ZYNLONTA® (loncastuximab tesirine-lpyl) – Use in Patients with Central Nervous System Involvement

Summary

- 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 relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) following ≥2 lines of prior systemic therapy.[1]
- Patients with active central nervous system(CNS) lymphoma, including leptomeningeal disease, were excluded.[1,2]
- One patient in LOTIS-2 was diagnosed with Grade 3 DLBCL with CNS involvement following 3 cycles of ZYNLONTA therapy.[3]
    - The event of DLBCL was categorized as a serious adverse event and was not considered to be related to the study drug.
    - The outcome of the event of DLBCL was recovered/resolved with sequelae.
- There is new emerging evidence of loncastuximab tesirine (Lonca) activity within CNS, primarily from an independent case report series and an early interventional study.

Clinical Data

- 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 relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) following ≥2 lines of prior systemic therapy.[1] Patients with active central nervous system (CNS) lymphoma, including leptomeningeal disease, were excluded from the study.[1,2]

LOTIS-2 Study Incidence of CNS Involvement[3]

- One patient, 94 years of age, was diagnosed with Grade 3 DLBCL, described as DLBCL with CNS involvement following 3 cycles of loncastuximab tesirine therapy (2 infusions of 0.15 mg/kg and one infusion of 0.075 mg/kg).
    - The event of DLBCL was categorized as a serious adverse event.
    - The patient received 3 lines of prior therapy.
        - Line 1 included rituximab, cyclophosphamide, doxorubicin, vincristine sulphate, and prednisone (R-mini-CHOP).
        - Line 2 consisted of rituximab and lenalidomideline and line 3 consisted of betalutin.
        - The patient also received prior radiotherapy to the left cheek and bilateral cutaneous skin lesions on legs.
    - The patient was treated with methotrexate for the event of DLBCL.
    - The outcome of the event of DLBCL was recovered/resolved with sequelae.
    - The event of DLBCL was considered not related to the study drug.
    - The patient discontinued treatment for reasons unrelated to the event of DLBCL with CNS involvement.

Emerging Clinical Evidence (2025)[4,5]

- The SOLAR study (NCT06607549) is evaluating loncastuximab tesirine plus rituximab (lonca-R) following stereotactic radiosurgery (SRS) in patients with primary or secondary CNS lymphoma. The trial is determining the maximum tolerated dose (MTD) and will assess CR in patients relapsed or ineligible for high-dose methotrexate-based therapy.[4]
    - The study excludes leptomeningeal-only and spinal cord disease but allows parenchymal or CSF-detectable involvement and will provide first prospective safety/efficacy data of lonca in CNS lymphoma once interim results are reported.
- An independent case series by Olszewski et al reported three patients with secondary CNS lymphoma treated with loncastuximab tesirine who achieved complete responses.[5]
    - All three patients had DLBCL with parenchymal or cerebrospinal fluid (CSF) CNS involvement.
    - Each patient achieved a complete response (CR) to lonca confirmed by clinical improvement and radiographic resolution of CNS lesions.
    - Responses were durable, lasting between 6 and 12 months at last follow-up, and treatment was well tolerated without neurotoxicity or serious CNS-specific adverse events.
    - The authors proposed that loncastuximab may achieve therapeutic CNS drug levels, given the responses observed in these otherwise refractory cases.
        - *Patient 1 – Complete Response*
            - A 69-year-old male with a third CNS relapse of CD5+, MYC+/BCL2+, CD10− DLBCL, maintained on Zanubrutinib, presented with isolated brain parenchymal and CSF involvement, having previously undergone 8 lines of therapy.
            - He received standard-dose lonca combined with weekly intrathecal methotrexate (12 mg), with corticosteroid premedication and daily dexamethasone for neurological symptoms.
            - MRI after two cycles showed complete resolution with negative CSF cytology. Treatment was stopped after four cycles due to pulmonary GVHD.
            - He remained disease-free on MRI at four months but relapsed at six months off therapy and died seven months after starting lonca. Adverse events were anemia and rash.
        - *Patient 2- Complete Response*
            - A 68-year-old female with a second CNS relapse presented with headache and back pain. Imaging revealed systemic recurrence (lungs, adrenal glands, spine), but no brain parenchymal lesions. CSF was positive for CD5+ and CD19, following 5 prior therapies.
            - She was treated with standard-dose lonca, plus weekly intrathecal methotrexate (12 mg), cytarabine (40 mg), and hydrocortisone (12 mg), with standard corticosteroid premedication and daily dexamethasone. CSF clearance and symptom resolution were achieved within three weeks; PET-CT confirmed a complete metabolic response.
            - Intrathecal therapy was stopped after six months, for a total of 17 cycles of lonca. Adverse events were grade 1 rash, fatigue, and neutropenia.

Parenchymal CNS progression occurred two months after stopping loncastuximab; the patient remains alive on BTKi therapy.

- *Patient 3- Partial Response*
  - A 66-year-old female with follicular lymphoma transformed to DLBCL, involving CNS and systemic sites on her fifth line of therapy, presented with right hand weakness and leg swelling. Systemic biopsy confirmed CD19+ DLBCL (pelvis) and brain lesions.
  - She started on standard-dose lonca only, with corticosteroid premedication and daily dexamethasone. MRI after three doses showed improvement in brain lesion; CT showed systemic response. Treatment was paused after six doses due to neutropenic fever, and she died from COVID-19 complications with no evidence of recurrent lymphoma.

CSF Pharmacokinetic Analysis[5]

- CSF concentrations of loncastuximab tesirine were measured in patients 1 and 2 by electrochemiluminescence immunoassay. The geometric mean CSF concentration of pyrrolobenzodiazepine dimer (PBD)-conjugated loncastuximab was 5.81 ng/mL (32.5 pM), exceeding previously established IC50 levels for most B-cell lymphoma cell lines (median 4.1 pM).[3,5]
  - This concentration was under 1% of the mean peak plasma concentration from LOTIS-2 (1694 ± 47.6 ng/mL).
- The authors concluded that the observed complete CNS responses likely reflect therapeutic exposure of lonca or its payload (SG3199) through localized blood brain barrier disruption, rather than systemic permeability.

Literature Search

- A PubMed biomedical literature search conducted on October 18, 2025, identified one peer-reviewed publication regarding the use of ZYNLONTA in patients with secondary CNS lymphoma and an ongoing interventional clinical study evaluating ZYNLONTA in CNS lymphoma.

Relevant Prescribing Information

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, 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.

References

[1] 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

[2] Caimi PF, Weiyun A, 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 [supplementary appendix]. *Lancet Oncol*. 2021 May 11. DOI: 10.1016/S1470-2045(21)00139-X.

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

[4] Clinicaltrials.gov/study/NCT06607549

[5] Olszewski AJ, Treaba DO, Winter A, Donnelly S, Ollila TA. Loncastuximab tesirine elicits complete responses in secondary central nervous system lymphoma. Br J Haematol. 2025 Sep 21. doi: 10.1111/bjh.70178. Epub ahead of print. PMID: 40976986.

[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.