Updated Results of the Safety Run-In 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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ABCL-515

SUMMARY

OBJECTIVE To characterize the safety and efficacy of Lonca + rituximab (Lonca-R) in patients with R/R DLBCL who have had ≥1 prior systemic therapy

METHODS

LOTIS-5

PART 1: Safety run-in (n = 20) → Lonca-R

PART 2: Lonca-R vs R-GemOx (n ≈ 330) → Lonca-R; R-GemOx

ORR 80%

CR 50%

FIXED DURATION TREATMENT OF LONCA + RITUXIMAB

There were no new safety signals

The most common grade ≥3 TEAEs were increased GGT (n = 5) and neutropenia (n = 3)

CONCLUSIONS Lonca-R demonstrated no new safety signals and showed encouraging antitumor activity in patients with R/R DLBCL; initial signs of response durability with Lonca-R are promising

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; GGT, gamma-glutamyltransferase; Lonca, loncastuximab tesirine; ORR, overall response rate; PFS, progression-free survival; R, rituximab; R-GemOx, rituximab + gemcitabine + oxaliplatin; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

INTRODUCTION

- Patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) typically have poor outcomes following treatment[1]
- Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is an antibody–drug conjugate (ADC) comprising an anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer toxin, indicated for patients with R/R DLBCL after ≥2 systemic treatments[2,3]
- Rituximab (R) is part of standard immunotherapy for DLBCL, both as frontline therapy and in subsequent treatments[4,5]
- Preclinical evidence suggests that the addition of R to anti-CD19 ADC therapy may result in prolonged tumor control[6]
- LOTIS-5 aims to evaluate Lonca + R (Lonca-R) versus standard immunochemotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in patients with R/R DLBCL
  - 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

OBJECTIVE

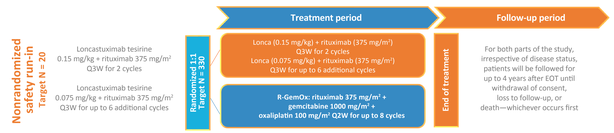
- To characterize the safety and efficacy of Lonca-R in patients with R/R DLBCL who have had ≥ 1 prior systemic therapy

METHODS

Study Design

- LOTIS-5 is a phase 3, randomized, open-label, 2-part, 2-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
  - Preliminary results presented at SOHO 2022 were updated with new safety/efficacy data collected in part 1 of the study[7]
- In part 2, approximately 330 patients will be randomly assigned 1:1 to receive Lonca-R or R-GemOx
- Patients received 0.15 mg/kg Lonca + 375 mg/m^2 R every 3 weeks for 2 cycles, then 0.075 mg/kg Lonca + 375 mg/m^2 R every 3 weeks for up to 6 additional cycles (**Figure 1**)

Figure 1. LOTIS-5 study design



EOT, end of treatment; Lonca, loncastuximab tesirine; QXW, every X weeks; R-GemOx, rituximab + gemcitabine + oxaliplatin.

Outcomes

- The primary end point is progression-free survival by independent central review
- Key secondary end points include overall survival, overall response rate, duration of response, safety, pharmacokinetic parameters, and changes in patient-reported outcomes

Eligibility Criteria

- Key inclusion criteria and exclusion criteria are shown in **Table 1**

Table 1. 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	• Previous treatment with Lonca or R-GemOx
• R/R disease following ≥1 multiagent systemic treatment regimen	• Autologous SCT within 30 days before the start of the study drug
• Measurable disease (2014 Lugano Classification[8])	• Allogeneic SCT within 60 days before the start of the study drug
• Not a candidate for SCT based on performance status, advanced age, and/or significant medical comorbidities (as considered by the investigator)	• Lymphoma with active CNS involvement, including leptomeningeal disease
• Patients who have received previous CD19-directed therapy must have a biopsy that shows CD19 expression after completion of the CD19-directed therapy	• Serologic evidence of chronic HBV infection and inability or unwillingness to receive standard prophylactic antiviral therapy or with detectable HBV viral load
• ECOG performance status score of 0-2	• Serologic evidence of HCV infection without completion of curative treatment or with detectable HCV viral load
• Adequate organ function	• 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 4 weeks before the start of the study drug, unless approved by the sponsor
	• 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.

