ZYNLONTA® (loncastuximab tesirine-lpyl) - Incidence of Neutropenia

Summary

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study that evaluated the safety and tolerability of loncastuximab tesirine-lpyl (Lonca) monotherapy in 183 adult patients with relapsed or refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL).[1]
  - All grade neutrophil count decrease was observed in 106 patients (59.2%) across all dose levels. Grade ≥3 neutrophil count decrease was reported in 71 patients (39.7%) across all dosage cohorts; of those 71 patients, Grade ≥3 neutrophil count decrease was reported in 35 patients (40.7%) receiving Lonca 150 µg/kg.
  - Grade ≥3 febrile neutropenia was reported in 10 patients (5.5%) across all dosage groups, while Grade ≥3 febrile neutropenia was reported in 6 patients (6.8%) within the 150 µg/kg dose cohort.
- LOTIS-2 was a pivotal Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 adult patients with R/R diffuse large B-cell lymphoma (DLBCL) following ≥2 lines of prior systemic therapy.[4]
  - Febrile neutropenia was reported in 5 patients (3.4%), at data cut-off, March 01, 2021.[5]
- In the long-term efficacy and safety report from LOTIS-2 study Grade ≥3 neutropenia was reported in 38 patients (26.2%), all grade neutropenia was observed in 58 of 145 patients (40%).[8.]
  - Grade ≥3 neutropenia in CR patients was observed in 10(27.8%), all grade neutropenia in CR patients was observed in 15 (41.7%).
  - Neutropenia occurred in 6 patients (37.5%) that were event-free ≥ 1 year, and in 4 patients (36.4%) that were event-free ≥2 years.
- The LOTIS-1 and LOTIS-2 protocols allowed for dose delays of Lonca to potentially help manage neutropenia and febrile neutropenia.[6,7.]
- Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia.[6,7.]
  - In the pooled safety population, Grade 3 or 4 neutropenia occurred in 32% of patients, while Grade 4 neutropenia occurred in 21% of patients. Febrile neutropenia occurred in 3%.
  - Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.
- See the **Relevant Prescribing Information** section for further information regarding incidence of neutropenia with ZYNLONTA treatment.

Background

- ZYNLONTA is a pyrrolobenzodiazepine (PBD)-based antibody drug conjugate (ADC) comprised of a humanized monoclonal antibody (mAb) directed against CD19+ cells in hematologic B-cell malignancies in patients with NHL.[1]
- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study that evaluated the safety and tolerability of Lonca monotherapy in 183 adult patients with R/R B-NHL.[1]
- LOTIS-2 was a pivotal Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA monotherapy in 145 adult patients with R/R DLBCL following ≥2 lines of prior systemic therapy.[2,4,8]

Clinical Data

LOTIS-1 (Phase 1)

- In Part 1 of LOTIS-1, 88 patients received Lonca at doses of 15–200 µg/kg every 3 weeks (Q3W). In Part 2 of the clinical trial, 26 patients received Lonca 120 µg/kg Q3W and 69 patients received Lonca 150 µg/kg Q3W, with some patients in the 150 µg/kg dose cohort reducing their Lonca dose to 75 µg/kg Q3W after 3 cycles.[1]
- Patients received a median of 2 doses (range 1–24) for a median treatment duration of 64 days (range 22–532).[1] Based on the safety analysis set of 183 patients (Part 1 + Part 2), all grade levels of neutrophil count decrease were reported in 106 patients (59.2%), with a higher proportion occurring in patients receiving Lonca 200 µg/kg. **Table 1** and **Table 2** contain additional information regarding reports of all grade neutrophil count decrease across all dosage cohorts.[1]

Table 1. Proportion of Patients Experiencing a Decrease in Neutrophil Count in LOTIS 1 (Safety Analysis Set). Adapted from Hamadani et al. *Blood* 2020[1]

TEAE, n (%)	Dose (µg/kg)				
	≤90	120	150	200	Total (N=183)
Preferred Term	**Part 1 (n = 17)**	**Part 1+2 (n = 42)**	**Part 1+2 (n = 88)**	**Part 1 (n = 36)**	
Any TEAE	16 (94.1)	42 (100)	87 (98.9)	36 (100)	181 (98.9)
Neutrophil count decreased[a]	10 (58.8)	21 (51.2)	50 (58.1)	25 (71.4)	106 (59.2)

Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion; B-NHL, B-cell non-Hodgkin lymphoma [a] Platelet count decreased and neutrophil count decreased are based on laboratory abnormality reporting and are reported out of number of patients with post-baseline test value; data for 4 patients (1 at 120 µg/kg, 2 at 150 µg/kg and 1 at 200 µg/kg) were missing for neutrophil count decreased.

