Investigational Loncastuximab Tesirine-Ipyl – LOTIS-7 Clinical Trial

The safety and efficacy regarding the use of Loncastuximab tesirine with polatuzumab vedotin, glofitamab or mosunetuzumab has not be established and the combination use has not been approved by any regulatory agency at this time. Loncastuximab tesirine 150 µg/kg is approved in the USA for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

Summary

- LOTIS-7 (NCT04970901) is a Phase 1b open-label study to evaluate the safety and anti-cancer activity of Loncastuximab tesirine (Lonca) in combination with other anti-cancer agents in patients with relapsed or refractory B-cell Non-Hodgkin Lymphoma (R/R B-NHL).[1,2]
    - The primary objective of this study is to characterize the safety and tolerability of Lonca in combination with polatuzumab vedotin, glofitamab or mosunetuzumab, and to identify the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) for the combinations.
    - Key select secondary outcomes are overall response rate (ORR), duration of response (DOR), complete response rate (CRR), progression-free survival (PFS), relapse-free survival (RFS), and overall survival (OS).
- As of April 14, 2025, data cutoff, 47 patients with R/R B-NHL had received ≥1 dose of treatment at the Lonca 90, 120, or 150-µg/kg dose level. Of these, 41 patients with LBCL were treated at Lonca 120 or 150 µg/kg and comprised the treated population for this presentation; 30 were evaluable for efficacy. Six patients who received Lonca 90 µg/kg or had another B-NHL histology (ie, FL grades 1-3a or marginal zone lymphoma) were excluded from the present analysis.
    - The most common Grade ≥ 3 Treatment emergent adverse events (TEAE) was neutropenia (24.4%), which also led to the majority of dose delays for both Lonca and Glofit.
    - Grade 3 cytokine release syndrome (CRS) occurred in 1 patient at the 120 µg/kg dose; no Grade 4 CRS events were reported.
    - Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) was reported in 3 patients.
    - No Grade ≥3 ICANS were observed. The rates of any-grade CRS or ICANS were lower in the 150 µg/kg cohort compared to the 120 µg/kg cohort.
- Please visit www.clinicaltrials.gov/study/NCT04970901 for the most up to date information regarding the LOTIS-7 study.

Study Overview

Study Design[1,2]

- LOTIS-7 is a Phase 1b open-label, non-randomized, sequential assignment clinical trial evaluating the safety and anti-cancer activity of Loncastuximab tesirine (Lonca) in combination with polatuzumab vedotin, glofitamab, or mosunetuzumab in participants with relapsed or refractory B-cell non-Hodgkin lymphoma (R/R B-NHL), including diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and Burkitt lymphoma (BL).
    - The study includes two parts, Dose Escalation (Part 1) and Dose Expansion (Part 2). Part 2 may include DLBCL, HGBCL, FL, MCL, MZL, and BL cohorts.
    - The study will enroll approximately 200 participants with R/R B-NHL (part 1: 60 participants; part 2: 140 participants).

- A Dose-Escalating Steering Committee (DESC) is responsible for safety monitoring and overall supervision of the study. Part 1 will use a standard 3+3 dose escalation design and Part 2 subpopulations of B-cell non-Hodgkin lymphomas with specific combination/dose levels will be determined from data collected in Part 1.[1,2.]
- For each participant, the study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 21 days), and a Follow-up Period (approximately every 12-weeks for up to two years). Participants may continue treatment for up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first.[1,2.]
- As of April 4, 2024, the Phase 1b dose escalation has been completed successfully.[3]
    - There were no dose-limiting toxicities (DLTs) observed, and no cases of immune effector cell-associated neurotoxicity syndrome (ICANS) detected across all patients receiving loncastuximab in combination with glofitamab or mosunetuzumab.
    - A few occurrences of cytokine release syndrome (CRS) were observed in low grade severity.
    - Per investigator assessment, a substantial portion of patients, with subtypes such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and marginal zone lymphoma (MZL), exhibited early signs of anti-tumor activity.
    - Based on favorable outcomes observed in Part 1, all three dose levels (90, 120, and 150 µg/kg) were deemed safe for further exploration, enrollment has begun for Part 2 dose expansion.
- Lonca exposure showed a dose-dependent increase over the first two cycles.[2]
    - Coadministration of Lonca + Glofit led to a lower Lonca Cmax, particularly in cycle 2, compared to Lonca monotherapy; however, AUClast remained within the expected range of Lonca monotherapy.
- There was no post-dose antidrug antibody (ADA) to Lonca detected, suggesting that there is a low immunogenicity of the lonca+Glofit combination.[2]
    - Flow cytometry revealed similar patterns of T-cell margination with the Lonca+Glofit combination as observed with Glofit monotherapy. Circulating activated T cells (HLA-DR+) increased during treatment.
    - Cytokine profiling showed immune activation, with transient increases in IFN-γ following the first Glofit dose, which decreased by the second infusion and returned to baseline thereafter.

