ZYNLONTA® (loncastuximab tesirine-lpyl) – Inclusion of Patients with High Grade B-Cell Lymphoma (HGBL)

Overview

- LOTIS-2 was a pivotal Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA as monotherapy in 145 adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) following >2 lines of prior systemic therapy.[4]
    - The primary endpoint was overall response rate (ORR) according to the 2014 Lugano classification in all-treated patients and was assessed by central review.
    - Key secondary endpoints included duration of response (DoR), complete response (CR), relapse-free survival (RFS), progression free survival (PFS), overall survival (OS), and frequency/severity of adverse events (AEs), and serious adverse events (SAEs) related to the safety profile.
- In the primary LOTIS-2 study, 15 patients (10%) were identified with DH/TH and 11 patients (8%) were identified as HGBL patients with MYC and BCL2 and/ or BCL6 rearrangements.[3] Upon further analysis, it was determined that one of the patients in the trial had been misdiagnosed to have HGBL. The patient was reclassified as DLBCL-not otherwise specified (NOS) and was thus, excluded from the HGBCL subgroup analysis.[2]
- Following this change, 10 HGBL patients (7%) with MYC and BCL2 and/or BCL6 rearrangements were enrolled and treated in LOTIS-2.[2,5]
    - Updated data from the LOTIS-2 clinical trial-2-year follow up results (Data cut-off September 15, 2022) show the ORR, and CR as 50.0% (n=5), respectively.[3,5]

Background

- Pathologic diagnosis of DLBCL, as defined by the 2016 World Health Organization (WHO) classification, included DLBCL (NOS); primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with MYC and B-cell lymphoma 2 apoptosis regulator (BCL2) and/or B-cell lymphoma 6 transcription repressor (BCL6) rearrangements.[3]
- HGBL with MYC and BCL2 and/or BCL6 rearrangements (HGBL-double-hit (DH)/triple-hit (TH)) is a newly created lymphoma subtype in the 2016 World Health Organization (WHO) classification of lymphoid neoplasms, characterized by concurrent chromosomal rearrangements involving MYC and BCL2 and/or BCL6 (DH, TH).[1]
- HGBL-DH/TH constitutes approximately 4% to 7% of newly diagnosed DLBCL and is frequently associated with early treatment failure.[1]
- 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.[4]

Clinical Data

Primary Analysis Study Design

- LOTIS-2 was a pivotal Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA as monotherapy in 145 adult patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) following >2 lines of prior systemic therapy.[4]
    - The primary endpoint was overall response rate (ORR) according to the 2014 Lugano classification in all-treated patients and was assessed by central review. ORR was defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR).[4]
    - Key secondary endpoints included DoR, CR, RFS, PFS, OS, and frequency/severity of adverse events (AEs), and serious adverse events (SAEs) related to the safety profile.[4]

HGBL Subgroup

- In the 2016 WHO classification, patients with HGBL double hit/triple hit were classified separately from those patients who had HGBL with (MYC and BCL2 and/or BCL6 rearrangements).[3]
    - Investigator sites classified patients with HGBL based on the 2016 WHO classification or the methodology which was utilized prior to the 2016 update.
- In the primary LOTIS-2 study, 15 patients (10%) were identified with DH/TH and 11 patients (8%) were identified as HGBL patients with MYC and BCL2 and/ or BCL6 rearrangements.[3]
- Upon further analysis due to a query raised during data cleaning, it was determined that one of the patients in the trial had been misdiagnosed to have HGBL. The patient was reclassified as DLBCL-NOS and was thus, excluded from the HGBL subgroup analysis.[2]
- Following this change, ten HGBL patients (7%) with MYC and BCL2 and/or BCL6 rearrangements were enrolled and treated in LOTIS-2.[2,3]
    - Updated data from the LOTIS-2 clinical trial-2-year follow up results (Data cut-off September 15, 2022) show the ORR, and CR as 50.0% (n=5), respectively. The median DOR was not reached, PFS was 14.6 months, and OS was not reached in these patients.[3,5]

An independent subgroup analysis from LOTIS-2 study[1]

- A subgroup analysis from the LOTIS-2 study evaluated the outcome of patients with high B cell lymphoma- double hit (DH)/triple-hit (TH), enrolled in the study at the time of data cut off March 1, 2021.
- There were 15 patients (10%) with HGBL-DH/TH enrolled in the study, and the ORR was 33.3% (95%CI: 11.8,61.6).[1]
    - All responding HGBL-DH/TH patients had a DOR of more than 12 months, with a median DOR not reached at the time of data cut off.
    - Five patients achieved a CR, the median time to first CR was 43 days.
    - Among HGBL-DH/TH patients treated with loncastuximab tesirine after chimeric antigen receptor (CAR) T-cell progression (n = 4), one patient achieved CR.
    - The median follow up was 5.8 months, the median progression free survival (PFS) and overall survival (OS) were 3.7 (95%CI 1.28-not reached), and 9.2 (95%CI 1.84-not reached), respectively.

    - In patients with HGBL-DH/TH who had a response, the duration of response was > 12 months and the median duration of response was not reached at the time of data cutoff.
    - Treatment-emergent adverse events were similar to patients with DLBCL-NOS, the most common included grade ≥3 neutropenia (26%), thrombocytopenia (18%), and increased gamma-glutamyl transferase (17%).
- The baseline characteristics of the patients enrolled with HGBL-DH/TH was as follows[1]:
    - Of the 15 patients, 12 patients were DH, and 3 patients were TH.
    - Of the 15 patients, there were 10 women (66.7%), with a median age of 74 (range 27-85) years, including 6 patients who were ≥75 years of age.
    - Eleven patients (73%) received three or more lines of therapy, 3 patients (20%) had prior ASCT, 1 patient received polatuzumab vedotin containing regimen prior to enrollment, and 4 patients (26.7%) had prior CAR modified T-cell therapy with new biopsy demonstrating persisting CD19 expression by immunohistochemistry.

Literature Search

- A PubMed biomedical literature search conducted on November 6, 2024, yielded no further relevant data regarding the inclusion of patients with HGBCL in ZYNLONTA's LOTIS- 2 trial.

Relevant Prescribing Information

Section 1: Indications and Usage[6]

- ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory 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.
- This indication is approved under accelerated approval based on overall response rate [see Clinical Studies (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Section 6.1: Clinical Trials Experience[6]

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

LOTIS-2

- The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies [see Clinical Studies (14.1)].

Section 14: Clinical Studies[6]

Section 14.1: Relapsed or Refractory Diffuse Large B-cell Lymphoma

- The efficacy of ZYNLONTA was evaluated in LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior systemic regimens. The trial excluded patients with bulky disease and active central nervous system lymphoma.

- Patients received ZYNLONTA 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and received treatment until progressive disease, or unacceptable toxicity.
- 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) and high-grade B-cell lymphoma in 7%.
- 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.
- Efficacy was established on the basis of overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria (Table 4). The median follow-up time was 7.3 months (range 0.3 to 20.2).

References

[1] Alderuccio JP, Ai WZ, Radford J, Solh MM, et al. Loncastuximab tesirine in relapsed/refractory high-grade B-cell lymphoma: a subgroup analysis from the LOTIS-2 study. Blood Adv. 2022 Jul 5: bloodadvances.2022007782. doi: 10.1182/bloodadvances.2022007782. Online ahead of print.
[2] Data on file, HGBCL memo. ADC Therapeutics
[3] Data on file, LOTIS-2 clinical study report. ADC Therapeutics
[4] 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
[5] 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
[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 at855-690-0340. Please consult the ZYNLONTA Prescribing Information