Phase 1b Open-Label Study of Loncastuximab Tesirine in Combination With Other Anticancer Agents in Patients With Relapsed/Refractory B-cell Non-Hodgkin Lymphoma (LOTIS-7)

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Product

Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is an ADC comprising a humanized **anti-CD19** antibody conjugated to a **PBD dimer cytotoxin** that is indicated for **R/R DLBCL**

Patients

Adults with **R/R B-NHL** with ≥2 prior systemic treatments (part 1) or ≥1 prior systemic treatment (part 2)

Trial

LOTIS-7 (NCT04970901) is a **phase 1b** study evaluating the safety/tolerability and antitumor activity of **Lonca in combination with other anticancer agents**

Current Status

As of May 23, 2024, **33 patients have been enrolled**

- Lonca + polatuzumab vedotin arm: 12 patients
- Lonca + glofitamab arm: 12 patients (9 in part 1; 3 in part 2)
- Lonca + mosunetuzumab arm: 9 patients

ADC, antibody–drug conjugate; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; PBD, pyrrolobenzodiazepine; R/R, relapsed/refractory.

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CONCLUSIONS

This phase 1b, 2-part, open-label study (LOTIS-7; NCT04970901) evaluates the safety, tolerability, and anticancer activity of loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) in combination with other anticancer agents in patients with relapsed/refractory B-cell non-Hodgkin lymphoma (R/R B-NHL)

INTRODUCTION

- Lonca, an antibody–drug conjugate comprising a humanized anti-CD19 antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer cytotoxin, received accelerated approval by the United States Food and Drug Administration and has received conditional marketing authorization by the European Commission to treat adult patients with R/R diffuse large B-cell lymphoma (DLBCL) after ≥2 lines of systemic therapy[1,2]
  - A phase 2 trial of Lonca monotherapy in patients with R/R DLBCL showed that an intravenous (IV) infusion over 30 minutes on day (D) 1 of each 3-week cycle produced durable responses with manageable toxicity using a dose of 150 µg/kg for 2 cycles and then 75 µg/kg for subsequent cycles[3]
- Combining agents with different mechanisms of action may enhance treatment efficacy in patients with R/R B-NHL
  - In preclinical WSU-DLCL2 and Ramos xenograft models, Lonca in combination with polatuzumab vedotin (Pola) showed improved antitumor activity with better response rates compared with either monotherapy alone[4]
  - In addition, combining CD20 × CD3 T-cell–engaging antibodies (eg, glofitamab [Glofit][5] or mosunetuzumab [Mosun][6]) with Lonca is expected to increase antitumor activity

OBJECTIVE

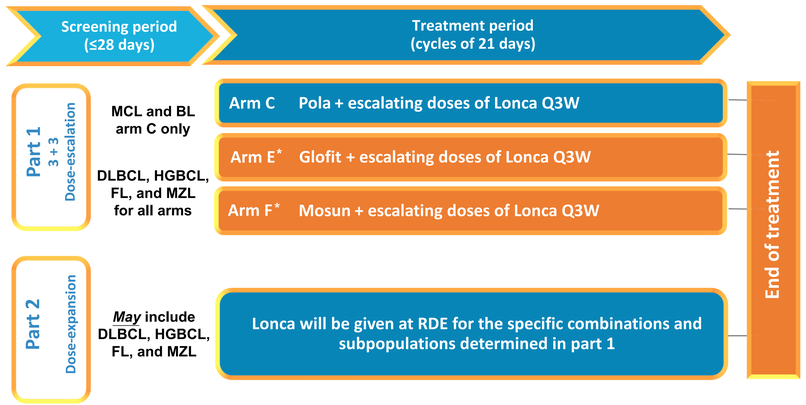
- To evaluate the safety, tolerability, and anticancer activity of Lonca in combination with other anticancer agents in patients with R/R B-NHL (LOTIS-7)

