ZYNLONTA® (loncastuximab tesirine-lpyl) – Use in Elderly Patients

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 with relapsed or refractory (R/R) B-Cell Non-Hodgkin's Lymphoma (B-NHL). The primary endpoint of Part 1 was to investigate the safety and tolerability of ZYNLONTA in R/R B-NHL and to determine the maximum tolerated dose (MTD) to recommend dose(s) for Part 2. The overall response rate (ORR) specifically for diffuse large B-cell lymphoma (DLBCL) patients in the LOTIS-1 study was 42.3% (95% CI: 33.9, 51.1).[1]
    - In patients 65 to <75 years of age with DLBCL (N=37), the overall response rate (ORR) was 48.6% (95% CI 31.9, 65.6). In patients ≥75 years of age with DLBCL (N=27), ORR was 55.6% (95% CI 35.3, 74.5).[4]
- 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 DLBCL following ≥2 lines of prior systemic therapy. The primary endpoint of the Phase 2 study was the overall response rate (ORR). In 145 evaluable patients, the ORR was 48.3% (95% CI 39.9, 56.7)
- Patients in LOTIS-2 were heavily pretreated, with 43.4% receiving 2 prior lines and a median of 3 prior systemic therapies, and 16.6% had received prior stem cell transplant.[5]
    - In patients 65 to <75 years of age (N=59), ORR was 45.8%. In patients ≥75 years of age (N=21), ORR was 52.4%.[6]
    - In patients <70 years of age (N=95), ORR was 48.4%, In patients ≥70 years of age (N=50), ORR was 48%.[5]
    - Incidence of treatment-emergent adverse events (TEAEs) were similar across all age groups (<65, <70, 65 to <75, ≥70, ≥75 years).[5,6.]
- Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients.[6]

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 relapsed or refractory R/R B-NHL. The study was conducted in two parts, dose-escalation (Part 1) followed by dose-expansion (Part 2). 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.[1]
    - The primary endpoint of Part 1 was to investigate the safety and tolerability of ZYNLONTA in R/R B-NHL and to determine the maximum tolerated dose (MTD) to recommend dose(s) for Part 2. The primary endpoint for Part 2 was to evaluate safety and tolerability at the recommended dose(s). In the DLBCL patient population of 137 patients, the ORR in 58 patients was 42.3% (95% CI: 33.9, 51.1).
- 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 DLBCL following ≥2 lines of prior systemic therapy.

- The primary endpoint was ORR according to the 2014 Lugano classification in all-treated patients. In 145 evaluable patients, the ORR was 48.3% (95% CI 39.9, 56.7). [2]
- Patients were heavily pretreated, with 43.4% receiving 2 prior lines and a median of 3 prior systemic therapies, and 16.6% had received prior stem cell transplant.[5]

Clinical Data

LOTIS-1 (Phase 1)

