Investigational Loncastuximab Tesirine–LOTIS-5 Study

The safety and efficacy regarding the use of Loncastuximab tesirine in combination with rituximab has not been established or 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 (R/R) 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-5 (NCT04384484) is a Phase 3, open-label, two-part, two-arm, multicenter confirmatory study evaluating the efficacy and safety of loncastuximab tesirine (Lonca) combined with rituximab (Lonca-R) compared to treatment with combination therapy of rituximab, gemcitabine, and oxaliplatin (R-GemOx) in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) who have received ≥1 multi-agent systemic therapy and who are not candidates for stem cell transplantation (SCT).[1]
- The primary endpoint of the study is progression-free survival (PFS) by independent central review, defined as the time between randomization and the first documentation of recurrence or progression, or death from any cause.[1]
- Key secondary endpoints include overall survival (OS), overall response rate (ORR), safety, duration of response (DOR), pharmacokinetic parameters, and changes in patient-reported outcomes.[1]
- In Part 1, patients will receive Lonca 150 µg/kg in combination with rituximab 375 mg/m^2 every 3 weeks (Q3W) for 2 cycles, followed by Lonca 75 µg/kg in combination with rituximab 375 mg/m^2 Q3W for 6 additional cycles.[1]
    - Both Lonca and rituximab are administered intravenously (IV) on Day 1 of each 21-day cycle.[1]
    - Twenty patients were enrolled in part 1 in a nonrandomized safety run-in study.[3]
    - At data cut off Oct 4, 2024, the ORR by central review was 16/20 (80%); a total of 10/20 (50%) and 6/20 (30%) patients attained CR and PR, respectively.[3]
    - At data cut off Oct 4, 2024, Lonca-R demonstrated no new safety signals in patients with R/R DLBCL in a nonrandomized safety run-in period (part 1).[3.]
    - Lonca-R showed encouraging antitumor activity in patients with R/R DLBCL in a nonrandomized safety run-in period (part 1) and initial signs of response durability with Lonca-R are promising.[3]
- In Part 2, approximately 420 patients will be randomized in a 1:1 fashion to receive either Lonca-R or R-GemOx. Patients randomized to the Lonca-R treatment arm will receive Lonca 150 µg/kg in combination with rituximab 375 mg/m^2 Q3W for 2 cycles, followed by Lonca 75 µg/kg in combination with rituximab 375 mg/m^2 Q3W for 6 additional cycles. Patients randomized to the R-GemOX arm will receive combination therapy with rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2, and oxaliplatin 100 mg/m^2 every 2 weeks (Q2W) for up to 8 cycles.[1,3.]
    - Rituximab, gemcitabine, and oxaliplatin are administered IV on Day 1 of each 14-day cycle.

- Enrollment for the nonrandomized safety run-in (part 1) and the randomized study (part 2) of LOTIS-5 is complete.[1,3]

Study Overview

LOTIS-5 Study Design

- LOTIS-5 (NCT04384484) is a Phase 3, open-label, two-part, two-arm, multicenter study evaluating the efficacy and safety of Lonca-R compared to R-GemOx in patients with R/R DLBCL who have received ≥1 multi-agent systemic therapy and who are not candidates for SCT.[1]
    - In Part 1, the first 20 patients will be non-randomly assigned to a safety run-in and the safety of Lonca-R in the first 20 patients who complete Cycle 1 will be compared with prior safety data for Lonca as a monotherapy.[1,3.]
        - A run-in is a planned time period from patient enrollment to randomization that increases the probability of detecting a potential treatment effect or enables exclusion of certain patients, for example, if they experience harms.[2]
    - If no significant increase in toxicity is observed, Part 2 will be initiated and approximately 420 patients will be randomized in a 1:1 fashion to receive Lonca-R or R-GemOx.[1,3.]
    - Enrollment for the nonrandomized safety run-in (part 1) and the randomized study (part 2) of LOTIS-5 is complete.[1,3]

Inclusion/Exclusion Criteria

- Key select inclusion criteria include adults (≥18 years of age) with a pathologic diagnosis of R/R DLBCL (including DLBCL transformed from indolent lymphoma), or high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements; R/R disease following at least one multi-agent systemic treatment regimen; measurable disease (2014 Lugano Classification); not a candidate for SCT based on performance status, advanced age, and/or significant medical comorbidities (as considered by the investigator); Eastern Cooperative Oncology Group (ECOG) performance status 0–2; and adequate organ function.[1,3]
- Key select exclusion criteria include previous treatment with Lonca or R-GemOx; known history of hypersensitivity to or positive serum human ADA to a CD19 antibody; pathologic diagnosis of Burkitt lymphoma; autologous SCT or allogeneic SCT within 30 days or 60 days, respectively, prior to study drug initiation (Cycle 1, Day 1); active graft-versus-host disease; post-transplantation lymphoproliferative disorders; lymphoma with active CNS involvement, including leptomeningeal disease; serologic evidence of chronic hepatitis B virus (HBV) infection and unable or unwilling to receive standard prophylactic antiviral therapy or with detectable HBV viral load; serologic evidence of hepatitis C virus (HCV) infection without completion of curative treatment or with detectable HCV viral load; clinically significant third-space fluid accumulation (i.e., ascites requiring drainage, or pleural effusion either requiring drainage or associated with shortness of breath); and major surgery, radiotherapy, chemotherapy, or other antineoplastic therapy within 14 days prior to start of study drug, unless approved by Sponsor.[1]