METHODS

Study Design

- This phase 1b, open-label, multicenter, multiarm study (NCT04970901) is divided into 2 parts (part 1: dose escalation; part 2: dose expansion) and will enroll ~200 patients with R/R B-NHL (part 1: up to 60 patients; part 2: up to 140 patients) (**Figure 1**)[7]
  - In part 1, eligible patients will have either failed or are intolerant to any approved therapy and have received ≥2 prior systemic treatment regimens
- The study will include a screening period (up to 28 days), a treatment period (with treatment cycles every 3 weeks [Q3W] for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria), and a follow-up period (every 12 weeks for up to 2 years after treatment completion or discontinuation)
- The study period is defined as the date of obtaining written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first

Figure 1. Study design

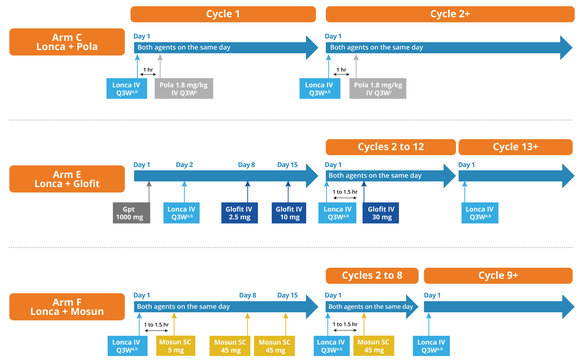


Participants may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first. The follow-up period is for ≤2 years from the end of treatment.

BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; Glofit, glofitamab; HGBCL, high-grade B-cell lymphoma; IV, intravenous; Lonca, loncastuximab tesirine; MCL, mantle cell lymphoma; Mosun, mosunetuzumab; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; Pola, polatuzumab vedotin; Q3W, every 3 weeks; RDE, recommended dose for expansion; R/R, relapsed/refractory.
*Arms E and F are still recruiting patients.

- The dosing schedule is shown in **Figure 2**
- For part 1,
  - Patients in arm C received escalating doses of Lonca + fixed doses of Pola
  - Patients in arm E received escalating doses of Lonca + fixed doses of Glofit after an initial pretreatment with obinutuzumab
  - Patients in arm F received escalating doses of Lonca + fixed doses of Mosun
- For part 2, patients will receive the maximum tolerated dose or recommended dose for expansion based on data from part 1

Figure 2. Dosing schedule



D, day; DLT, dose-limiting toxicity; Glofit, glofitamab; Gpt, obinutuzumab; IV, intravenous; Lonca, loncastuximab tesirine; Mosun, mosunetuzumab; Pola, polatuzumab vedotin; Q3W, every 3 weeks; SC, subcutaneous.
[a]Dose level 1, 90 µg/kg; dose level 2, 120 µg/kg; and dose level 3, 150 µg/kg.
[b]If the starting dose of Lonca is ≥120 µg/kg, the dose will be reduced to 75 µg/kg in cycle 3 and beyond.
[c]If a DLT is clearly related to Pola, the DLT does not recur after a dose reduction of Pola, and Lonca has not been escalated to the 150 µg/kg dose level, dose escalation of Lonca will be continued with a reduced Pola dose of 1.4 mg/kg.

