ZYNLONTA® (loncastuximab tesirine-lpyl) – Rationale for Dose Selection

Summary

- The recommended dosing of ZYNLONTA was based on data from the dose finding Phase 1 (LOTIS-1) study and the subsequent dosing of LOTIS 2 which was 150 µg/kg (0.15 mg/kg) every 3 weeks (Q3W) for the first two cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles.[1,3,5]
- The initial 150 µg/kg dose was selected based on good anti-tumor activity and increase rates of hematologic and hepatic adverse events at the 200 µg/kg dose seen in the Phase 1 clinical trial. In the Phase 1 clinical trial, dose-limiting toxicities (all hematologic) were reported in 4 patients, and the maximum tolerated dose (MTD) was not reached, although an accumulation of adverse events was apparent at the 200 µg/kg dose.[1,2]
- The dose reduction to 75 µg/kg following two cycles of 150 µg/kg allows for continued exposure to ZYNLONTA with less toxicity to optimize the durability of response based on findings from the Phase 1 study which were carried over into Phase 2.[2,4]
- ZYNLONTA as an intravenous infusion should be administered over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows: 0.15 mg/kg every 3 weeks for 2 cycles followed by 0.075 mg/kg every 3 weeks for subsequent cycles.[5]

Clinical Data

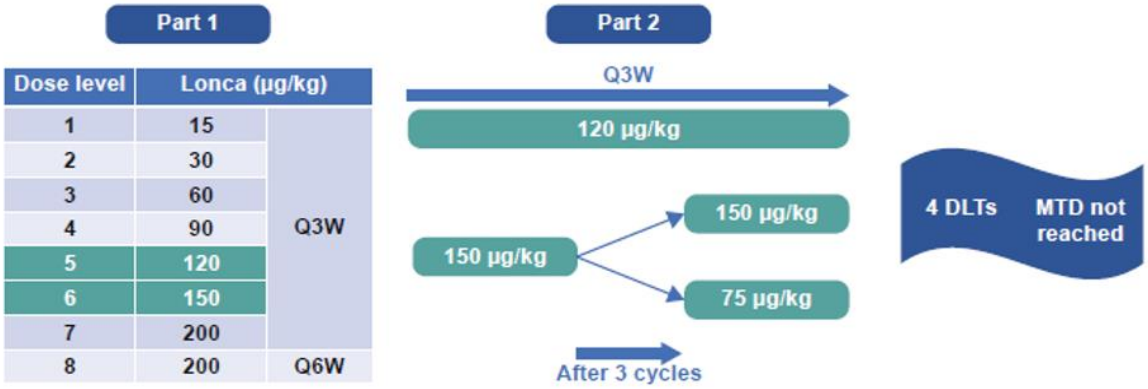
LOTIS-1

- LOTIS 1 was the first-in-human phase 1, open-label, dose-escalation (Part 1) and dose-expansion (Part 2) clinical trial of ZYNLONTA monotherapy in 183 adult patients with relapsed or refractory B-cell Non-Hodgkin's Lymphoma (R/R B-NHL).[1] The primary objectives of Part 1 were to evaluate the safety and tolerability of treatment and to determine the MTD and recommended dose(s) for Part 2. The primary objective of Part 2 was to evaluate safety and tolerability at the recommended dose(s).
- In Part 1, an MTD was defined as the highest dose level at which none of the first 3 treated patients, or no more than one of the first 6 treated patients, experienced a dose-limiting toxicity (DLT). The DLT observation period was during Cycle 1.[2]

Dose Escalation and Dose Expansion

- ZYNLONTA was administered by intravenous infusion over 60 minutes Q3W (Day 1 of each 21-day cycle).[1] Based on a 3+3 dose escalation design, patients were assigned to different dose cohorts, starting with 15 µg/kg once Q3W (Figure 1, Part 1). In Part 2, patients were assigned to recommended dose(s) identified from Part 1, based on safety, efficacy, and pharmacokinetics (PK) data.

Figure 1. Dose during Part 1 and Part 2. *Adopted* from Hamadani M, et al. *Blood*. 2020.[1]



MTD, maximum-tolerated dose; DLT, dose-limiting toxicity; Q3W, every 3 weeks; Q6W, every 6 weeks.