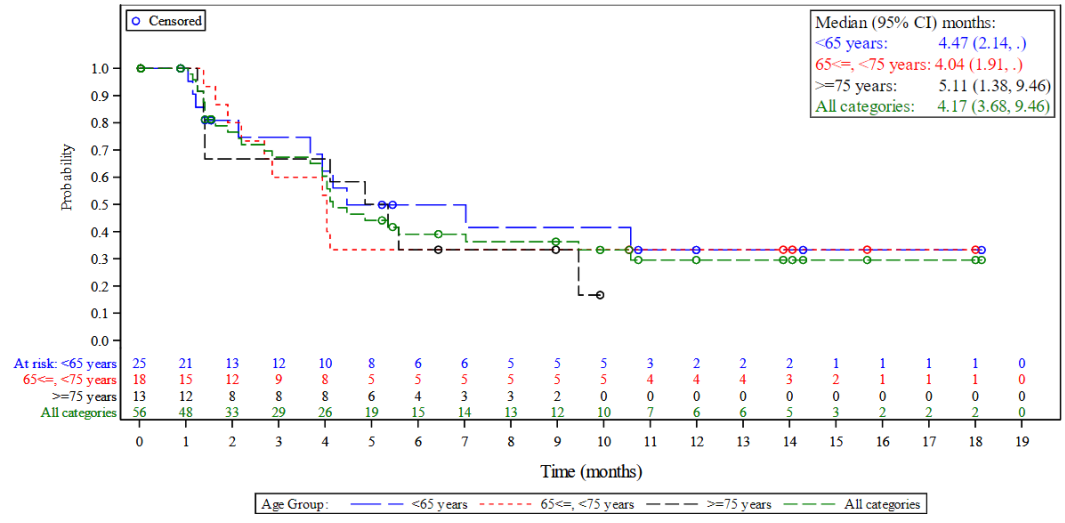
Efficacy

- In LOTIS 1, 183 patients (median age 63 years, range 20–87) received doses of ZYNLONTA from 15 µg/kg to 200 µg/kg every 3 weeks. Fifty (27.3%) patients were aged 65 to <75 years, and 34 (18.6%) patients were aged ≥75 years.
- Overall response rate (ORR) in all patients with B-NHL (180 evaluable) was 45.6% (95% CI: 38.1–53.1), including 48 (26.7%) complete responses (CR) and 34 (18.9%) partial responses (PR); median duration of response (DoR) was 5.4 months (95% CI: 4.0, not reached).[1,4]

DLBCL Subset

- From the overall population, 139 patients (76%) had DLBCL and 137 of these patients were evaluable. In patients 65 to <75 years of age (n=37), overall response rate (ORR) was 48.6% (95% CI 31.9, 65.6). In patients ≥75 years of age (n=27), ORR was 55.6% (95% CI 35.3, 74.5).
- Median duration or response (DOR) for patients ≥65 years of age to < 75 years of age was 4.04 months. For patients' ≥ 75 years of age, the DOR was 5.11 (95% CI: 1.38–9.46).[4]
- Figure 1 provides additional information regarding the DOR by age group.

Figure 1. Kaplan-Meier Plot of Duration of Response by Age Group for Dose ≥ 120 µg/kg in Diffuse Large B-Cell Lymphoma Patients - Efficacy Analysis Set (Part 1 and 2 Combined). Adopted from ADCT Data on File [4]



CI; confidence interval

Safety

- In the safety analysis set (N=183), 181 patients (98.9%) experienced at least one treatment emergent adverse event (TEAE). The most common hematologic TEAEs were as follows: platelet count decreased (71.1%), neutrophil count decreased (59.2%), anemia (32.8%), and white blood

cell count decreased (12%). Most commonly reported (≥ 20%) non-hematologic TEAEs were as follows: fatigue (42.6%), nausea (32.2%), peripheral edema (31.7%), gamma-glutamyl transferase (GGT) increase (31.1%), rash (24.6%), dyspnea (22.4%), constipation (21.9%), pleural effusion (21.3%), and blood alkaline phosphatase (ALP) increase (20.2%).

- Any Grade ≥3 TEAEs occurred in 141 (77%) of the 183 patients enrolled. Most common Grade ≥3 TEAEs included neutrophil count decreased (39.7%), platelet count decreased (26.7%), gamma glutamyl transferase (GGT) increased (21.3%), and anemia (15.3%).[1]

LOTIS-2 (Phase 2)

Efficacy

- 145 patients were enrolled in LOTIS 2 (median age 66 years, (range 23–94). Patients received ZYNLONTA 150 µg/kg as 30-minute intravenous infusion every 3 weeks for the first 2 cycles, followed by 75 µg/kg every 3 weeks for subsequent cycles.
- A total of 59 patients (40.7%) were 65 to <75 years of age; 95 patients (65.5%) were <70 years of age, 50 patients (34.5%) were ≥ 70 years of age and 21 patients (14.5%) were ≥ 75 years of age.[2,5.]
    - In patients 65 to <75 years of age, ORR was 45.8% (95% CI: 32.7,59.2) with complete response rate (CRR) of 25.4% (95% CI: 15.0, 38.4). No overall differences in effectiveness were observed between these patients and younger patients.[2]
    - In patients ≥75 years of age, ORR was 52.4% (95% CI: 29.8, 74.3) with CRR of 38.1% (95% CI: 18.1, 61.6). The median DOR was 9.63 months for patients <65 years, 10.25 months for patients 65 to <75 years, and 13.37 months for patients ≥75 years.[2]
    - In patients <70 years of age, ORR was 48.4% (95% CI: 38-58.9) with CRR of 22.1% (95% CI: 14.2-31.8). In patients ≥ 70 years of age, ORR was 48% (95 CI: 33.7-62.6) with CRR of 30% (95% CI: 17.9-44.6).[5]
    - The median DOR was 9.26 months (95% CI, 4.63-NA) in the younger group (<70 years of age) and not reached in the older group (≥ 70 years of age).[5.]
        - Median progression-free survival (PFS) was numerically longer in the older group, 7.36 months (95% CI, 2.99 – NA), compared with the younger group, 3.81 months (95% CI, 2.69-8.08).[5]
        - Median overall survival (OS) was similar across groups, younger group: 9.89 months (95% CI, 6.14-12.09), and the older group: 8.90 months (95% CI, 6.74-12.42).[5]