Table 1: LOTIS-7 key eligibility criteria

Key inclusion criteria (all arms)
• Age ≥18 years • Pathologic diagnosis of R/R B-NHL (2016 WHO classification) with treatment failures/intolerance – DLBCL (including transformed diseases, but for arms E and F only transformed FL is included) – HGBCL – FL – MZL – For arm C only - MCL - BL • ≥2 prior systemic treatment regimens for part 1 and ≥1 for part 2 • Measurable disease (2014 Lugano classification) • ECOG performance status of 0-2 • Adequate organ function based on laboratory parameters: – Absolute neutrophil count ≥1.5 × 10⁹/µL – Platelet count ≥75 × 10⁹/µL without transfusion in the past 7 days – Hemoglobin ≥9 g/dL; transfusion allowed – ALT, AST, or GGT ≤2.5 × ULN – Total bilirubin ≤1.5 × ULN • Calculated CrCl ≥60 mL/min (Cockcroft–Gault)
Key exclusion criteria (all arms)
• Previously received study medication (applied to relevant arm only)[a] • Lymphoma with active CNS involvement • Clinically significant third-space fluid accumulation (ascites or pleural effusion requiring drainage or associated with breath) • Active acute graft-versus-host disease • Post-transplant lymphoproliferative disorder • Known history of hypersensitivity resulting in treatment discontinuation or positive serum human ADA to a CD19 antibody • History of confirmed progressive multifocal leukoencephalopathy • History of Stevens–Johnson syndrome, toxic epidermal necrolysis, or macrophage activation syndrome/hemophagocytic lymphohistiocytosis • Significant medical comorbidities
Additional key exclusion criteria (arm C)
• Received a stem cell transplant within 60 days before study treatment
Additional key exclusion criteria (arms E and F)
• Received autologous stem cell transplant within 100 days before study treatment • Received prior allogenic stem cell or solid organ transplant • History of CNS lymphoma or leptomeningeal infiltration • Current or history of CNS disease • Known active infection; reactivation of a latent infection, whether bacterial, viral, fungal, mycobacterial, or other pathogens; or any major episode of infection requiring hospitalization or treatment with IV antibiotics within four weeks prior to C1D1 • Active or history of autoimmune disease or immune deficiency • Prior treatment with CAR T-cell therapy within 30 days prior to C1D1

ADA, anti-drug antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, Burkitt lymphoma; C, cycle; CAR, chimeric antigen receptor; CNS, central nervous system; CrCl, creatinine clearance; D, day; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; GGT, gamma-glutamyl transferase; HGBCL, high-grade B-cell lymphoma; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R B-NHL, relapsed/refractory B-cell non-Hodgkin Lymphoma; ULN, upper limit of normal; WHO, World Health Organization.
[a]Patients who received previous polatuzumab vedotin treatment were excluded from arm C; patients with previous glofitamab treatment were excluded from arm E; and patients with previous mosunetuzumab treatment were excluded from arm F. Patients would still be eligible for the other arms as long as they did not receive that treatment while enrolled in LOTIS-7.

Outcomes

- Primary endpoints include the following:
  - Frequency and severity of adverse events (AEs) and serious AEs
  - Dose-limiting toxicities (part 1 only)
  - Frequency of dose delays, dose interruptions, and dose reductions due to AEs
  - Changes from baseline of safety laboratory variables, vital signs, Eastern Cooperative Oncology Group performance status, and 12-lead electrocardiograms
- Secondary endpoints include the following:
  - Overall response rate and complete response rate (2014 Lugano criteria[8]); duration of response; and progression-free, relapse-free, and overall survival
  - Concentrations and pharmacokinetic (PK) parameters of Lonca total antibody, PBD-conjugated antibody, and unconjugated cytotoxin PBD dimer in combination with Pola, Glofit, or Mosun
  - Antidrug antibody titers
- Exploratory endpoints include the following:
  - Glofit and Mosun concentrations in circulation
  - Relation between tumor tissue and/or blood biomarkers and selected PK with clinical endpoints

Table 2: Study assessments

Efficacy
Disease assessment • Imaging • Clinical examination
Safety
• AEs • SAEs • Physical examination • ECOG performance status • Height and weight • Vital signs • Laboratory tests • Pregnancy test • ECGs
PK, PD, and immunogenicity
• PK of Lonca total antibody, PBD-conjugated antibody, and unconjugated PBD dimer cytotoxin in serum • ADA in whole blood • Blood cfDNA, gDNA, mRNA, flow cytometry, and cytokines • Tumor tissue biomarkers

ADA, anti-drug antibody; AE, adverse event; cfDNA, cell-free DNA; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; gDNA, genomic DNA; Lonca, loncastuximab tesirine; PBD, pyrrolobenzodiazepine; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event.

Study Status

- The study opened for recruitment in June 2022
- As of May 23, 2024, 33 patients have been enrolled, with 12 patients treated in arm C (Lonca + Pola), 12 in arm E (Lonca + Glofit; 9 in part 1, 3 in part 2), and 9 in arm F (Lonca + Mosun)

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