- Overall, 183 patients received ZYNLONTA during Part 1 and Part 2.[1] In Part 1, 88 patients received ZYNLONTA at doses of 15-200 µg/kg Q3W (15, 30, or 60 µg/kg; n=4 in each group, 90 µg/kg: n=5; 120 µg/kg: n=16; 150 µg/kg: n=19; 200 µg/kg: n=36). Four patients experienced dose-limiting toxicities (DLTs) (grade 4 thrombocytopenia in 1 patient at 120 µg/kg, grade 3 febrile neutropenia in 1 patient at 150 µg/kg, grade 4 thrombocytopenia in 2 patients at 200 µg/kg). The MTD was not reached. Based on accumulating hematologic and hepatic adverse events at grades 2 or 3 the 200 µg/kg dose and anti-tumor activity at the 120 and 150 µg/kg doses, 120 µg/kg Q3W and 150 µg/kg Q3W were recommended for Part 2.
- In Part 2, 26 patients received 120 µg/kg Q3W and 69 patients received 150 µg/kg Q3W, with some patients in the 150 µg/kg group reducing their dose to 75 µg/kg Q3W after 3 cycles due to adverse events.
- Based on cumulative safety, PK, and efficacy data, the recommended dose of ZYNLONTA for the Phase 2 clinical trial was 150 µg/kg Q3W for 2 doses followed by 75 µg/kg Q3W for subsequent doses. The decision to dose reduce following 2 cycles of treatment was based on the rapid onset of response observed in a majority of patients (median 2 cycles), and the desire to mitigate onset of late-developing and difficult to manage toxicities, such as edema.[1,2]

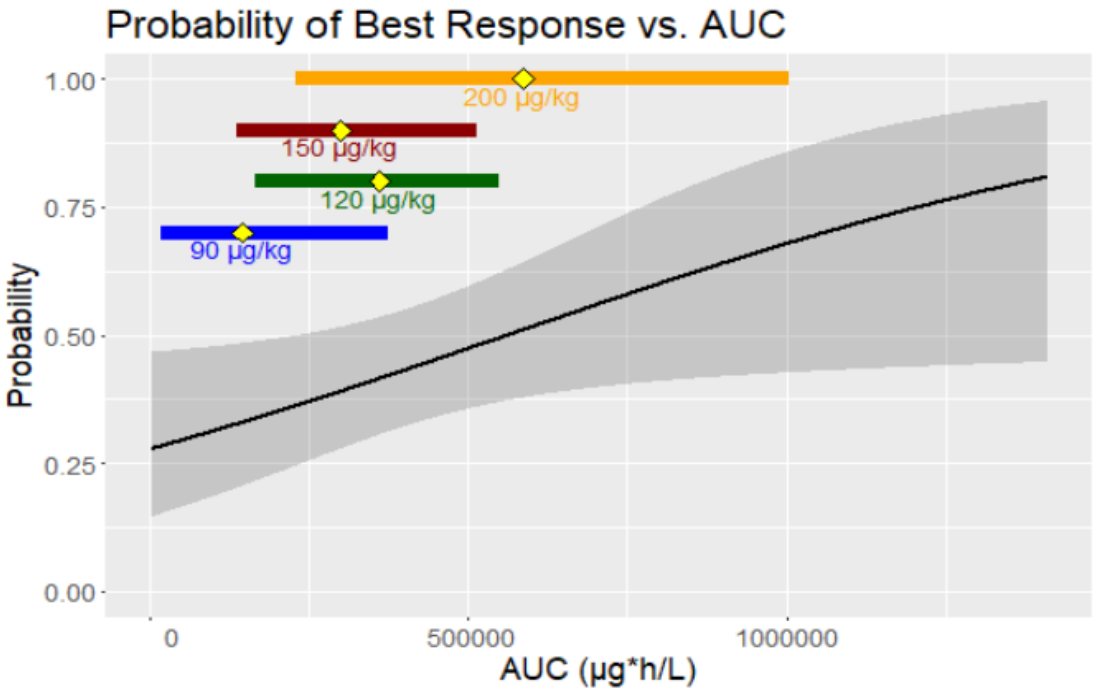
LOTIS-2

- LOTIS-2 is a pivotal phase 2, multicenter, open-label single-arm study that evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) following ≥2 lines of prior systemic therapy.[3]

Scientific Rationale for Dose Selection

- For efficacy, the decision for initial dosing at the 150 µg/kg dose level is predicated on higher observed and objective response rate as compared to the 120 µg/kg and lower doses as shown in Figure 2.[2]

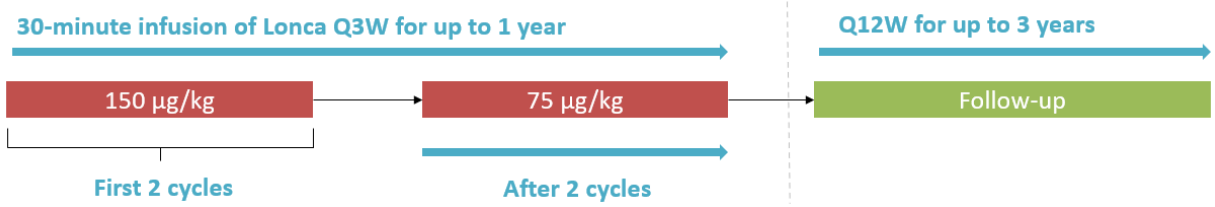
Figure 2. Predicated Probability for Objective Response versus PBD-conjugated Antibody AUC. *Adopted* from Data on File, IB ADC Therapeutics.[2]



