Investigational Loncastuximab Tesirine-Ipyl – LOTIS-7 Clinical Trial

The safety and efficacy regarding the use of Loncastuximab tesirine with glofitamab has not been 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 glofitamab and to identify the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) for the combination.
    - 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 the Nov 17, 2025, data cutoff, 49 efficacy-evaluable 2L+ large B-cell Lymphoma patients (LBCL) treated with Loncastuximab tesirine (120 or 150 µg/kg) with ≥6 months follow-up were included. Eligible patients had R/R B-NHL, ECOG 0–2, measurable disease per Lugano 2014, and met regimen-specific prior therapy requirements (≥2 prior lines in Part 1; ≥1 prior line in Part 2). Patients with clinically significant third-space fluid accumulation were excluded. Prior ASCT or CAR-T (>100 days) was permitted.
    - The grade ≥3 treatment emergent adverse events (TEAEs) occurring in >5% of patients included neutropenia (32.7%), increase in GGT (16.3%), anemia (10.2%), decrease in WBC (8.2%), generalized edema (8.2%), increase in ALT (8.2%), increase in AST (6.1%), and thrombocytopenia (6.1%).
    - Two Grade 5 AEs were reported: one non-treatment-related sepsis event and one treatment-related generalized edema occurring >105 days after the last dose.
    - CRS occurred in 25.0% of patients in the 150 µg/kg cohort and 52.4% in the 120 µg/kg cohort; all but one event were considered low grade.
    - ICANS was reported in 4.1% of patients (all Grade 1–2), with all cases resolving completely.
- 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.
    - 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

- As of November 17, 2025, 49 patients with R/R B-NHL had received ≥1 dose of treatment at the Lonca 120(n=21) or 150 (n=28) µg/kg dose level and with ≥ 6months follow up.[4]
    - 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[1,4]

- 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 November 17, 2025, the treated population (N=49) 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.[4]
    - Among these patients, the median age was 70 years; 71.4% had de novo DLBCL, 14.5% had trFL; 38.8% had received ≥2 prior therapies (median of 2 prior lines), and 16.3% had received prior CAR-T therapy.
    - There were 51% (25/49) patients who were refractory to primary therapy and 51% (25/49) were refractory to last prior therapy.

Results[3,4]

- As of the cutoff date November 17, 2025, there were 49 efficacy-evaluable patients.
    - The ORR was 89.8% (44/49) as assessed by Lugano criteria, and CR was achieved in 77.8% (38/49) across the 120 and 150ug/kg dose levels. Of the 49 efficacy evaluable patients, 33 of 38 CRs remained in CR at the data cutoff.
        - Fourteen patients converted from stable disease (SD) or partial response (PR) to CR overtime.
        - Among patients previously treated with CAR-T, 6/8 achieved CR.
    - The median time to first response was 42 days (range 36-148)**.** The median time to complete response (CR) was 43 days (37-336)

Safety[3,4]

- As of the cutoff date November 17, 2025, in the treated population (n=49) 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.[3,4]
    - The grade ≥3 TEAEs occurring in >5% of patients included neutropenia (32.7%), increase in GGT (16.3%), anemia (10.2%), decrease in WBC (8.2%), generalized edema (8.2%), increase in ALT (8.2%), increase in AST (6.1%), and thrombocytopenia (6.1%).
    - There were two grade 5 AEs reported, one non-treatment-related sepsis event and one treatment-related generalized edema that occurred >105 days after the last dose.
    - CRS occurred in 25.0% of patients in the 150 µg/kg cohort and 52.4% in the 120 µg/kg cohort; all but one event were considered low grade (based on American Society for Transplantation and Cellular Therapy (ASTCT) guidelines).
        - Grade 1 and 2 CRS cases were managed with tocilizumab, corticosteroids, acetaminophen, and/or fluid bolus, without ICU admittance or pressor support.
        - Grade 3 CRS case was managed with tocilizumab, acetaminophen, dexamethasone, norepinephrine with ICU admittance.
    - ICANS was reported in 4.1% of patients (all Grade 1–2), with all cases resolving completely.

- Both patients resumed treatment and achieved a CR.
- ICANS were managed primarily with corticosteroids.

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 November 13, 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.

[4] Data on File. ADC Therapeutics, LOTIS 7 update memo, December 3, 2025.

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.