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Updated Safety Run-In Results From LOTIS-5: A Phase 3, Randomized Trial of Loncastuximab Tesirine With Rituximab Versus Immunochemotherapy in Patients With R/R DLBCL/HGBL

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OBJECTIVE

To characterize the safety, efficacy, and PK profile of loncastuximab tesirine + rituximab (Lonca-R) and explore the correlation of clinical activity and tumor/blood biomarkers in the safety run-in population of the LOTIS-5 trial

PHASE 3 LOTIS-5 TRIAL

Eligibility criteria

- ✓ R/R DLBCL/HGBL
- ✓ ≥1 prior systemic therapy
- ✓ Not a candidate for SCT

Part 1: Safety run-in (N=20)

Lonca-R

Part 2: Lonca-R vs R-GemOx (N=420)

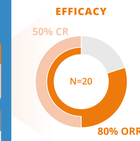
Lonca-R | R-GemOx

Up to 8 cycles of treatment

UPDATED SAFETY RUN-IN RESULTS

Median duration of follow-up: 37.2 (range, 34.1-41.5) months

EFFICACY



Median DOR: 8.0 months
Median PFS: 8.3 months

SAFETY

- There were no new safety signals
- The most common grade ≥3 TEAEs were increased GGT (n=5) and neutropenia (n=4)

BIOMARKERS

- CD19 IHC staining was not predictive of efficacy
- Response to therapy was associated with early ctDNA decrease
- All 3 CR patients with ctDNA results were MRD negative at C3D1

CONCLUSIONS

Fixed treatment duration of Lonca-R showed no new safety signals and demonstrated encouraging antitumor activity, with early signs of durable response in patients with R/R DLBCL/HGBL maintained for >28 months after EOT

CR, complete response; ctDNA, circulating tumor DNA; C1D1, cycle 3 day 1; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EOT, end of therapy; GemOx, gemcitabine + oxaliplatin; GGT, gamma-glutamyltransferase; HGBL, high-grade B-cell lymphoma; IHC, immunohistochemistry; Lonca, loncastuximab tesirine; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetic; R, rituximab; R/R, relapsed/refractory; SCT, stem cell transplant; TEAE, treatment-emergent adverse event.

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CONCLUSIONS

- In this updated safety run-in of LOTIS-5, fixed treatment duration of loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) combined with rituximab (R) (Lonca-R) showed no new safety signals compared to previous Lonca studies and demonstrated encouraging antitumor activity, with early signs of durable response in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL)
  - Response was sustained beyond end of treatment (EOT) in 5 patients; 1 went to stem cell transplant (SCT) and 4 maintained complete response (CR) for 28.5+ months beyond EOT
- Maximum concentration (C_{max}) and trough concentration (C_{trough}) values were generally comparable between Lonca monotherapy and combination therapy with R. Antidrug antibody (ADA) testing did not demonstrate any immunogenicity
- CD19 staining by immunohistochemistry (IHC) was not predictive of efficacy
- Further response to therapy was associated with early (cycle 3, day 1 [C3D1]) circulating tumor DNA (ctDNA) decrease; all 3 CR patients with ctDNA results were minimal residual disease (MRD) negative at C3D1
- Part 2 of LOTIS-5 is ongoing, with enrollment completed

INTRODUCTION

- For patients with R/R DLBCL/HGBL, outcomes are generally poor, with median overall survival (OS) of 6-7 months, with 2-year OS of approximately 20%[1]
- Lonca is a CD19-targeted, antibody–drug conjugate (ADC) that is approved by the US Food and Drug Administration (under accelerated approval) and European Medicines Agency (under conditional approval) for R/R DLBCL/HGBL after ≥2 systemic therapies[2,3]
- R is a monoclonal antibody that targets and binds to CD20 on the surface of B lymphocytes, resulting in cell lysis[4]
- Preclinical and clinical evidence suggests that adding R to an anti-CD19 ADC therapy may enhance tumor control[5,6]
- LOTIS-5 (NCT04384484) is the confirmatory phase 3 trial for the accelerated approval of Lonca, evaluating Lonca-R vs R + gemcitabine + oxaliplatin (R-GemOx) in patients with R/R DLBCL/HGBL who were not a candidate for SCT

