ZYNLONTA® (loncastuximab tesirine-lpyl) – Subsequent Chimeric Antigen Receptor T-cell (CAR-T) Therapy

Summary

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study which evaluated the safety and tolerability of ZYNLONTA monotherapy in 183 adult patients (≥ 18 years of age) with relapsed or refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL).[1]
    - One patient received subsequent chimeric antigen receptor T-cell (CAR-T) therapy. No additional Information regarding this patient was available.
- LOTIS-2 was a Phase 2, open-label, single-arm, multicenter study which evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 patients (≥18 years of age) with R/R diffuse large B-cell lymphoma (DLBCL) following ≥2 lines of prior systemic therapy.[2]
    - The LOTIS-2 publication data cut-off (April 6, 2020) reported that 15 patients (10%) received CD19-directed CAR-T therapy following treatment with ZYNLONTA.[2]
    - The final analysis from LOTIS-2, data cut-off (September 15, 2022) reported 16 patients (11%) received CD19-directed CAR-T therapy with an investigator-assessed ORR of 56.3%, CR was reported in 8 (50%) patients, and PR was reported in 1 (6.3%) patient.[4]
- In an independently conducted retrospective analysis prior to the Phase 2 publication and subsequent data cut-off of March 01, 2021, investigators retrieved data from 14 patients from the Phase 1 and Phase 2 studies with ZYNLONTA. The patients' median age was 58.5 years.[5]
    - Following CAR-T therapy (at 3 months), the ORR was 50%, with 6 patients (43%) and 1 patient (7%) attained a complete and partial response, respectively. Seven patients (50%) had refractory disease following CAR-T therapy.
    - Grade 1 to 2 cytokine release syndrome occurred in 7 patients (50%). Grade 1 immune effector cell–associated neurotoxicity syndrome (ICANS) was reported in 4 patients (29%), while 1 patient experienced Grade 4 ICANS.

Background

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study which evaluated the safety and tolerability of ZYNLONTA monotherapy in 183 adult patients with R/R B-NHL. The study was conducted in two parts, dose-escalation (Part 1) followed by dose-expansion (Part 2).[1]
    - Male or female patients (≥18 years of age) with histologically confirmed R/R B-NHL were enrolled if they failed or became intolerant to established therapies or if they had no other treatment options available. Patients who might receive hematopoietic stem cell transplant in the future were eligible for enrollment.
- LOTIS-2 was a Phase 2, open-label, single-arm, multicenter study which evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 male or female patients (≥18 years of age) with R/R DLBCL following ≥2 lines of prior systemic therapy.[2,3]

Clinical Data

LOTIS-1 (Phase 1)

- In LOTIS-1, one patient received subsequent CAR-T therapy. No additional information regarding this patient was available.[1]

LOTIS-2 (Phase 2)

- The LOTIS-2 publication data cut of (April 6, 2020) reported that 15 patients (10%) received CD19-directed CAR-T therapy following treatment with ZYNLONTA.[2]
    - Investigator-assessed ORR to CAR-T therapy after treatment with ZYNLONTA was 47% (n=7), with a CR of 40% (n=6) and a PR of 6.7% (n=1).
- The final analysis from LOTIS-2, data cut-off (September 15, 2022) reported 16 patients (11%) received CD19-directed CAR-T therapy with an investigator-assessed ORR of 56.3%, CR was reported in 8 (50%) patients, and PR was reported in 1 (6.3%) patient.[4]
    - Two patients (12.5%) of the 16 patients who received CAR-T therapy following treatment with ZYNLONTA experienced at least one Grade ≥3 AE.
        - Grade ≥3 AEs included anemia, hypophosphatemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia.[4]

Retrospective Analysis from LOTIS-1 and LOTIS-2[5]

