Use of Loncastuximab Tesirine in the Treatment of Marginal Zone Lymphoma

The safety and efficacy regarding the use of Loncastuximab tesirine for the treatment of marginal zone lymphoma (MZL) 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-1 was a Phase 1, open-label, dose-escalation (Part 1) and dose-expansion (Part2) study that evaluated the safety and tolerability of loncastuximab tesirine (Lonca), used as monotherapy, in 183 adult patients with relapsed or refractory B-cell Non-Hodgin Lymphoma (r/r/B-NHL).[1]
    - Lonca demonstrated an overall response rate (ORR) of 45.6%, which included a small subset of patients (n=6) with marginal zone lymphoma (MZL).
- A Phase 2, investigator-initiated multicenter, open-label study was conducted to evaluate the efficacy and safety of loncastuximab tesirine (Lonca), in adult patients (≥18 years of age) with relapsed or refractory (R/R) marginal zone lymphoma (MZL). Please refer to clinicaltrials.gov for more information.[2,3] www.clinicaltrials.gov/study/NCT05296070
    - As of data cut off February 10, 2025, the study enrolled 27 patients with R/R MZL, who had received at least one prior line of systemic therapy. This included patients with progression of disease within 24 months (POD24).
    - The analysis showed an overall response rate (ORR) of 85% (n=22/26 evaluable patients), with a complete response (CR) rate of 69% (n=18/26).
        - Among POD24 patients (n=13), the CR rate was 62%. Of note, one patient who had previously received CAR-T therapy achieved CR.
    - The median duration of CR at 18 months is 83%, the longest duration of CR is 27months.[2,3]
- Most adverse events (AEs) were Grade 1 or 2, all 27 patients experienced AEs:

Background

- MZL accounts for approximately 7% of all non-Hodgkin lymphomas and is subdivided into extranodal (EMZL), nodal (NMZL), and splenic (SMZL) forms.[2]
    - Relapsed or refractory (R/R) MZL is characterized by limited treatment options, and achieving a complete response (CR) is rare in this setting.
    - Lonca is a novel CD19-targeting antibody-drug under investigation for its ability to induce durable CRs in R/R MZL patients.

Investigator Initiated Trial

Study Design

- NCT05296070 is a Phase 2, open-label, study evaluating the safety and efficacy of loncastuximab tesirine in R/R MZL. The study enrolled adults with R/R MZL requiring treatment due to symptomatic disease or POD24.[2,4]

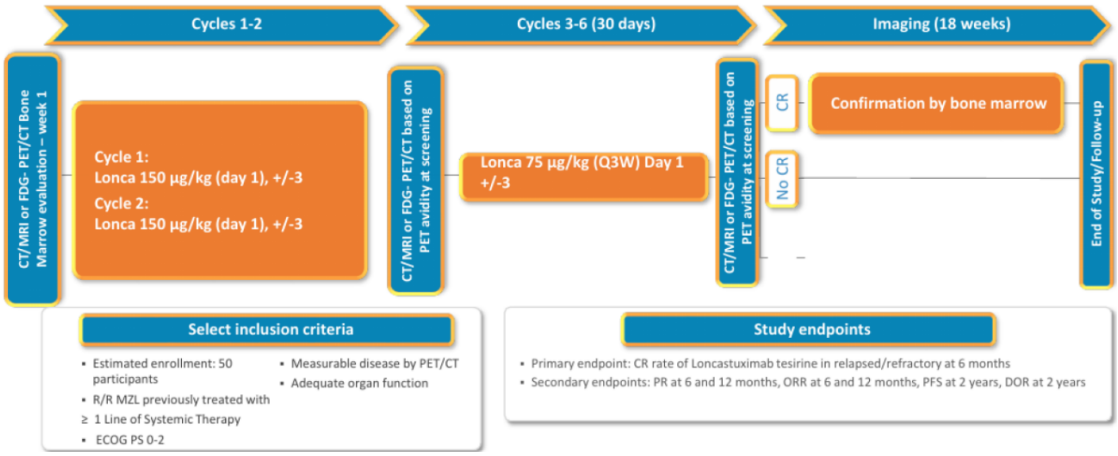
    - Patients were included if they had prior systemic therapy (≥1 line), disease staging for patients was done via (Positron Emission Tomography-Computed Tomography) (PET-CT), CT, or magnetic resonance imaging) MRI per Lugano 2014 criteria.
- The study applied a Bayesian Optimal Phase 2 design with interim analyses after 20 and 40 evaluable patients, with a final analysis projected at 50 evaluable patients.[2]
    - Key baseline characteristics included a median age of 67years with majority being female (70%). Most patients presented with advanced-stage disease (Stage IV, 74%), 59% had EMZL, 26% had NMZL, and 15% had SMZL. Additionally, 48% of patients experienced POD24 following immunochemotherapy.
    - Patients had a median line of prior therapy of 2 (range 1-4), Rituximab was the most common previously used systemic treatment (37%).
    - A total of 27 patients were enrolled from July 2022 to February 2025.