Safety

- In LOTIS-2, ZYNLONTA had an acceptable safety and tolerability profile and produced quick and durable responses in both younger and older patients with R/R DLBCL. Overall TEAEs were similar across age groups.[5]
- Percentages of patients with any TEAE leading to dose delay or reduction years, or any TEAE leading to withdrawal were also similar.[5]
    - Grade ≥3 AEs occurring in ≥10% of patients revealed similar rates of hematologic TEAEs; however, there was a lower percentage of increased gamma-glutamyltransferase in older patients (<70 years, 23.2%; ≥70 years, 6%).[5.]
- Incidence of TEAEs were similar across all age groups (<65, <70, 65 to <75, ≥70, ≥75 years).[5,6]

Literature Search

- A PubMed biomedical literature search conducted on May 6, 2025, yielded an independent case study by Dr. Christopher Maisel, on the use of ZYNLONTA in an 80-year-old female with DLBCL.

Independent Case Study[6]

- Patient was an 80-year-old female, who presented with subcutaneous skin lesions on back, trunk, breast tissue, with increasing abdominal discomfort.
- After initial biopsy, she was diagnosed with marginal zone lymphoma (MZL) with transformation into DLBCL.
    - Immunophenotype showed CD19, 20, 79a +, CD30 negative; BCL-2 positive, C-myc negative; Ki-67: 70%.
    - A positron emission tomography (PET) scan showed hypermetabolic subcutaneous nodules and enlarged lymph nodes.

Treatment/Efficacy[6]

- The patient was treated with first line mini-R-CHOP x 6 cycles, after 3 cycles, she had good PR, and a near CR at the end of the 6 cycles.
- She was also treated with 2nd line Bendamustine-rituximab and polatuzumab, in which she received PR, but with significant adverse effects.
- Lastly, she was treated with ZYNLONTA 3rd line. Her response to treatment is as follows.
    - In cycle 1 of ZYNLONTA treatment, she observed improvement in night sweats.
    - In cycle 2 of ZYNLONTA treatment, she observed significant reduction in size of subcutaneous nodules.
    - In cycle 3 of ZYNLONTA treatment, there was clinical resolution of lesions; PET scan showed radiographic complete response.
    - Patient remained on ZYNLONTA treatment for a duration of 17 cycles (1 year).
    - During therapy, her hemoglobin levels remained in the 11.5-12.3 g/dL range, white blood cells (WBC) remained without > Grade 2 neutropenia, and platelet count remained > 130,000/uL.

Safety[6]

- During the 1 year of treatment with ZYNLONTA, the patient developed Grade 1 bilateral ankle edema, managed with prn (as needed) furosemide.

Relevant Prescribing Information

Section 8: Use in Specific Population[7]

8.5 Geriatric Use

- Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older.
- No overall differences in safety or effectiveness were observed between these patients and younger patients.

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; 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, Weiyun Ai, Juan Pablo Alderuccio, et al. Duration of Response to Loncastuximab Tesirine in Relapsed/Refractory Diffuse Large B-cell Lymphoma by Demographic and Clinical Characteristics: Subgroup Analyses from LOTIS-2. ASCO 2021 June 4-8. Poster

[4] Data on File, LOTIS 1 Clinical Study Report. ADC Therapeutics.

[5] Hamadani, M., Spira, A. et al. Clinical outcomes of older and younger patients treated with loncastuximab tesirine in the LOTIS-2 clinical trial. Blood advances, 8(1), 93–98. https://doi.org/10.1182/bloodadvances.2023010636

[6] Maisel, C. (2024). What 3rd Line treatment is next for an 80-year-old female with large B Cell Lymphoma? - Case Study: 3rd Line of Therapy in DLBCL (The US Oncology Network). Retrieved from https://go.mckesson.com/index.php/email/emailWebview?email=ODI4LVpPTy04MDMAAAGS_PDrrqywOmWcNt2EXzTBzMBYp6TvdSbVgQ4uoRLe2ehEr7Obt2XKPHLMd04OGkd3Aprise4mRBrqUECjwrDy72sIbetPMrFXww

[7] ZYNLONTA® (loncastuximab tesirine) FDA-approved 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.