A Phase 2 randomized study of loncastuximab tesirine (Lonca) vs idelalisib in patients with relapsed or refractory (R/R) follicular lymphoma (FL) — LOTIS-6

Carmelo Carlo-Stella[1], Julien Depaus[2], Brian T. Hess[3], Edwin Kingsley[4], Pier Luigi Zinzani[5], David Ungar[6], Vivian Dai[6], Luqiang Wang[6], Kirit M. Ardeshna[7]

[1]Department of Oncology and Hematology, Humanitas Clinical and Research Center – IRCCS, and Humanitas University, Rozzano, Milano, Italy; [2]Department of Hematology, CHU UCL Namur site Godinne, Yvoir, Belgium; [3]Division of Hematology and Medical Oncology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA; [4]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", and Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale Università di Bologna, Bologna, Italy; [6]Clinical Development, ADC Therapeutics America, Inc., Murray Hill, NJ, USA; [7]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK

BACKGROUND

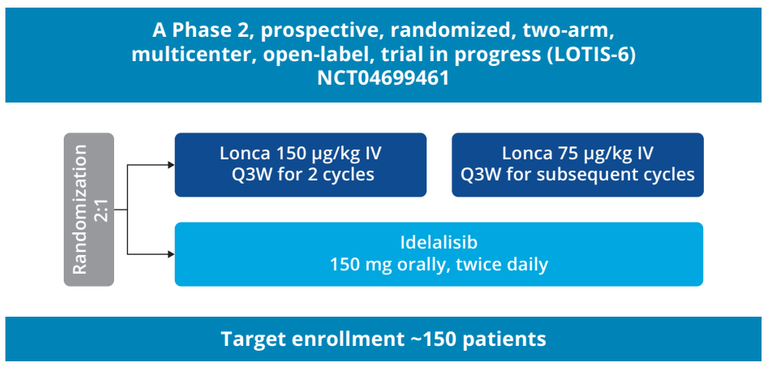
- Many patients with follicular lymphoma (FL), the second most common type of non-Hodgkin lymphoma[1], respond to first-line therapy but have successive relapses and the duration of response to treatment commonly shortens after each relapse[2], presenting a substantial unmet need in these patients
- Single-agent loncastuximab tesirine (Lonca), an antibody (Ab)-drug conjugate comprising a humanized anti-CD19 monoclonal Ab conjugated to a pyrrolobenzodiazepine dimer toxin[3,4], has shown antitumor activity and manageable safety in:
  - Patients with relapsed or refractory (R/R) B-cell FL in a Phase 1 trial (NCT02669017), with an overall response rate (ORR) of 78.6%[5]
  - Heavily pretreated patients with R/R diffuse large B-cell lymphoma in a Phase 2 trial (NCT03589469), with durable responses and an ORR of 48.3%[6]
- Idelalisib is a phosphatidylinositol 3-kinase inhibitor approved for patients with relapsed FL who have received ≥2 prior systemic therapies[7]
- Here, we present the design, objectives, eligibility criteria, and assessments of this Phase 2, prospective, randomized, two-arm, multicenter, open-label trial in progress of Lonca vs idelalisib in patients with FL, which opened in Spring 2021 (NCT04699461)

METHODS

Study design

- Patients will be randomized 2:1 to receive Lonca or idelalisib based on time since last systemic therapy (stratified as ≤2 years or >2 years). Treatment regimens for patients are shown in **Figure 1**

Figure 1. Study design



IV, intravenously; Lonca, loncastuximab tesirine; LOTIS-6; LOncastuximab Tesirine ClinIcal AsSessment 6; Q3W, every 3 weeks.