OBJECTIVE OF THE SAFETY RUN-IN

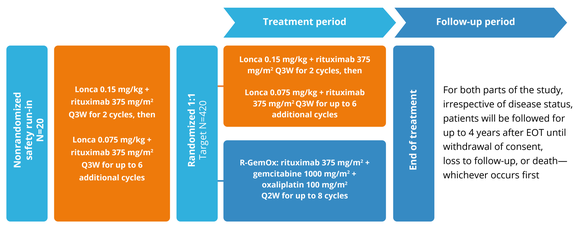
- To characterize the preliminary safety, efficacy, and pharmacokinetic (PK) profile of Lonca-R and explore correlations of clinical activity and tumor and blood biomarkers in the safety run-in population

METHODS

Study Design

- LOTIS-5 (NCT04384484) is a phase 3, randomized, open-label, 2-part, multicenter trial in patients with R/R DLBCL (**Figure 1**)
  - Part 1: nonrandomized safety run-in evaluating Lonca-R (updated results presented here)
  - Part 2: 1:1 randomized trial to evaluate the efficacy and safety of Lonca-R vs the standard immunochemotherapy, R-GemOx
- Lonca-R regimen: Lonca 0.15 mg/kg + R 375 mg/m^2 every 3 weeks for 2 cycles, then Lonca 0.075 mg/kg + R 375 mg/m^2 every 3 weeks for up to 6 additional cycles
- Efficacy assessments were assessed via PET/CT at screening, and at week 6, 12, and every 12 weeks after C1D1
- PK of Lonca and its analytes were assessed using validated methods, with key parameters (eg, C_{max} and C_{trough}) derived via non-compartmental analysis
- ADA responses were evaluated using a tiered immunogenicity testing strategy
- Peripheral blood samples were assessed for ctDNA by PhasEDSeq, and available archival or nonarchival tissue was assessed for CD19 by IHC

Figure 1. Study design of LOTIS-5



EOT, end of treatment; Lonca, loncastuximab tesirine; Q3W, every 3 weeks.

Study Endpoints

- The primary endpoint is progression-free survival (PFS) by independent central review
- Secondary endpoints include OS, overall response rate (ORR), CR rate, duration of response (DOR), safety, PK parameters, Lonca ADAs, and patient-reported outcomes (PROs)
- Exploratory endpoints include correlations between clinical activity and Lonca exposure (ie, Lonca dose and PK metrics) and tumor and/or blood biomarkers

Eligibility Criteria

- Main inclusion criteria include
  - Adults with a pathologic diagnosis of R/R DLBCL (including DLBCL transformed from indolent lymphoma) or HGBCL, following ≥1 multi-agent systemic treatment regimen
  - Measurable disease (2014 Lugano Classification[7])
  - Not a candidate for SCT
  - Eastern Cooperative Oncology Group performance status score of 0-2

RESULTS

Patient Population

- The safety run-in included 20 patients with a median age of 74.5 (range, 35-93) years (**Table 1**)
- In the safety run-in, as of the October 4, 2024, data cutoff date:
  - Patients received a median of 5 (range, 1-8) Lonca-R cycles
  - The median duration of follow-up was 37.2 (range, 34.1-41.5) months
  - 7 (35%) patients completed up to 8 cycles of treatment
  - 4 (20%) patients withdrew from treatment due to adverse events

Table 1. Baseline characteristics for patients enrolled in LOTIS-5 safety run-in

Characteristics	N=20
Sex, female, n (%)	11 (55)
Median (range) age, years	74.5 (35-93)
Race, White, n (%)	20 (100)
ECOG score, n (%)	
Grade 0	6 (30)
Grade 1	10 (50)
Grade 2	4 (20)
Disease stage (Lugano criteria[a]), n (%)	
Stage I	1 (5)
Stage II	7 (35)
Stage III	5 (25)
Stage IV	7 (35)
Histology, n (%)	
DLBCL NOS	18 (90)
HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements	2 (10)
Prior stem cell transplant, n (%)	1 (5)
Median (range) number of prior therapy	1 (1-7)
≥2 prior therapies, n (%)	8 (40)
Response to last prior therapy, n (%)	
Relapsed	9 (45)
Refractory[a]	11 (55)

