ZYNLONTA® (loncastuximab tesirine-lpyl)-Use in Patients with Hepatic Impairment

Summary

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study which evaluated the safety and tolerability of ZYNLONTA monotherapy in adult patients with relapsed or refractory (R/R) B-Cell Non-Hodgkin's Lymphoma (B-NHL).[1]
  - For study inclusion, patients were required to have serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤2 × the upper limit of normal (ULN) (≤5×ULN if there was liver or bone involvement).[2]
- LOTIS-2 was a Phase 2, open-label, single-arm, multicenter study which evaluated the efficacy and safety of ZYNLONTA monotherapy in patients (≥18 years of age) with R/R DLBCL following ≥2 lines of prior systemic therapy.[3]
  - Patients were required to have adequate organ function, and a patient's ALT, AST, and GGT concentrations were required to be ≤2.5 × ULN to be included in the study.
- A follow up analysis of patients who were enrolled in LOTIS-2 trial ≥ 17 months after they received the first dose of Loncastuximab dose were further evaluated with a data cut off of March 1, 2021.
  - All-grade TEAEs considered likely related to the PBD warhead included liver enzyme abnormalities 76(52.4%).
  - Treatment-related TEAEs leading to treatment discontinuation and dose delays were reported in 27 (18.6%) and 62 (42.8%) patients, respectively; most common reason for both was increased GGT 17 (11.7%) and 26 (17.9%) patients, respectively.
- Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 × ULN and any AST) may increase the exposure of unconjugated SG3199 (the pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent), however there was no clinically significant effect on ZYNLONTA pharmacokinetics.[4]
- The effect of moderate (total bilirubin >1.5 to ≤3 × ULN and any AST) or severe (total bilirubin >3 ULN and any AST) hepatic impairment on ZYNLONTA pharmacokinetics is unknown.[4]
- There is no standardized guidance on how to adjust ZYNLONTA doses with pre-existing or developing hepatic dysfunction.[5]
  - An independent study presented two cases in which both patients with R/R DLBCL and concurrent hepatic dysfunction demonstrated tolerability to full-dose ZYNLONTA without exhibiting increased hematological or nonhematological toxicities in comparison with those reported in the LOTIS-2 trial.[5]
  - In both cases, there was no dose reduction of ZYNLONTA, and no dose delays were implemented for hepatic dysfunction.
- See **Relevant Prescribing Information** for additional information.

Background

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study which evaluated the safety and tolerability of ZYNLONTA monotherapy in adult patients with relapsed or refractory (R/R) B-Cell Non-Hodgkin's Lymphoma (B-NHL). The study was conducted in two parts, dose-escalation (Part 1) followed by dose-expansion (Part 2).[1,2]

- LOTIS-2 was a Phase 2, open-label, single-arm, multicenter study which evaluated the efficacy and safety of ZYNLONTA monotherapy in patients (≥18 years of age) with R/R DLBCL following ≥2 lines of prior systemic therapy.[3]

Clinical Data

LOTIS-1 (Phase 1)

- In LOTIS-1 (Part 2, dose expansion), patients were required to have ALP, ALT, and AST ≤2 × the ULN (≤5×ULN if there was liver or bone involvement) for study inclusion. Patients were required to have total serum/plasma bilirubin ≤1.5×ULN (patients with known Gilbert's syndrome could have a total bilirubin up to ≤3×ULN).[2]
- There is no available safety data specific to these patients.