- A non-binding futility analysis for the primary endpoint (complete response rate; CRR) will be performed for the first 60 patients, ~12 weeks after the 60th patient is randomized, allowing sufficient time for two disease assessments
- Patients can continue therapy until disease progression, unacceptable toxicity, or other discontinuation criteria. The follow-up period is up to 3 years after patients' last study treatment

Objectives and endpoints

- The primary objective of the study is to evaluate single-agent Lonca compared with idelalisib, assessed by CRR (per 2014 Lugano Classification), as determined by central review in patients with R/R FL. Objectives and endpoints are shown in **Table 1**

Table 1. Study objectives and endpoints

Objectives	Endpoints
Primary	
Evaluate efficacy of Lonca vs idelalisib	• CRR (proportion of patients with a BOR of CR), per 2014 Lugano Classification, in the ITT population (central review)
Secondary	
Further evaluate efficacy of Lonca	• ORR (key secondary endpoint): proportion of patients with CR + PR (central review) • PFS: time from randomization to first disease recurrence, disease progression, or death • OS: time from randomization to death from any cause • DoR: time from first tumor response to disease progression or death
Assess safety profile of Lonca	• Incidence and severity of AEs and SAEs • Change from baseline in ECOG performance status, laboratory tests, physical examination, vital signs, and 12-lead ECG
Characterize PK profile of Lonca	• Concentration and PK parameters of Lonca total Ab, PBD-conjugated Ab, and unconjugated warhead (SG3199)
Evaluate immunogenicity of Lonca	• ADA titers to Lonca
Evaluate impact of Lonca vs idelalisib on PROs and overall health status	• Change from baseline in PROs • Incidence, severity, and interference of specific symptomatic AEs per PRO version of CTCAE

Ab, antibody; ADA, anti-drug antibody; AE, adverse event; BOR, best overall response; CR, complete response; CRR, complete response rate; CTCAE, Common Terminology Criteria for Adverse Events; DoR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; Lonca, loncastuximab tesirine; ORR, overall response rate; OS, overall survival; PBD, pyrrolobenzodiazepine; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; PRO, patient-reported outcome; SAE, serious adverse event.

Study eligibility criteria

- Key inclusion and exclusion criteria are shown in **Table 2**

Table 2. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥18 years • Pathologic diagnosis of FL (Grade 1, 2, 3A) from most recent tumor biopsy • Relapsed or refractory disease after ≥2 prior therapy lines (≥1 of which included an anti-CD20 therapy) • Measurable disease (per 2014 Lugano Classification) • ECOG performance status 0–2 • Adequate organ function	• Previous treatment with Lonca • Previous treatment with idelalisib • FL that has transformed to DLBCL or other aggressive lymphoma • Patient requirement for treatment or prophylaxis with a strong cytochrome P450 (CYP) 3A inhibitor, inducer, or sensitive substrate • History of/or ongoing drug-induced pneumonitis, and/or IBD • Any condition with the potential to interfere with absorption of metabolism of idelalisib

DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; IBD, inflammatory bowel disease; Lonca, loncastuximab tesirine.

Statistical analysis

- The primary endpoint (CRR) will be assessed in the intent-to-treat population between treatment arms using the Cochran–Mantel–Haenszel method, with adjustments for stratification factors from the randomization list (as generated by block randomization, for balance between treatment groups)
- The study is 99% powered for the primary endpoint, assuming a 55% CRR to Lonca and a 15% CRR to idelalisib. Target sample size for enrollment is approximately 150 patients, to allow for a robust safety data set

Study assessments

- Study assessments are shown in **Table 3**

Table 3. Study assessments

Efficacy	Safety
Disease assessment • Imaging (PET-CT)[a] • Additional disease assessments if clinically indicated	• AEs/SAEs 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 (only for patients receiving Lonca) • ADA (only for patients receiving Lonca)	• PROs: EQ-5D-5L and FACT-Lym GP5, with selected items from the PRO version of CTCAE

[a]Performed at baseline, and at 6 and 12 weeks after Cycle 1, Day 1; then every 12 weeks for up to 2 years after Cycle 1, Day 1; then every 6 months. [b]Hematology, chemistry, coagulation, CMV tests, and urinalysis.

Ab, antibody; ADA, anti-drug antibody; AE, adverse event; CMV, cytomegalovirus; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; Lonca, loncastuximab tesirine; PBD, pyrrolobenzodiazepine; PET-CT, positron emission tomography and computerized tomography; PK, pharmacokinetic; PRO, patient-reported outcome; SAE, serious adverse event.

CONCLUSION

- This Phase 2, randomized, open-label trial in progress (LOTIS-6) is evaluating Lonca vs idelalisib in patients with R/R FL
  - *The study opened in Spring 2021; enrollment is ongoing*

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Contact information

Prof. Carmelo Carlo-Stella: carmelo.carlostella@hunimed.eu

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