[a]Refractory is defined either as having stable disease or progressive disease as the best disease response to prior therapy, or if partial response or complete response was achieved, as disease relapse within 6 months from the last treatment date.
DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBCL, high-grade B-cell lymphoma; NOS, not otherwise specified.

Efficacy Outcomes

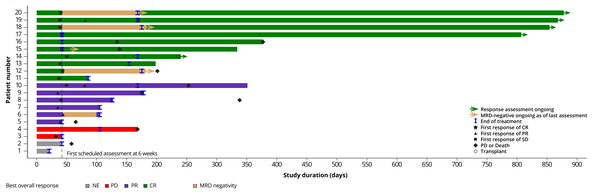
- The ORR by central review was achieved in **16/20 (80%)** patients, with CR observed in **10/20 (50%)** patients (**Table 2**)
- Five patients who achieved CR were refractory to their most recent prior treatment
- Median DOR was 8.0 months (95% CI, 3.2-not estimable [NE]) for all responders and not reached for CRs
- Median PFS was **8.3 months** (95% CI, 4.5-NE)
- Response was sustained beyond EOT and last assessment in 5 patients; 1 went to SCT and 4 maintained CR for more than 28.5 months beyond EOT
  - Among the 4 ongoing CRs, 2 were ctDNA evaluable, and both were MRD negative

Table 2. Efficacy outcomes for the LOTIS-5 safety run-in

Efficacy outcomes in safety run-in population (N=20)	
ORR (95% CI), %	80.0 (56.3-94.3)
CRR (95% CI), %	50.0 (27.2-72.8)
Median PFS (95% CI), months	8.3 (4.5-NE)
Efficacy outcomes in responders (n=16)	
Median DOR (95% CI), months	8.02 (3.19-NE)
Events, n (%)	5 (31.3)
Efficacy outcomes in complete responders (n=10)	
Median DOR, months (95% CI)	NE (3.19-NE)
Events, n (%)	3 (30.0)
MRD results in patients with ctDNA measurements (n=8)	
CR and MRD negative, n (%)	4 (50.0)
MRD negative at end of treatment, n (%)	4 (50.0)

CRR, complete response rate; ctDNA, circulating tumor DNA; DOR, duration of response; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; PFS, progression-free survival.

Figure 2. Swimmer plot of safety run-in population (N=20)



Each bar represents one patient in the study. Response is determined by independent reviewer.
CR, complete response; MRD, minimal residual disease; NE, not estimable; PD, progressive disease; PR, partial response.

Safety Outcomes

- All patients had ≥1 treatment-emergent adverse event (TEAE), and 11 (55%) patients had grade ≥3 TEAEs (**Table 3**)
- The most common grade ≥3 TEAEs occurring in ≥20% of patients were increased gamma-glutamyl transferase in 5 (25%) patients and neutropenia in 4 (20%) patients
- Serious adverse events were observed in 9 (45%) patients, with infection being the most common in 6 (30%) patients
- With a median follow-up time of 37.2 months, 9 (45%) patients died with 5 (25%) due to disease progression, 2 (10%) due to COVID-19 infection, 1 (5%) due to pancreatic neoplasia, and 1 (5%) due to liver failure