Inclusion/Exclusion Criteria[4]

- Key inclusion criteria were adult patients diagnosed with R/R MZL, who previously received ≥ 1 line of systemic therapy, including ≥ 1 anti-CD20 antibody. Additional criteria were an ECOG performance status of 0-2, measurable disease confirmed by PET/CT, and adequate organ function.[3]
- Key exclusion criteria included evidence of DLBCL transformation or transformed lymphoma, prior treatment with anti-CD19 therapies, more than six lines of systemic therapy, clinically significant pleural effusions, pericardial effusions, or ascites requiring drainage or associated with symptoms, concurrent use of investigational agents, known central nervous system involvement of lymphoma, unresolved treatment-related toxicities (Grade ≥2), uncontrolled intercurrent illness, breastfeeding or pregnant women, active hepatitis B or C infection, history of HIV infection, and patients with impaired decision-making capacity.[4]

Treatment

Adopted from Lossos et al 2025[2]



- Lonca was given 0.15 mg/kg IV every 3 weeks for two cycles, followed by 0.075 mg/kg for four cycles.[2,4]
    - Premedication with dexamethasone (4mg twice daily for 3 days) and spironolactone (100mg) were required per protocol and were used to mitigate fluid retention.

Study Objectives and Endpoints

- The primary study objective was CR of lonca in patients with R/R MZL after 6 cycles based on Lugano 2014 criteria using PETCT (if FDG avid at presentation) or MRI or CT (for nonavid disease)[2,4]
- The secondary study objective was partial response (PR) at 6 and 12 months, ORR at 6 and 12 months, progression-free survival (PFS) at 2 years, overall survival (OS) at 2 years, duration of response (DoR) at 2 years, and treatment related toxicities at 7 months.[2,4]

Results

- As of the data cutoff (February 10, 2025), 26 patients were evaluable for response.[2,3]
    - The ORR achieved was 85% (n=22/26), with a CR in 69% of the patients (n=18/26).
        - CR was achieved in 62% of POD24 patients (n=8/13).
        - One patient previously treated with CAR-T therapy achieved CR.
- At the conclusion of the treatment, 17 patients remained in CR, with a median CR duration of 18 months.[2,3]
    - The median duration of CR (DoCR) at 18months is 83%, with ongoing responses at 27 months in certain patients.
    - The median DoCR was not reached, but by reverse Kaplan-Meier method the median DoCR was estimated to be 13.7 months, and the median duration of CR/PR was 13.2 months with 20 of 22 responses ongoing.
    - The estimated PFS rate at 12months was 92.9%, all 27 patients are alive as of the data cutoff.

Safety

- Lonca was generally well tolerated, and the observed safety was consistent with the known profile.[2,3]
- All 27 patients experienced at least one treatment-emergent adverse event (TEAE), but they were mostly in Grade 1 or 2.[2,3]
    - Grade 3 and Grade 4 AEs occurred in 65.2% (n=15/23), including Grade 3 LFT elevations (n=5), Grade 4 neutropenia (n=1), RSV lung infection (n=1) and hyponatremia (n=1).
- Three patients required dose reductions, while one patient discontinued treatment after cycle 4 due to cholestatic hepatitis. The patient fully recovered, with LFTs returning to normal levels.[2,3]

References

[1]Hamadani M, Radford J, Carlo-Stella C, et al. Final Results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood. 2020. https://doi.org/10.1182/blood.2020007512.

[2]Lossos IS, et al. Updated Analysis of a Phase 2 multicenter study of loncastuximab in relapsed/refractory marginal zone lymphoma demonstrates high rate of complete responses Presented at International Conference on Malignant Lymphoma (ICML) June 17-21 Lugano Switzerland.

[3]Data on File, MZL presentation Dr.Lossos June 2025

[4]Open-label of loncastuximab tesirine (ADCT-402) in relapsed/refractory marginal zone lymphoma. ClinicalTrials.gov identifier: NCT05296070. Updated May 21, 2025. Accessed June 16, 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.