- In an independently conducted retrospective analysis prior to the Phase 2 publication and subsequent data cut-off of March 01, 2021, investigators retrieved data from 14 patients who received CAR-T therapy following ZYNLONTA. The patients' median age was 58.5 years.
- Patients were identified from 2 open-label studies with ZYNLONTA (LOTIS-1 and LOTIS-2). The median interval between diagnosis of DLBCL and initiation of ZYLONTA was 21.5 months (range, 6.8 to 258), and patients received a median of 2 cycles (range, 1 to 7) of ZYNLONTA.
    - Following therapy with ZYNLONTA, 8 patients (57%) had refractory disease, 5 patients (36%) achieved a PR, while 1 patient (7%) attained a CR–the ORR was 43%. All responding patients experienced disease progression prior to receiving CAR-T.
    - Six patients (43%) received additional lines of therapy between ZYNLONTA and CAR-T treatment (median of 1 therapy line; range, 1 to 3), and of the 10 patients (71%) assessed for CD19 expression via immunohistochemical staining on repeat biopsies, all tested positive for C19 after ZYNLONTA failure.
    - Information regarding CD19 expression was not available for 4 patients (29%).
- All patients received standard lymphodepletion with fludarabine and cyclophosphamide prior to receiving CAR-T therapy. The median interval between treatment with ZYNLONTA and CAR-T was 120 days (range 22 to 600).
- Anti-CD19 CAR-T therapy received by patients consisted of the following: axicabtagene ciloleucel (n=5, 36%), tisagenlecleucel (n=2, 14%), investigational targeting CD19 (n=4; 29%), and JCAR017 (n=3, 21%).
    - Following CAR-T therapy, the best response at 3 months, included 6 patients (43%) with a CR and 1 patient (7%) with a PR (ORR = 50%), Seven patients (50%) had refractory disease following CAR-T therapy.[5]
    - Five of 6 complete remissions are ongoing at a median of 6 months (range, 6 to 11). One patient with complete remission relapsed after 11 months and was alive at the last follow-up (+22 months), whereas the patient attaining a partial remission died due to progressive lymphoma. Six out of the 7 patients who did not attain a CR died at a median of 5 months (range, 1 to 9) following CAR-T therapy. None of the 2 patients who received dual antigen targeting CARs (targeting CD19/ CD22 and CD19/CD20) attained a response.

- All 4 patients (29%) with unknown CD19 expression status following treatment with ZYNLONTA attained a complete remission with anti-CD19 CAR-T therapy.
- The median follow-up of survivors was 6 months (range, 3 to 22). Grade 1 to 2 cytokine release syndrome occurred in 7 patients (50%). Grade 1 ICANS was reported in 4 patients (29%) and only 1 patient (7%) experienced Grade 4 ICANS.

Literature Search

- A PubMed biomedical literature search conducted on April 14, 2025, yielded no further relevant data regarding the subsequent use of CAR-T therapy after ZYNLONTA; however, relevant real-world evidence exists, including a study on treatment patterns and outcomes in patients with large B-cell lymphoma (LBCL) who received ZYNLONTA prior to CAR-T therapy. (Hamadani et al Tandem 2024)

Relevant Prescribing Information

- Of the 145 patients enrolled, the median age was 66 years (range 23 to 94), 59% male, and 94% had an ECOG performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. The diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low-grade lymphoma), high-grade B-cell lymphoma in 8%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy.[6]

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*. 2021;137(19):2634-2645. doi:10.1182/blood.2020007512

[2] Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22(6):790-800. doi:10.1016/S1470-2045(21)00139-X

[3] Caimi PF, Ai WZ, Alderuccio JP, et al. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase 2 LOTIS-2 study. Haematol. Published online August 31, 2023. doi: 110.3324/haematol.2023.283459

[4] Data on File, LOTIS-2 Clinical Study Report. ADC Therapeutics.

[5]Thapa B, Caimi PF, Ardeshna KM, et al. CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy. Blood Adv. 2020;4(16):3850-3852. *Blood Adv*. 2020;4(19):4606. doi:10.1182/bloodadvances.2020003378

[6] ZYNLONTA® (loncastuximab tesirine-lpyl) for injection Prescribing Information, October 2022.

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.