Treatment

- There are three arms in the study (Arms C, E and F) in which participants will receive one of the three anti-cancer treatments (polatuzumab vedotin, glofitamab or mosunetuzumab) in combination with Lonca.[1]
- For Part 1, (arm C) participants will receive escalating doses (90 µg/kg to 150 µg/kg) of Lonca plus polatuzumab (1.8mg/kg) on Day (D) 1 of each cycle.[1]
- For Part 1, (arms E and F) participants will receive escalating doses (90 µg/kg to 150 µg/kg) of Lonca on day 2 of cycle (arm c) and then day 1 of all other cycles.[1]
    - Arm E: Participants will also receive intravenous (IV) infusion of glofitamab at the following doses (2.5mg on cycles (C) 1 D8, glofitamab 10mg on C1 D15, and glofitamab 30 mg for C2-12 day 1.[1]
        - In addition, participants will also receive IV infusion of obinutuzumab pre-treatment 1000mg on day 1 of cycle 1.
    - Arm F: Participants will also receive subcutaneous (SC) injection of mosunetuzumab at the following doses (5mg on C1 D1, 45mg on C1 D8, C1 D15 and day 1 C2-8).

- As of April 14, 2025, 47 patients with R/R B-NHL had received ≥1 dose of treatment at the Lonca 90, 120, or 150 µg/kg dose level.[2]
    - Patients received Lonca Q3W for up to 8 cycles. Lonca doses of 120 or 150 µg/kg were reduced to 75 µg/kg for cycles ≥3.
    - Obinutuzumab 1000 mg was given on Cycle 1 Day 1 as pretreatment**.** Lonca was administered on Cycle 1 Day 2**.**
    - Glofitamab followed with step-up dosing on Cycle 1 Day 8 and Day 15, then continued at 30mg Q3W for up to 12 cycles**.**

Study Objectives and Endpoints

- Select key select primary outcome measures are the number of participants who experience a treatment-emergent adverse event (TEAE), dose-limiting toxicity, adverse events leading to dose delay, dose interruption, or dose reduction.[1,2.]
- Key secondary outcome measures are ORR, DOR, CRR, PFS, RFS, OS, and pharmacokinetic profile of Lonca.[1,2.]

Inclusion/Exclusion Criteria

- Key select inclusion criteria include patients 18 years or older, pathologic diagnosis of R/R B-NHL who had failed or have been intolerant to any approved therapy and have received at least two previous systemic treatment regimens, measurable disease defined by the 2014 Lugano Classification, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.[1,2]
- Key select exclusion criteria for all study arms, include patients with clinically significant third space fluid accumulation, significant medical comorbidities, and previous treatment with study drugs.[1,2]
    - Key select exclusion criteria specifically to (arm C) include patients who received a stem-cell transplant within 100 days before study treatment.
    - Key select exclusion criteria specifically for (arms E and F) include patients who received autologous stem-cell transplant within 100 days prior to study treatment, allogenic stem cell or solid organ transplant, and prior treatment with CAR-T cell therapy with 100 days prior to cycle 1 day 1 of treatment.[1]
- At data cut off April 14, 2025, the treated population (N=41) included patients from Parts 1 and 2 who received Lonca at 120 or 150 µg/kg and had large B-cell lymphoma (LBCL), encompassing R/R de novo DLBCL, HGBCL, transformed follicular lymphoma (trFL), or FL grade ≥3b.[2]
    - Among these patients, the median age was 71 years; 73.2% had de novo DLBCL, 14.6% had HGBCL, 9.8% had trFL; 51.2% had received ≥2 prior therapies (median of 2 prior lines), and 19.5% had received prior CAR-T therapy.
    - Among these patients, 15% (6/41) had HGBCL, 10% (4/41) had transformed FL; 2% (1/41) had grade 3b FL, 19.5% (8/41) had double or triple hit, 32% (13/41) had the non-GCB subtype, 10% (4/41) had bulky disease (>10 cm), 51% (21/41) had elevated LDH 6/41, 54% (22/41) had an IPI score of 3-5, 19.5% (8/41) had prior CAR-T and 10% (4/41) had prior SCT.
    - There were 51% (21/41) patients who were refractory to primary therapy and 49% (20/41) were refractory to last prior therapy.
    - In the 19 patients who had an end of treatment date, patients received a median of 6 cycles of Lonca+Glofit, with a median duration of treatment of 5 months (range 1-9).

