Initial Safety Run-In Results of the Phase 3 LOTIS-5 Trial: Novel Combination of Loncastuximab Tesirine With Rituximab (Lonca-R) Versus Immunochemotherapy in Patients With R/R DLBCL

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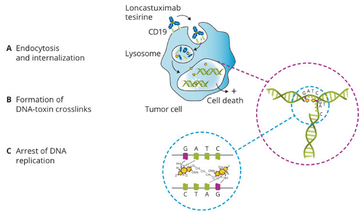
INTRODUCTION

- Patients with refractory or relapsed diffuse large B-cell lymphoma (R/R DLBCL) typically have poor outcomes following standard treatment[1]
- Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca) is a novel antibody-drug conjugate comprising an anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, indicated for the treatment of R/R DLBCL after ≥2 systemic treatments[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 immunotherapy 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 immunotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in patients with R/R DLBCL

Figure 1. Mechanism of action of loncastuximab tesirine



OBJECTIVE

To characterize the safety and preliminary efficacy of Lonca + rituximab (Lonca-R)

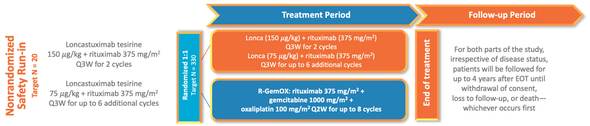
METHODS

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)
- In part 1, 20 patients were enrolled in a nonrandomized safety run-in period with Lonca-R to characterize the safety of Lonca-R combination therapy
- In part 2, approximately 330 patients will be randomized 1:1 to receive Lonca-R or rituximab-gemcitabine-oxaliplatin (R-GemOx)
- Key inclusion criteria include age ≥18 years, diagnosis of DLBCL (including DLBCL transformed from indolent lymphoma) or high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, ≥1 line of prior systemic therapy, ineligible for stem-cell transplantation, and measurable disease per the 2014 Lugano criteria
- All patients in the safety run-in received Lonca 0.15 mg/kg + rituximab 375 mg/m^2 every 3 weeks for 2 cycles and then Lonca 0.075 mg/kg + rituximab 375 mg/m^2 Q3W for up to 6 additional cycles **(Figure 2)**

Figure 2. LOTIS-5 trial design

Phase 3 trial of loncastuximab tesirine in combination with rituximab



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 the efficacy of Lonca-R versus R-GemOx	• PFS[a] (by independent central review)
Secondary objectives	**Secondary endpoints**
• Further efficacy evaluation • Characterize the 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 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 the start of the study drug • Allogeneic SCT within 60 days before 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, radiotherapy, chemotherapy, or other antineoplastic therapy within 14 days before 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 (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, and 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.

RESULTS

RESULTS FOR LOTIS-5 SAFETY RUN-IN (PART 1)

- The 20 patients in the safety run-in were a median age of 74.5 years (range 35-93) and received a median of 1 previous therapy (range 1-6)
- As of the February 28, 2022, data cutoff:
  - The median number of doses administered was 5 (range 1-8), and the median duration of follow-up was 5.83 months (range 1.9-10.3)
  - 19 (95%) patients had at least 1 treatment-emergent adverse event (TEAE), and 10 (50%) patients had grade ≥3 TEAEs
  - The most common all-grade TEAEs, regardless of the relationship to the study treatment, were rash (5 [25%]), fatigue (4 [20%]), and increased gamma-glutamyltransferase (4 [20%])
  - The most common grade ≥3 TEAEs were increased gamma-glutamyltransferase (3 [15%]), increased alanine aminotransferase (2 [10%]), and neutropenia (2 [10%])
  - The overall response rate by central review was 15/20 (75%); a total of 8/20 (40%) and 7/20 (35%) patients attained complete response and partial response, respectively

Table 4. Baseline characteristics for patients enrolled in LOTIS-5 safety run-in (n = 20)

Baseline characteristics	
Age, median (min, max), years	74.5 (35-93)
Prior systemic therapies, median (min, max)	1 (1-6)
Sex, n (%)	
Female	11 (55)
Male	9 (45)
Disease stage (Ann Arbor criteria), n (%)	
Stage I	0
Stage II	6 (30)
Stage III	6 (30)
Stage IV	8 (40)
Primary category, n (%)	
DLBCL, NOS	17 (85)
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements	3 (15)
Prior stem cell transplant, n (%)	
Yes	0
No	20 (100)
First line prior systemic response, n (%)	
Relapse	18 (90)
Refractory	2 (10)
Other	0
Last line prior systemic response, n (%)	
Relapse	14 (70)
Refractory	5 (25)
Other	1 (5)

Table 5. Results for LOTIS-5 safety run-in (n = 20)

Efficacy in patients with R/R DLBCL		
	n (%)	95% CI
Overall response rate[a]	15 (75%)	(50.9, 91.3)
Complete response	8 (40%)	(19.1, 63.9)
Partial response	7 (35%)	(15.4, 59.2)
Safety endpoints		
Any grade TEAE, n (%)	19 (95%)	
Rash	5 (25%)	
Fatigue	4 (20%)	
Increased gamma-glutamyltransferase	4 (20%)	
Grade ≥3 TEAEs, n (%)	10 (50%)	
Increased gamma-glutamyltransferase	3 (15%)	
Increased alanine aminotransferase	2 (10%)	
Neutropenia	2 (10%)	

Data cutoff: February 28, 2022
[a]By central review

CONCLUSIONS

- Lonca-R demonstrated no new safety signals and showed encouraging antitumor activity in patients with R/R DLBCL in a nonrandomized safety run-in period (part 1)
- The randomized part of LOTIS-5 (part 2) commenced in January 2022; recruitment is ongoing

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