LOTIS-2 (Phase 2)

- To be included in LOTIS-2, patients were required to have adequate organ function. A patient's ALT, AST, and gamma-glutamyltransferase (GGT) concentrations were required to be ≤2.5 × ULN. A patient's total bilirubin (Tbili) was required to be ≤1.5 × ULN (patients with known Gilbert's syndrome could have a total bilirubin up to ≤3 × ULN).[3]
- A follow up analysis of patients who were enrolled in LOTIS-2 trial ≥ 17 months after they received the first dose of Loncastuximab dose were further evaluated with a data cut off of March 1, 2021.[4]
    - All-grade TEAEs considered likely related to the PBD warhead included liver enzyme abnormalities 76 (52.4%)
    - Treatment-related TEAEs leading to treatment discontinuation and dose delays were reported in 27 (18.6%) and 62 (42.8%) patients, respectively; most common reason for both was increased GGT 17 (11.7%) and 26 (17.9%) patients, respectively.

Literature Search

- A PubMed biomedical literature search conducted on May 21, 2025, yielded analysis from a 2023 in vitro pooled study by Baek GT et al, which supports the safety of ZYNLONTA use in patients with severe hepatic dysfunction.

Independent case study report[5]

- An independent study reported two cases of R/R DLBCL safely treated with full dose ZYNLONTA, in the setting of severe hepatic dysfunction.
    - Patient 1 was a 50-year-old man with a history of advanced -stage DLBCL who had received 10 prior lines of therapy. Laboratory values before treatment with ZYNLONTA included the following: 7.9 x ULN for ALT, 4.9 x ULN for AST, and 1.5 x ULN for Tbili.
        - Within 2 weeks of the first ZYNLONTA dose, Tbili normalized; within 5 weeks, AST and ALT had both decreased to < 2 x ULN.
        - The patient achieved a partial response (PR) after receiving 2 doses of treatment with ZYNLONTA.
        - The patient tolerated ZYNLONTA with the exception of one episode of grade >4 neutropenia after the fifth dose. AST and ALT have remained normal to date.

- Patient 2 was a 40-year-old man with a history of advanced-stage bulky abdominal DLBCL (germinal B-cell) who had received five prior lines of therapy. Laboratory values before treatment with ZYNLONTA included the following: AST, 3.5 x ULN; ALT, 1.54 x ULN; and Tbili, 1.77 x ULN.
    - Similar to patient 1, the patient started treatment with ZYNLONTA and tolerated the infusion without adverse events.

- In both cases, there was no dose reduction of ZYNLONTA, and no dose delays were implemented for hepatic dysfunction. Both cases had notable, rapid decreases in liver function tests elevations from grade >3 LFT elevations to grade 0–1 after initiation of ZYNLONTA.

Relevant Prescribing Information

Section 8: Use in Specific Populations[6]

Section 8.6: Hepatic Impairment

- No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions [see Dosage and Administration (2.3)].
- ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST) [see Clinical Pharmacology (12.3)].

Section 12: Clinical Pharmacology[6]

Section 12.3: Pharmacokinetics, Specific Populations, Patients with Hepatic Impairment

- Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 × ULN and any AST) may increase the exposure of unconjugated SG3199, however there was no clinically significant effect on ZYNLONTA pharmacokinetics.
- The effect of moderate (total bilirubin >1.5 to ≤3 × ULN and any AST) or severe (total bilirubin >3 ULN and any AST) hepatic impairment on ZYNLONTA pharmacokinetics is unknown.

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] Data on File, LOTIS-1 Clinical Study Report. ADC Therapeutics.
[3] Data on File, LOTIS-2 Clinical Study Report. ADC Therapeutics.
[4] Kahl BS, Hamadani M, Caimi PF, Carlo-Stella C, et al. LOTIS-2 follow-up analysis: Updated results from a Phase 2 study of loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma. Poster presented at: the International Conference of Malignant Lymphoma (ICML) Virtual Congress; June 18-22, 2021; Virtual.
[5] Baek GT, Huang IJ, Gopal AK. Safety of loncastuximab tesirine-lpyl in diffuse large B-cell lymphoma with severe hepatic dysfunction [published online ahead of print, 2023 May 19]. Cancer. 2023;10.1002/cncr.34816. doi:10.1002/cncr.34816
[6] ZYNLONTA® (loncastuximab tesirine-lpyl) 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.