Results[2,3]

- As of the cutoff date April 14, 2025, an initial efficacy analysis was conducted on all 30 evaluable patients. The efficacy evaluable population (N=30), as defined included all patients in the treated population who had a baseline and ≥1 postbaseline disease assessment.

- The ORR was 93.3% (28/30) as assessed by Lugano criteria, and CR was achieved in 86.7% (26/30). Of the 30 efficacy evaluable patients, 28 were responders with a best response of CR or PR, including 26 CRs.
    - Of the 28 responders, 27 remained in response, with 25 of 26 maintaining their CR.
    - Twelve patients converted from stable disease (1) or partial response (11) to CR over time and most responses were observed at the initial assessment at 6 weeks for both doses
- The median time to first response was 42 days**.** The median time to first complete response (CR) was 70.5 days. Quicker responses were observed in the 150 µg/kg cohort compared to the 120 µg/kg cohort.
- The median DOR was not reached and the event-free rate at 6 months was 95.2%**,** indicating that 95.2% of responders remained in response at 6 months.

Safety[2,3]

- As of the cutoff date April 14, 2025, in the treated population (n=41) the combination of Lonca at 120 and 150 µg/kg with Glofit 30 mg demonstrated a manageable safety profile consistent with the known profiles of each drug.[3]
    - The most common Grade ≥ 3 TEAE was neutropenia 24.4%, which also led to the majority of dose delays for both Lonca (12.2%) and Glofit (17.1%).
    - Grade 3 CRS occurred in 1 patient (5%) at the 120 µg/kg dose, no Grade 4 CRS events were reported.
        - Grade 1 CRS occurred in 7 patients (35%) at the 120µg/kg dose, 5 patients (23.8%) at 150µg/kg dose.
        - Grade 2 CRS occurred in 3 patients (15%) at the 120µg/kg dose, and none at the 150µg/kg dose.
    - ICANS was reported in 3 patients across both doses.
        - Grade 1 occurred in 1 patient (2.4%) at the 120µg/kg dose and Grade 2 occurred in 1 patient in both the 120µg/kg (5%) and 150µg/kg (4.8%) dose levels. No Grade ≥3 ICANS were observed.
        - The rates of any-grade CRS or ICANS were lower in the 150 µg/kg dose compared to the 120 µg/kg dose.
        - The rate of any-grade ICANS was 4.8% in the Lonca 150-µg/kg dose and 10.0% in the Lonca 120-µg/kg dose.
- Neutropenia was the most common TEAE, leading to a dose delay of Lonca (12.2%) and Glofit (17.1%).
    - One patient had a dose reduction of lonca during treatment.

References

[1] ADCT Therapeutics SA. A study to evaluate the safety and anti-cancer activity of loncastuximab tesirine in combination with other anti-cancer agents in participants with relapsed or refractory B-cell non-Hodgkin lymphoma (LOTIS 7). ClinicalTrials.gov registration number: NCT04970901. Updated May 22, 2025. Accessed June 12, 2025. https://clinicaltrials.gov/ct2/show/NCT04970901

[2] Alderuccio JP, Okada C, et al. Initial Results From LOTIS-7: A Phase 1b Study of Loncastuximab Tesirine Plus Glofitamab in Patients With Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) Poster presented at the European Hematology Association (EHA) Annual Meeting. June 12-15, 2025, Milan, Italy

[3] Data on File. ADC Therapeutics Press release Memo, November 11, 2024.

ADC Therapeutics encourages all health care professionals to report any adverse events and product quality complaints to medical information at 855-690-0340. Please consult the ZYNLONTA Prescribing Information.