Use of Loncastuximab Tesirine in the treatment of Follicular Lymphoma

The safety and efficacy regarding the use of Loncastuximab tesirine for the treatment of follicular lymphoma (FL) 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. ADC Therapeutics plans to support the expansion of Loncastuximab + rituximab (Lonca-R) Investigator-initiated study to further evaluate the efficacy, safety, and durability of Lonca-R in patients with high-risk follicular lymphoma (including those with POD24, high disease burden and/or advanced disease).

Summary

- LOTIS-1 was a Phase 1, open-label, dose-escalation (Part 1) and dose-expansion (Part 2) study that evaluated the safety and tolerability of loncastuximab tesirine, used as monotherapy, in 183 adult patients with relapsed or refractory B-cell Non-Hodgkin Lymphoma (r/r B-NHL).[1]
- Tumor burden was assessed in the phase 1 study, and tumor was found to be responsive to loncastuximab tesirine, with durable responses seen in a proportion of patients with diffuse large B-cell Lymphoma (DLBCL), marginal cell lymphoma (MCL), and follicular lymphoma (FL).[1]
    - Of the 183 patients, 14 patients (7.7%) that had FL were included in the study,
    - The overall response rate (ORR), complete response (CR), and partial response (PR) in the FL group was 11/14 (78.6%), 9/14 (64.3%), 2/14 (14.3%) respectively.
    - Of the 11 patients that had a CR, 4 were dosed with loncastuximab tesirine 120 µg/kg, 5 were dosed with 150µg/kg, and 2 were dosed with 200µg/kg.
    - The median duration of response (DOR) and median overall survival (OS) of loncastuximab in the FL group was not reached.
    - The median progression free survival (PFS) could not be determined in the FL group because of the low number of events.
    - In addition, 26 patients with transformed FL were treated in the Phase 1 study.[1] Subsequently, 13 patients with transformed FL were enrolled on the phase II study testing single agent loncastuximab tesirine in r/r DLBCL (NCT03589469). No safety signals were observed, and duration of response was not reached in transformed FL.
- Preclinical data has demonstrated synergistic activity between rituximab-induced cytotoxicity in combination with Loncastuximab tesirine. The combination (lonca +R) had a significant survival benefit compared to rituximab monotherapy.[3]
- A Phase 2, investigator-initiated study was conducted to evaluate the safety and tolerability of Loncastuximab tesirine (Lonca) and Rituximab in R/R FL. Please refer to clinicaltrials.gov for more information. www.clinicaltrials.gov/study/NCT04998669
    - At the data cutoff of September 13, 2024, thirty-nine patients were evaluated for response, the ORR was 97%, with a CR rate of 67%.
    - After a median follow-up of 18.2 months, the median duration of CR was 16.2 months.
    - The median PFS and overall survival (OS) were not yet reached.
    - The most common grade 3 adverse events (Aes) included neutropenia (13%), and lymphopenia (21%)

Background

- B-NHL includes both aggressive, most commonly DLBCL, and indolent types, most commonly FL.[1]
- Indolent forms of B-NHL, such as FL, generally respond to treatment but are infrequently curable, and patients with early relapse have particularly poor outcomes.[1]
- Expression of CD19 is maintained in B-cell malignancies, including DLBCL, Burkitt's lymphoma, and FL.[1]
- There is currently no standard of care for the treatment of r/r FL particularly in patients with worse prognosis, including patients with disease progression within 24 months (POD24) of 1L immunochemotherapy treatment.[3]

Investigator Initiated Trial (IIT)

Study Design[3,4]