RESULTS

Patient Population

- The 20 patients in the safety run-in were a median age of 74.5 years (range, 35-93 years) (**Table 2**)
  - Patients received a median of 1 previous therapy (range, 1-7)
  - Seven patients (35%) received ≥2 previous therapies
- As of the April 10, 2023, data cutoff date:
  - The median number of doses administered was 5 (range, 1-8), and the median duration of follow-up was 10.8 months (range, 1.9-21.9 months)

Safety Outcomes

- All patients had ≥1 treatment-emergent adverse event (TEAE), and 11 (55%) patients had grade ≥3 TEAEs (**Table 3**)
- The most common all-grade TEAEs, regardless of the relationship to the study treatment, were increased gamma-glutamyltransferase (5 [25%]), rash (5 [25%]), decreased appetite (4 [20%]), and fatigue (4 [20%])
- The most common grade ≥3 TEAEs were increased gamma-glutamyltransferase (5 patients [25%]) and neutropenia (3 patients [15%])
- Serious adverse events (SAE) were observed in 9 patients (45%). The most common SAE was infection in 6 patients (30%)
- Overall, including survival follow-up, 8 of 20 patients died (4 due to disease progression, 2 due to COVID-19 infection, 1 due to pancreatic neoplasia, and 1 due to stroke), 2 of which occurred within 30 days of last treatment (1 due to disease progression and 1 due to COVID-19 infection).

Efficacy Outcomes

- The overall response rate by central review was 16/20 (80%) patients (**Table 3**)
- Complete responses were observed in 10/20 (50%) patients
- Partial responses were observed in 6/20 (30%) patients
- The median duration of response was 8.0 months (95% CI, 3.2-NR) (**Figure 2**)
- The median progression-free survival was 8.3 months (95% CI, 4.5-NR) (**Figure 3**)

Table 2. Baseline characteristics for patients enrolled in LOTIS-5 safety run-in (n = 20)

Age, median (min, max), years	74.5 (35, 93)
Prior systemic therapies, median (min, max)	1 (1, 7)
Sex, n (%)	
Female	11 (55)
Male	9 (45)
ECOG PS	
Grade 0	7 (35)
Grade 1	10 (50)
Grade 2	3 (15)
Disease stage (Ann Arbor criteria), n (%)	
Stage I	1 (5)
Stage II	6 (30)
Stage III	6 (30)
Stage IV	7 (35)
Primary category, n (%)	
DLBCL, NOS	18 (90)
HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements	2 (10)
Prior stem cell transplant, n (%)	
Yes	1 (5)
No	19 (95)
First-line prior systemic response, n (%)	
Relapsed	18 (90)
Refractory	2 (10)
Last-line prior systemic response, n (%)	
Relapsed	15 (75)
Refractory	5 (25)

DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HGBCL, high-grade B-cell lymphoma; NOS, not otherwise specified.

Table 3. Results for LOTIS-5 safety run-in (n = 20)

	n (%)	95% CI
Efficacy in patients with R/R DLBCL		
Overall response rate	16 (80)	56.3-94.3
Complete response	10 (50)	27.2-72.8
Partial response	6 (30)	11.9-54.3
Safety end points		
All TEAEs	20 (100)	
Increased gamma-glutamyltransferase	5 (25)	
Rash	5 (25)	
Decreased appetite	4 (20)	
Fatigue	4 (20)	
Grade ≥3 TEAEs	11 (55)	
Increased gamma-glutamyltransferase	5 (25)	
Neutropenia	3 (15)	
Serious adverse events	9 (45)	
Infection	6 (30)	
Hyponatremia	1 (5)	
Anaphylactic reaction	1 (5)	
Pleural effusion	1 (5)	
Malaise	1 (5)	
Neurological decompensation	1 (5)	
Deaths		
During treatment	1 (5)	
During follow up	7 (35)	

DLBCL, diffuse large B-cell lymphoma; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event.

Figure 2. Kaplan–Meier curve of the duration of response by independent review

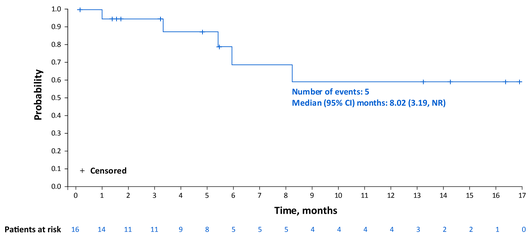
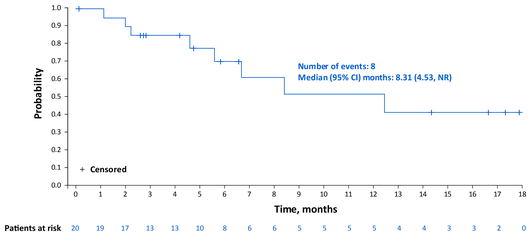


Figure 3. Kaplan–Meier curve of progression-free survival by independent review



CONCLUSIONS

- Lonca-R demonstrated no new safety signals and showed encouraging antitumor activity in patients with R/R DLBCL
- Initial signs of response durability (8.02 months) with Lonca-R are promising
- Lonca-R has a fixed treatment duration, potentially making it an appealing alternative to continuous therapies
- Part 2 of LOTIS-5 commenced in January 2022; recruitment is ongoing

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Disclosures

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