Table 3. Safety outcomes for the LOTIS-5 safety run-in

Safety endpoint, n (%)	N=20
All grade TEAE	20 (100)
Grade ≥3 TEAE	11 (55)
GGT increased	5 (25)
Neutropenia	4 (20)
COVID-19/COVID-19 pneumonia	3 (15)
Alanine aminotransferase increased	1 (5)
Anemia	1 (5)
Aspartate aminotransferase increased	1 (5)
Blood alkaline phosphatase increased	1 (5)
Cataract	1 (5)
Cellulitis gangrenous	1 (5)
Cytomegalovirus infection reactivation	1 (5)
Hyponatremia	1 (5)
Malaise	1 (5)
Neurological decompensation	1 (5)
Photosensitivity reaction	1 (5)
Pleural effusion	1 (5)
Tumor lysis syndrome	1 (5)
Urinary tract infection	1 (5)
Serious adverse events	9 (45)
Infection	6 (30)
Hyponatremia	1 (5)
Anaphylactic reaction	1 (5)
Pleural effusion	1 (5)
Malaise	1 (5)
Neurological decompression	1 (5)
TEAEs leading to any study drug withdrawal	8 (40)

GGT, gamma-glutamyl transferase; TEAE, treatment-emergent adverse event.

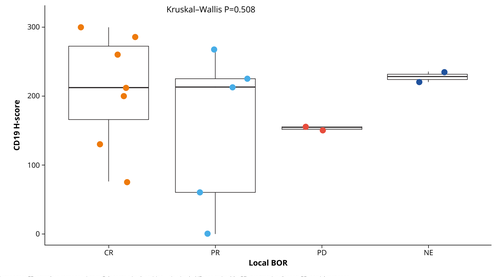
Exploratory Outcomes

- Median C_{max} and C_{trough} values were lower in C1 compared to C2 for total and conjugated antibodies in Lonca combination therapy with R; as expected, total antibody concentrations consistently exceeded conjugated antibody concentrations
- C_{max} and C_{trough} values were generally comparable between Lonca monotherapy and combination therapy with R
- No pre- or postdose ADA positivity was observed

Biomarkers

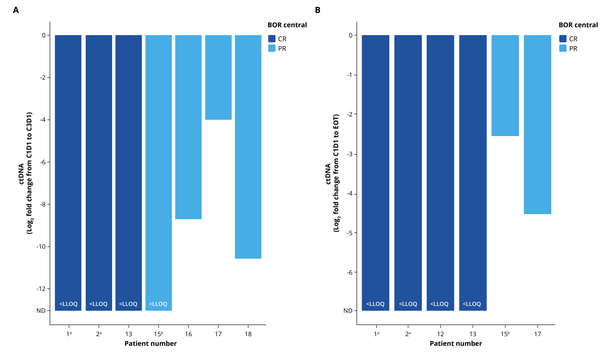
- Of the 16 tumors examined for CD19 IHC expression, 12 had H-scores ≥150, indicating high CD19 expression. No correlation was observed between CD19 H-score and best overall response (**Figure 3**)/PFS (data not shown), suggesting that CD19 IHC expression is not predictive of response to Lonca-R
- In the 8 patients with ctDNA measurements, 7 (3 CR/4 partial response) had ctDNA results at baseline and C3D1 (**Figure 4**)
  - ctDNA decrease from baseline was noted at C3D1 in all 7 patients
  - All 3 CR patients reached MRD negativity at C3D1
  - Of the 4 patients with undetectable ctDNA levels at EOT, 3 reached MRD negativity by C3D1
- Of the 4 patients with CR with the longest DOR that are still ongoing, 2 patients had evaluable ctDNA measurements and both were MRD negative at C3D1 (**Figure 2**)

Figure 3: Baseline tumor CD19-positive H-score by response to Lonca-R assessed by independent review



BOR, best overall response; CR, complete response; Lonca-R, loncastuximab tesirine + rituximab; NE, not estimable; PD, progressive disease; PR, partial response.

Figure 4. Change in ctDNA from C1D1 to (A) C3D1 and (B) EOT



[a]Patients continue to be in sustained CR; follow-up is ongoing (**Figure 2**).
[b]Reduced analytical sensitivity in baseline sample; results reported at risk.
BOR, best overall response; C, cycle; CR, complete response; ctDNA, circulating tumor DNA; D, day; EOT, end of therapy; LLOQ, lower limit of quantification; ND, not defined; PR, partial response.

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