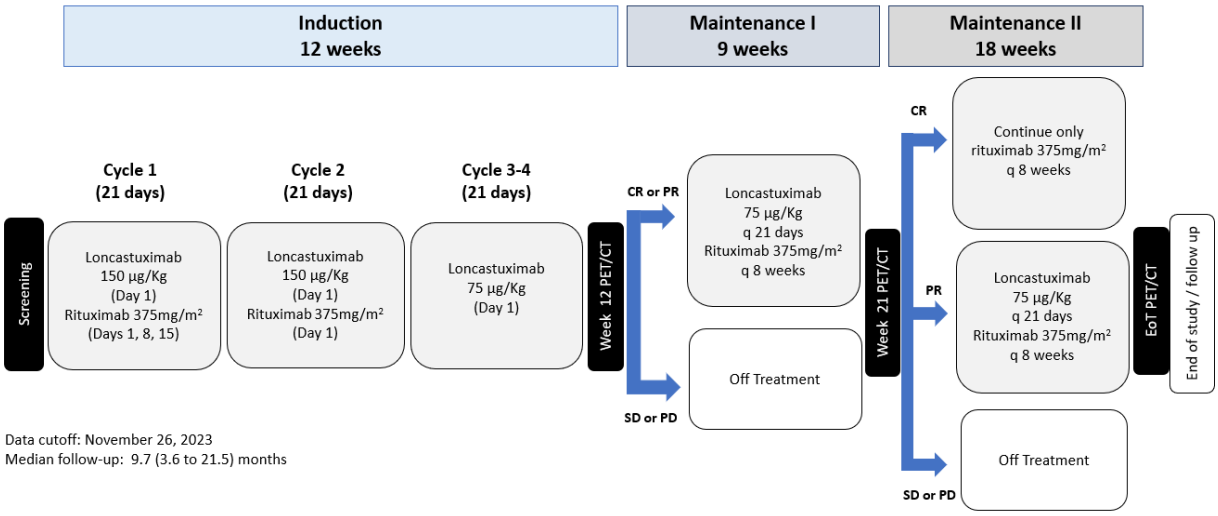
- NCT04998669 is a phase 2 single-arm, open-label, study of Loncastuximab Tesirine in combination with Rituximab in patients with relapsed or refractory Follicular Lymphoma.[3,]
- Enrollment of patients occurred according to simon's minimax two-stage design with a total estimated enrollment of 39 patients based upon a projected CR rate ≥50% vs ≤30% null hypothesis(H0).
- At data cut off September 13, 2024, thirty-nine patients were enrolled between January 22 to June 2024:
    - Key baseline characteristics of the patients enrolled in the study included a median age of 68 years (range: 47–89), with the majority being male (54%). 51% (20) of patients experienced progression of disease within 24 months (POD24) following immunochemotherapy, and 92% of patients met the high-tumor burden criteria as defined by the Groupe d'Etude des Lymphomes Folliculaires (GELF).
    - Patients had a median line of prior therapy of 1 (range 1-6), R-CHOP was the most common first-line therapy (56%) followed by bendamustine with rituximab and single-agent rituximab (26% and 15% respectively).

Inclusion/Exclusion Criteria

- Key inclusion criteria are age ≥18 years, histologic confirmation of FL (Grade 1, 2, 3A) from most recent tumor biopsy; relapsed or refractory (R/R) disease following ≥1 treatment regimens (having ≥ 1 Groupe d'Etude des Lymphomes (GELF) criteria for therapy, or POD24, or second relapse), at least one measurable disease per 2014 Lugano Classification, Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, normal organ and marrow function (defined by protocol).[2]
- Furthermore, patients with progression or relapse within 24 months of frontline treatment previously treated with ≥1 line of systemic therapy; or second FL relapse/progression after ≥1 line of systemic therapy. These patients will be eligible independently of GELF criteria and POD24.[2]
- Key exclusion criteria include FL grade 3B or transformed FL, ≥ 6 lines of systemic immunochemotherapy for treatment of FL, patients with clinically significant pleural effusions and/or ascites requiring drainage or associated with shortness of breath, receiving any other investigational agents, patients with known central nervous system involvement of lymphoma, uncontrolled intercurrent illness, breastfeeding, or pregnant women, serologic status reflecting active hepatitis B or C infection, history of Human immunodeficiency virus (HIV) infection and patients with impaired decision-making capacity.[2]

Treatment

Table 1: Study schema. Adopted from Alderuccio[3]



- Patients were given intravenous (I.V) infusion of Loncastuximab tesirine and I.V Rituximab at induction, and maintenance phases.[2,3.]
    - Lonca was administered on day 1 of a 21-day cycle, at 150 ug/kg for two cycles, then 75 ug/kg thereafter. Intravenous rituximab was administered on day 1 of cycle 1, at 375 mg/m2 for four once-weekly doses during induction, followed by one dose every 8 weeks during the 9-week maintenance (for a total of seven doses of lonca and five doses of rituximab during the initial 21 weeks).
    - Patients achieving CR at week 21 discontinued lonca and received two more doses of rituximab every 8 weeks. Patients achieving PR at week 21 continued lonca every 21 days and rituximab every 8 weeks for 18 more weeks (for a total of 13 doses of lonca and 7 doses of rituximab).
    - Bone marrow biopsy was required at screening and repeated at 12 weeks if there was initial involvement.[2.]
    - Premedication with dexamethasone 4mg twice daily for 3 days was required for all patients.[2]

