ZYNLONTA® (loncastuximab tesirine-lpyl) – CD19 Expression, Response and Treatment Sequencing

Summary

- Preclinical data show that expression of CD19 is maintained in hematologic B-cell Malignancies, Including diffused large B-cell lymphoma, (DLBCL), follicular lymphoma (FL), and marginal cell lymphoma (MCL).[2,4]
    - Bystander killing of CD19-negative cells by ZYNLONTA was observed in preclinical studies, supporting the antitumor activity in lymphomas with heterogenous CD19 expression.[2,4.]
- 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 Lymphoma (B-NHL). The study was conducted in two parts, dose-escalation (Part 1) followed by dose-expansion (Part 2).[1]
    - An exploratory pharmacokinetic/pharmacodynamic analysis was conducted to determine the correlation between clinical response and archival tumor CD19 expression.[2]
    - These exploratory analyses suggested no correlation of archival tumor CD19 expression with pharmacokinetic exposure or with the clinical response.[2]
- 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.[3]
    - Prior to initiation of ZYNLONTA, immunophenotypic analyses were performed in the all-treated population.[4]
    - Immunophenotypic analyses revealed that 32 patients (22.1%) were CD19 positive, and 8 patients (5.5%) were CD19 negative. Testing for CD19 expression was not done in 105 patients (72.4%).[4.]
- CD19 expression was assessed by immunohistochemistry (IHC) and H-Score in a subgroup of LOTIS-2 patients that had a biopsy taken after the last systemic anticancer treatment, prior to receiving ZYNLONTA.[6]
    - ZYNLONTA showed potent cytotoxicity across a panel of six B-cell Non-Hodgkin Lymphoma (NHL) cell lines, including cell lines with very low CD19 expression.[6]
- CAR-T targets and specifically binds to the FMC63 epitope of CD19. ZYNLONTA on the other hand, targets RB4 epitope.[9]

Clinical Studies

LOTIS-1 (Phase 1)

- 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 Lymphoma (B-NHL). The study was conducted in two parts, dose-escalation (Part 1) followed by dose-expansion (Part 2).[1]

- An exploratory pharmacokinetic/pharmacodynamic analysis was conducted to determine the correlation between clinical response and archival tumor CD19 expression.[2]
    - Based on the evaluable CD19-positive tumor expression in archival/pretreatment tumor samples, the percentage of CD19-positive tumor cells in tumor tissue ranged from 0 to 99%.[2]
    - These exploratory analyses suggested no correlation of archival tumor CD19 expression with pharmacokinetic exposure or with the clinical response.[2]
    - Three patients (1.6%) had received prior chimeric antigen receptor T-cell (CAR-T) therapy in LOTIS-1.
        - Two of those patients were diagnosed with diffuse large B-cell lymphoma (DLBCL) and no additional safety or efficacy information regarding those patients are available.[1]
    - In the overall population, the overall response rate (ORR) in evaluable patients (N=180) was 45.6% (95% CI: 38.1, 53.1) with a complete response rate (CR) of 26.7% (n=48) and a partial response rate (PR) of 18.9% (n=34).[1]
    - The most frequently reported treatment emergent adverse events (TEAEs) were hematologic related which included platelet count decreased in 128 patients (71.1%), neutrophil count decreased in 106 patients (59.2%), anemia in 60 patients (32.8%) and white blood cell (WBC) count decreased in 22 patients (12%).[1]
    - Fatigue was the most common non-hematological TEAE in 78 patients (42.6%), followed by nausea in 59 patients (32.2%), peripheral edema in 58 patients (31.7%), and gamma glutamyltransferase (GGT) increased in 57 patients (31.1%).[1]

LOTIS-2 (Phase 2)

- 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.[3]
    - Prior to initiation of ZYNLONTA, immunophenotypic analyses were performed in the all-treated population.[4]
    - Immunophenotypic analyses revealed that 32 patients (22.1%) were CD19 positive, and 8 patients (5.5%) were CD19 negative. Testing for CD19 expression was not done in 105 patients (72.4%).[4.]
    - Select key exclusion criteria were autologous hematopoietic stem cell transplant (HSCT) within 30 days, allogeneic HSCT within 60 days, or major surgery, radiotherapy, or anticancer or experimental treatment within 14 days before starting ZYNLONTA.[3]
    - Patients with prior CD19-directed therapy, including CAR-T therapy, were required to have a biopsy that showed CD19 protein expression after completion of the CD19-directed therapy and prior to initiating therapy with ZYNLONTA.[3]
    - The response to ZYNLONTA was not evaluated based on CD19 expression at baseline.
- In the final LOTIS-2 analysis, it was reported that 16 (11.0%) patients received CD19-directed CAR-T therapy following ZYNLONTA, and 14 (9.7%) patients had received CAR–T therapy prior to receiving ZYNLONTA.[4,8.]

