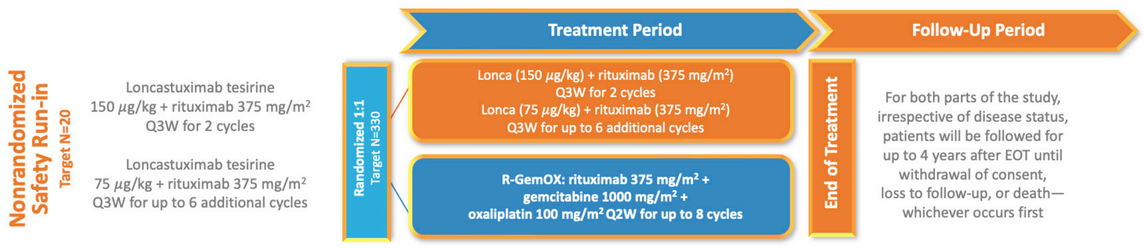
- To evaluate the efficacy of the Lonca-R combination compared with R-GemOx in patients with R/R DLBCL.

METHODS

Study Design

- This is a phase 3, randomized, open-label, two-part, two-arm, multicenter study of Lonca-R in patients with relapsed/refractory DLBCL (NCT04384484).
- Part 1: A nonrandomized safety run-in period with Lonca-R to characterize the safety of Lonca-R combination therapy.
  - A review of safety data from part 1 comparing the safety of Lonca-R to previous Lonca safety data was completed in January 2022.
- The trial is now continuing to the randomized phase (part 2). In part 2, approximately 330 patients will be randomized 1:1 to receive Lonca-R or R-GemOx.
- Dosing regimens are shown in **Figure 2**. Lonca-R, Lonca, and R are administered intravenously (IV) on day 1 of each 21-day cycle; R-GemOx, R, Gem, and Ox are administered IV on day 1 of each 14-day cycle.

Figure 2. Study design



EOT, end of treatment; Q2W, every 2 weeks; Q3W, every 3 weeks; SCT, stem cell transplant.

Outcomes

- The primary endpoint is progression-free survival by independent central review.
- Key secondary endpoints include overall survival, overall response rate, safety, duration of response, pharmacokinetic parameters, and changes in patient-reported outcomes (**Table 1**).

Table 1. Study objectives 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 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 criteria 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 at least one 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) • Patients who have received previous CD19-directed therapy must have a biopsy that shows CD19 expression after completion of the CD19-directed therapy • ECOG performance status 0–2 • Adequate organ function	• Previous treatment with Lonca or R-GemOx • Autologous SCT within 30 days before start of study drug • Allogeneic SCT within 60 days prior to start of 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 (i.e., ascites requiring drainage or pleural effusion either requiring drainage or associated with shortness of breath) • Major surgery, radiotherapy, chemotherapy, or other antineoplastic therapy within 14 days prior to start of 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 (PFS) events have occurred.

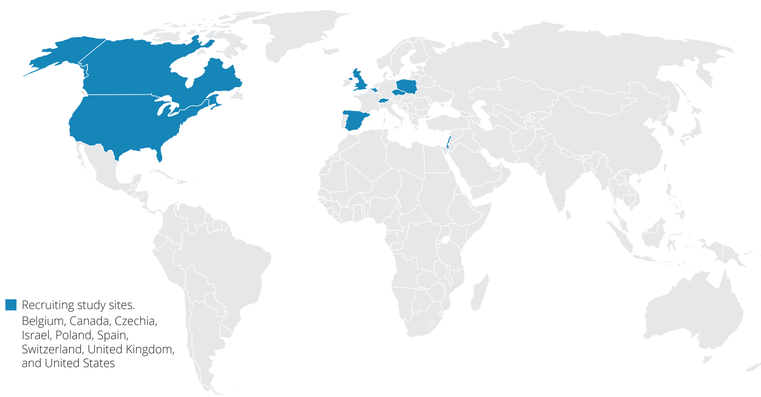
Table 3. Study assessments

Efficacy	Safety
Disease assessment • Imaging (PET-CT)[a] • Clinical examination for lymphoma	• AEs graded to CTCAE v5.0 • ECOG performance status • Clinical laboratory tests[b] • 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 PBD-conjugated Ab, total Ab, and SG3199 free warhead • ADA in blood	• EORTC QLQ-C30 • EQ-5D-5L • LymS subscale of FACT-Lym • GP5 item of FACT-Lym

[a]Performed at baseline and at 6 and 12 weeks after cycle 1, day 1, then every 12 weeks until the end of treatment. [b]Hematology, chemistry, coagulation, and urinalysis. Ab, antibody; ADA, antidrug antibody; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; GP5, "I am bothered by side effects of treatment;" Lonca, loncastuximab tesirine; LymS, lymphoma subscale; PBD, pyrrolobenzodiazepine; PET-CT, positron emission tomography and computerized tomography; PK, pharmacokinetic; PRO, patient-reported outcome; QLQ, Quality of Life Questionnaire.

STUDY STATUS

- The study opened in September 2020.
- The randomized part of the study commenced in January 2022, and recruitment is ongoing.



KEY MESSAGE

- This phase 3, randomized, open-label, trial-in-progress evaluates Lonca in combination with rituximab versus standard immunochemotherapy in patients with R/R DLBCL.

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