Study Objectives and Endpoints

- The primary study objective was to determine the CR rate at end of induction phase (around week 12 of treatment) in patients with R/R FL previously treated with ≥1 line of systemic therapy receiving the combined treatment loncastuximab tesirine plus rituximab by Fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET) (FDG-PET)/ Computerized Tomography (CT).[2,3.]
    - Response to treatment (CR, PR, SD (Stable Disease), PD (Progressive Disease) will be assessed using FDG-PECT/CT following Lugano 2014 criteria by week 12 of treatment. CR will be defined by a Deauville score of ≤ 3.
- The secondary study objective was to determine the overall response rate (CR + PR) at end of induction phase in FL.[2,3.]
    - Response to treatment will be assessed using FDG-PET/CT following Lugano 2014 criteria by week 12 of treatment. CR will be defined by a Deauville score of ≤ 3, and PR by a Deauville score of 4 or 5 with reduced uptake from baseline.

- The exploratory study objective was to confirm the safety and tolerability of combined treatment loncastuximab tesirine plus rituximab in patients with r/r FL.[2,3]

Efficacy [3,4]

- At the data cutoff of September 13, 2024, thirty-nine patients were evaluated for response:
    - The ORR was 97%, with a CR rate of %.
        - At week 12, the ORR was 97% (38/39), with 67% (26/39) achieving CR. All patients achieving CR at week 12 maintained their response.
        - Of the 12 patients with a PR at week 12, 4 subsequently improved to CR on later imaging assessments, resulting in an overall best CR rate of 79% (30/39).
- The first response assessment occurred 12 weeks after the first dose of Lonca-R, with a median time to response and time to CR of 2.7 months. After a median follow-up of 18.2 months:
    - The median duration of CR was 16.2 months.
    - The median progression-free survival (PFS) and overall survival (OS) were not yet reached.
- In the post-hoc efficacy analysis, patients with POD24 (n=20) demonstrated a best overall ORR of 100%, with a best CR rate of 85%. Additionally, patients with high-risk FLIPI scores (n=24) achieved a best ORR of 96% and a best CR rate of 67%.

Adverse Events[3,4]

- The safety profile in patients with FL was consistent with prior studies in large B-cell lymphoma with no new safety signals.
- The most common treatment-emergent adverse events (TEAEs) included hyperglycemia (44%), alkaline phosphatase elevation (41%), neutropenia (38%), fatigue (38%), increased AST (38%), and increased ALT (38%).
    - TEAEs leading to treatment discontinuation occurred in 1/39 (3%) of patients.
    - A dose reduction for loncastuximab tesirine was required in 4 patients (10%).
    - Sixteen serious AEs occurred in 10 patients, with 4/10 considered related to study drugs.
- Grade 3 neutropenia occurred in 5 cases (13%), with a single episode of neutropenic fever in a patient with cellulitis after upper extremity trauma.
    - Fluid accumulation was mostly grade ≤2 and manageable with diuretics.
    - Infections were uncommon and were mostly upper respiratory infections (13%).
    - No treatment-related deaths occurred during the study.
- All patients received planned doses of lonca except 4 patients who were removed from the study.
    - Of the 4 patients removed from the study, one was removed due to disease progression on week 12 PET/CT with biopsy-proven dlbcl in a kidney mass, and cholangiocarcinoma. As of data cut off, Patient is currently in CR from both malignancies.
    - Two patients had transformation to large B-cell lymphoma (LBCL), and one patient had adrenal insufficiency.

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]A Phase 2, Single-arm, Open-label, study of Loncastuximab Tesirine in Combination with Rituximab in Patients with Relapsed or Refractory Follicular Lymphoma. ClinicalTrials.gov Identifier: NCT04998669. Updated August 22, 2024. Accessed December 2, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT04998669
[3]Alderuccio JP, Alencar AJ, Schatz JH, et al. Loncastuximab Tesirine with Rituximab in patients with relapsed or refractory follicular lymphoma- A single-centre, single-arm, phase 2 trial. Lancet Hematol 2024. doi: 10.1016/S2352-3026(24)00345-4. Epub ahead of print.
[4]Alderuccio JP, Alencar AJ, Schatz JH, et al. Loncastuximab Tesirine with Rituximab in patients with relapsed or refractory follicular lymphoma- A single-centre, single-arm, phase 2 trial. Oral presentation at ASH 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.