- The type of subsequent CD19 CAR-T therapy received was not reported.[4]
- The investigator assessed ORR in patients who received CAR-T therapy following ZYNLONTA was 56.3% (9/16) patients, 8 patients had CR, (50%), and 1 patient had PR (6.3%).[8.]
- The ORR in patients who received CAR-T therapy prior to receiving ZYNLONTA was 42.9% (6/14) patients, 3 patients had CR (21.4%).[8.]
- No prior CAR-T patients who were screened failed due to a lack of CD19.[4]

- CD19 expression was assessed by immunohistochemistry (IHC) and H-Score in a subgroup of LOTIS-2 patients that had a biopsy taken after the last systemic anticancer treatment, prior to receiving ZYNLONTA.[6]
    - H-Score is a semi quantitative assessment of percentage of CD19 positive cells and staining intensity.
    - Results from a LOTIS-2 clinical trial and (QSP) show responses to ZYNLONTA were seen in patients across all levels of CD19 expression, including patients with extremely low or no detectable CD19 expression at baseline and extremely low H-scores and H-scores of zero.
    - QSP modeling predicts that CD19 expression level by IHC is not predictive of response to ZYNLONTA, although the addition of CD19 surface density improves the response prediction. Virtual patients responded to ZYNLONTA with estimated CD19 tumor cell surface densities as low as 1,000 molecules/cell, which is normally below the level of IHC detection.
    - ZYNLONTA showed potent cytotoxicity across a panel of six B-cell Non-Hodgkin Lymphoma (NHL) cell lines, including cell lines with very low CD19 expression.
    - Arthur's findings indicate that ZYNLONTA is an effective treatment option for patients with R/R DLBCL following ≥ 2 lines of treatment, even in patients expected to have a low level of CD19 expression.

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

- In an independently conducted retrospective analysis, investigators retrieved data from 14 patients diagnosed with DLBCL who received CD19-directed CAR-T therapy following ZYNLONTA in LOTIS-1 and LOTIS-2 studies.
    - The median interval between diagnosis of DLBCL and initiation of ZYNLONTA was 21.5 months (range, 6.8 to 258), and these patients received a median of 2 cycles (range, 1 to 7) of ZYNLONTA.
    - Six patients received additional lines of therapy between ZYNLONTA and CAR-T treatment (median of 1 therapy line; range, 1 to 3).
    - Ten patients (71%) had CD19 expression assessed via immunohistochemical staining on repeat biopsies and all 10 patients tested positive for CD19 after antibody-drug conjugate (ADC) failure.
        - Information regarding CD19 expression was not available for 4 patients (29%).
    - The median interval between ZYNLONTA and CAR T-cell therapy was 120 days (range, 22 to 600).
    - CD19 expression on DLBCL was reassessed in 10 patients after relapse or progression on ZYNLONTA treatment; no cases of CD19 antigen-negative relapse were seen.

    - Following CAR-T therapy (at 3 months), the best response included 6 patients (43%) with a CR and 1 patient (7%) with a PR. Seven patients (50%) had refractory disease following CAR-T therapy.

Retrospective analysis of first therapy after CD19-directed CAR-T failure[7.]

- A retrospective analysis of patients with R/R large B-cell lymphoma treated with CD19-directed CAR-T cell therapy described patient outcomes following CAR-T treatment failure.
    - CD19 expression was assessed by flow cytometry in 52 available tumor biopsies.
    - Patients with CAR-T resistance had a similar CD19 expression at disease progression to those with relapsed disease.
    - Loss of CD19 was infrequent (6%) and CD19 expression at CAR-T treatment failure showed no correlation with CAR-T refractoriness versus later relapse; persistence of CD19 may render tumor susceptible to further CD19-directed therapies.

Literature Search

- A PubMed biomedical literature search conducted on April 18, 2025, yielded no further relevant information regarding CD19 expression in patients receiving ZYNLONTA.

Relevant Prescribing Information

Section 1: Indications and Usage[10]

- ZYNLONTA is a CD19-directed antibody and alkylating agent conjugate 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.

Section 14: Clinical Studies[10]

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), 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.

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] Data on File, LOTIS-1 Clinical Study Report. ADC Therapeutics.
[3] 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
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[6] Caimi PF, Hamadani M, Carlo-Stella C, Nickaeen M, Jordie E, Utsey K, et al. In relapsed or refractory diffuse large B-cell lymphoma, CD19 expression by immunohistochemistry alone is not a predictor of response to loncastuximab tesirine. eJHaem. 2023;1–8. https://doi.org/10.1002/jha2.816
[7] Alarcon Tomas A, Fein JA, Fried S, et al. Outcomes of first therapy after CD19-CAR-T treatment failure in large B-cell lymphoma. Leukemia. 2023;37(1):154-163. doi:10.1038/s41375-022-01739-2
[8] 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
[9] Zammarchi F, Corbett S, Adams L, et al. ADCT-402, a PBD dimer-containing antibody drug conjugate targeting CD19-expressing malignancies. Blood. 2018; 131:1094–105.
[10] 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.