Treatment

- In Part 1, patients will receive Lonca 150 µg/kg in combination with rituximab 375 mg/m^2 every 3 weeks (Q3W) for 2 cycles, followed by Lonca 75 µg/kg in combination with rituximab 375 mg/m^2 Q3W for 6 additional cycles.[1,3.]
    - Both Lonca and rituximab are administered intravenously (IV) on Day 1 of each 21-day cycle.
    - Twenty patients were enrolled in part 1 in a nonrandomized safety run-in study.[3]
- In Part 2, patients will be randomized in a 1:1 fashion to receive either Lonca-R or R-GemOx.[1,3.]
    - Patients randomized to the Lonca-R treatment arm will receive Lonca 150 µg/kg in combination with rituximab 375 mg/m^2 Q3W for 2 cycles, followed by Lonca 75 µg/kg in combination with rituximab 375 mg/m^2 Q3W for 6 additional cycles.
    - Patients randomized to the R-GemOX will receive rituximab 375 mg/m^2 + gemcitabine 1000 mg/m^2 + oxaliplatin 100 mg/m^2 every 2 weeks (Q2W) for up to 8 cycles.
    - Rituximab, gemcitabine, and oxaliplatin are administered IV on Day 1 of each 14-day cycle.
- For both parts of the study, irrespective of disease status, patients will be followed for up to 4 years after end of treatment (EOT) until withdrawal of consent, loss of follow up, or death, whichever occurs first.[1,3.]

Study Objectives and Endpoints

- The primary objective of the study is to evaluate the efficacy of Lonca-R versus R-GemOx.[1,3.]
- The primary endpoint is PFS by independent central review; PFS is defined as the time between randomization and the first documentation of recurrence or progression, or death from any cause.[1]
- Secondary objectives include further efficacy evaluation; characterization of the safety profile of Lonca-R; characterization of the PK profile of Lonca-R; evaluation of the immunogenicity of Lonca-R; and evaluation of the impact of Lonca-R on PROs and overall health status.[1,3.]
- Secondary endpoints include OS, ORR, complete response (CR), partial response (CR), DoR, frequency and severity of adverse events, PK parameters for Lonca, ADA titers to Lonca, and changes in PROs from baseline.[1,3.]

Results[3]

- At data cut off October 4, 2024, the ORR by central review was 16/20 (80%); a total of 10/20 (50%) and 6/20 (30%) patients attained CR and PR, respectively.
    - The median duration of response (DOR) in responders was 8.0 months (95% CI, 3.2, NR),the median PFS was 8.3 months (95% CI, 4.5, NR) and the median duration of complete response was NR.
        - Seven (35%) patients in the safety run-in completed up to 8 cycles of treatment.
        - Four (20%) patients withdrew from treatment due to adverse events.
    - Five patients have remained in CR beyond the end of treatment (EOT). One patient went to stem cell transplant (SCT) and 4 patients maintained CR for more than 28.5 months beyond EOT (follow-up for these 4 patients is still ongoing)

        - Among the 4 ongoing CRs, 2 were ctDNA evaluable, and both were MRD negative
    - One patient who achieved CR was refractory to most recent prior treatment.
- The median age of the 20 patients included in the safety run-in was 74.5 years (range 35-93) and they received a median of 1 previous therapy(range1-7).
    - The median number of doses administered was 5 (range 1-8), and the median duration of follow-up was 37.2 months (range 34.1-41.5).
- C_{max} and C_{trough} values were comparable between Lonca monotherapy and combination therapy with rituximab, which suggests that there's no significant pharmacokinetic (PK) interaction, with no dose adjustments needed when combining Lonca with rituximab.

Safety[3]

- At data cut off October 4, 2024, Lonca-R demonstrated no new safety signals in patients with R/R DLBCL in a nonrandomized safety run-in period (part 1).
- All patients had at least 1 TEAE, and 11 (55%) patients had grade ≥3 TEAEs.
    - The most common grade ≥3 TEAEs were increased GGT 25% (n=5), and neutropenia 20% (n=4).
    - Serious AEs were observed in 45% (n=9) patients, the most common of which was infection in 30% (n=6).
    - Additional adverse events of interest (any grade): photosensitivity, in 15% (n=3); pleural effusion, 15% (n=3), and edema, 5% (n=1).
    - There were 9 deaths observed at data cut off, 25% (n=5) from disease progression, 10% (n=2) from COVID-19 infection, 5% (n=1) from pancreatic neoplasia, and 5% (n=1) from liver failure.

References

[1] Study to Evaluate Loncastuximab Tesirine with Rituximab Versus Immunochemotherapy in Participants with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (LOTIS 5). ClinicalTrials.gov Identifier: NCT04384484. Updated May 30, 2025. Accessed June 4, 2025. https://clinicaltrials.gov/ct2/show/NCT04384484

[2] Laursen DRT, Paludan-Müller AS, Hróbjartsson A. Randomized clinical trials with run-in periods: frequency, characteristics, and reporting. Clin Epidemiol. 2019;11:169-184. Published 2019 Feb 11. doi:10.2147/CLEP.S188752

[3] Carlo-Stella C, Kwiatek M, et al. 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. Poster presented at the 30th annual congress of the European Hematology Association (EHA 2025). June 12-15, 2025, Milan Italy.