Graphics depict the mean (black line) and 95% confidence interval (gray ribbon) predicted probability.
Width of horizontal bars denotes the observed 10th and 90th percentile of individual predicted AUC values with median (yellow diamond) in serum for respective dose groups.

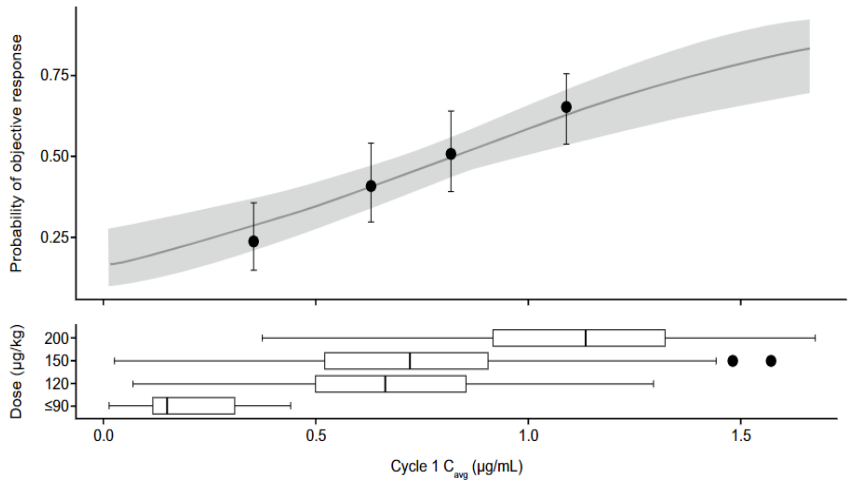
- Overall, 145 patients were enrolled and received treatment with ZYNLONTA as a 30-minute intravenous infusion at a dose of 150 µg/kg Q3W for the first 2 cycles, followed by 75 µg/kg Q3W for subsequent cycles as seen in Figure 3.[3] A treatment cycle was defined as 3 weeks (21 days). All patients, regardless of disease status, were followed every 12 weeks for up to 3 years, or until withdrawal of consent, loss to follow-up, or death, whichever occurred first.

Figure 3. Study Design: Single-arm, Open-label Phase 2 Study. *Adopted* from Caimi PF, et al 2021.[3]



Q3W, every 3 weeks; Q12W, every 12 weeks; ZYLONTA, loncastuximab tesirine

Figure 4. ORR Increases with Increasing Lonca Exposure. Adopted from Hess B, et al 2021.[4]



The dose and cycle 1 C_{avg} of Lonca (bottom graph) correlate with the predicted ORR (top graph). The solid black circles (vertical line segments) represent the observed objective response rate (95% CI, Clopper-Pearson method) for each quartile of cycle 1 C_{avg}. The solid black line and shaded grey area represent the predicted objective response rate (95% CI) from a univariate logistic regression using individual patient level cycle 1 C_{avg}.

- Analysis of the exposure/response showed a high correlation between the initial exposure to ZYNLONTA and the probability of a response. Therefore, the initial dosing for 2 cycles is anticipated to optimize the frequency of overall response (OR), while dose reduction in subsequent cycles allows for continued exposure with the potential to generate more manageable toxicity to optimize the durability of response. This optimizes the durability of response to ZYNLONTA, while reducing the need for dose delay or further dose reduction.[2,4]

Literature Search

- A PubMed biomedical literature search conducted on April 5, 2025, yielded no further relevant data regarding the rationale for dose selection in ZYNLONTA.

Relevant Prescribing Information

Section 2: Dosage and Administration[5]

2.1: Recommended Dosage

- ZYNLONTA as an intravenous infusion should be administered over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows:
    - 0.15 mg/kg every 3 weeks for 2 cycles.
    - 0.075 mg/kg every 3 weeks for subsequent cycles

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, IB. ADC Therapeutics.

[3] 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

[4] Hess B, Townsend W, Ai W, et al. Efficacy and Safety Exposure-Response Analysis of Loncastuximab Tesirine in Patients with B cell non-Hodgkin Lymphoma. AAPS J. 2021;24(1):11. Published 2021 Dec 10. doi:10.1208/s12248-021-00660-3

[5] 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.