Phase 3 Randomized Study of Loncastuximab Tesirine plus Rituximab versus Immunochemotherapy in Patients with Relapsed/Refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL) — LOTIS-5

TPS7574

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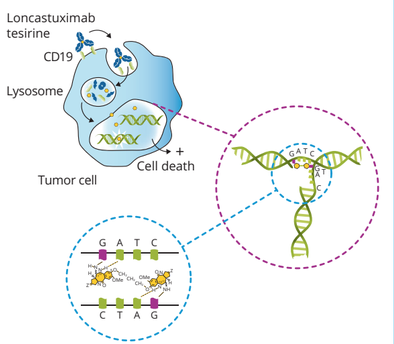
BACKGROUND

- Patients who have diffuse large B-cell lymphoma (DLBCL) for whom frontline therapy is unsuccessful and who are ineligible for autologous hematopoietic stem cell transplantation (SCT) have poor outcomes with salvage therapy[1,2]
- Loncastuximab tesirine (Lonca) is an antibody-drug conjugate comprising a humanized monoclonal anti-CD19 antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer cytotoxin, SG3199, through a protease-cleavable valine–alanine linker.[3] Lonca is internalized by cells expressing CD19, the linker is cleaved, and the PBD dimer payload causes interstrand DNA crosslinks that lead to cell death (**Figure 1**)[3,4]
- Single-agent Lonca has shown antitumor activity and manageable toxicity in patients with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma in a Phase 1 trial,[5] and in patients with R/R DLBCL who had received ≥2 prior lines of therapy in a Phase 2 trial[6]
- Rituximab (R) is an anti-CD20 monoclonal antibody used as a standard component of immunochemotherapy for DLBCL, both as frontline therapy and in subsequent treatments. This study, loncastuximab tesirine clinical assessment 5 (LOTIS-5), is designed to evaluate Lonca + R (Lonca-R) in comparison with a standard immunochemotherapy regimen of R + gemcitabine + oxaliplatin (R-GemOx) in patients with R/R DLBCL

Figure 1. Mechanism of action of loncastuximab tesirine



Key Message

This Phase 3, randomized, open-label, trial-in-progress is evaluating Lonca-R versus standard immunochemotherapy in patients with R/R DLBCL

The study opened in September 2020

Enrollment is ongoing

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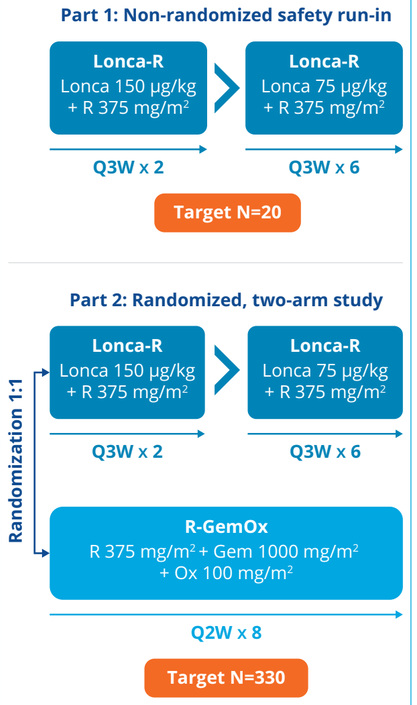
METHODS

Study Design

- This is a Phase 3, open-label, two-part, two-arm, multicenter study (NCT04384484). It comprises a non-randomized safety run-in (Part 1), in which the safety of Lonca-R in the first 20 patients who complete Cycle 1 will be compared with previous safety data for Lonca as a monotherapy. If no significant increase in toxicity is observed, Part 2 will commence and ~330 patients will be randomized 1:1 to receive Lonca-R or R-GemOx
- Dosing regimens are shown (**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



Lonca-R, loncastuximab tesirine + rituximab; Q2W, every 2 weeks; Q3W, every 3 weeks; R, rituximab; R-GemOx, rituximab + gemcitabine + oxaliplatin.

Objective

- The primary objective of the study is to evaluate the efficacy of Lonca-R versus R-GemOx using a primary endpoint of progression-free survival (PFS) by independent central review (**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 or progression, or death from any cause.
Ab, antibody; ADA, anti-drug 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.

Study Eligibility Criteria

- Patients with R/R DLBCL after ≥1 prior therapy and who are not candidates for SCT are being enrolled (**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 which 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 (ie, 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 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 expected 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 end of treatment. [b]Hematology, chemistry, coagulation, and urinalysis.
Ab, antibody; ADA, anti-drug 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; 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.