- Information regarding incidence of Grade 3 or higher neutrophil count decrease and febrile neutropenia is contained in **Table 2**. Grade ≥3 neutrophil count decrease was experienced in a higher proportion of patients treated with Lonca 200 µg/kg compared to lower dose groups. Excluding disease progression, the most common serious treatment-emergent adverse event (TEAE) was febrile neutropenia, observed in 10 of 183 patients (5.5%).[1]

Table 2. Grade ≥3 Neutrophil Count Decreased and Febrile Neutropenia in LOTIS 1 Adapted from Hamadani et al. *Blood* 2020[1]

TEAE, n (%)	Dose (µg/kg)				
	≤90	120	150	200	Total (N=183)
Preferred Term	**Part 1 (n = 17)**	**Part 1+2 (n = 42)**	**Part 1+2 (n = 88)**	**Part 1 (n = 36)**	
Any Grade ≥3 TEAE	9 (52.9)	32 (76.2)	69 (78.4)	31 (86.1)	141 (77.0)
Neutrophil count decreased	6 (35.3)	12 (29.3)	35 (40.7)	18 (51.4)	71 (39.7)
Febrile neutropenia	1 (5.9)	2 (4.8)	6 (6.8)	1 (2.8)	10 (5.5)

Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion; B-NHL, B-cell non-Hodgkin lymphoma [a]Platelet count decreased and neutrophil count decreased are based on laboratory abnormality reporting; data for 4 patients (1 at 120 µg/kg, 2 at 150 µg/kg and 1 at 200 µg/kg) were missing for neutrophil count decreased. *Please note, some investigators reported neutropenia, while others reported neutrophil count decrease.

- A total of 68 out of 183 patients (37.2%) experienced dose delays due to TEAEs, including 10 patients (5.5%) who experienced neutropenia.[1]

LOTIS-1, Safety in DLBCL Patients

- In the subset of patients with DLBCL (N=139) in LOTIS-1, neutropenia, neutrophil count decreased, and febrile neutropenia were reported in 32 (23%), 20 (14.4%), and 6 (4.3%) of patients, respectively.[3,6]
- **Table 3** provides additional information regarding incidence of neutropenia, neutrophil count decreased, and febrile neutropenia across all dosage cohorts.

Table 3. TEAEs by Preferred Term for DLBCL Patients limited to Neutropenia, Neutrophil Count Decrease, and Febrile Neutropenia (safety analysis set) Adapted from ADCT LOTIS-1 Data on File[3]

TEAE, n (%)	Dose (µg/kg)				
	≤90	120	150	200	Total (N=139)
Preferred Term	**Part 1 (N=10)**	**Part 1+2 (N = 32)**	**Part 1+2 (N = 70)**	**Part 1 (N = 27)**	
Patients with Any TEAE	10 (100)	32 (100)	69 (98.6)	27 (100)	138 (99.3)
Neutropenia	1 (10)	5 (15.6)	17 (24.3)	9 (33.3)	32 (23.0)
Neutrophil count decreased	1 (10)	5 (15.6)	8 (11.4)	6 (22.2)	20 (14.4)
Febrile neutropenia	1 (10)	0 (0)	4 (5.7)	1 (3.7)	6 (4.3)

Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion; DLBCL, diffuse-large B-cell lymphoma. *Please note, some investigators reported neutropenia, while others reported neutrophil count decrease.

- 108 patients (77.7%) with DLBCL experienced at least one Grade ≥3 TEAE. At all dose levels combined, Grade ≥3 neutropenia was experienced by a total of 25 patients (18%) and Grade ≥3 neutrophil count decrease was experienced by a total of 19 patients (13.7%).[3]

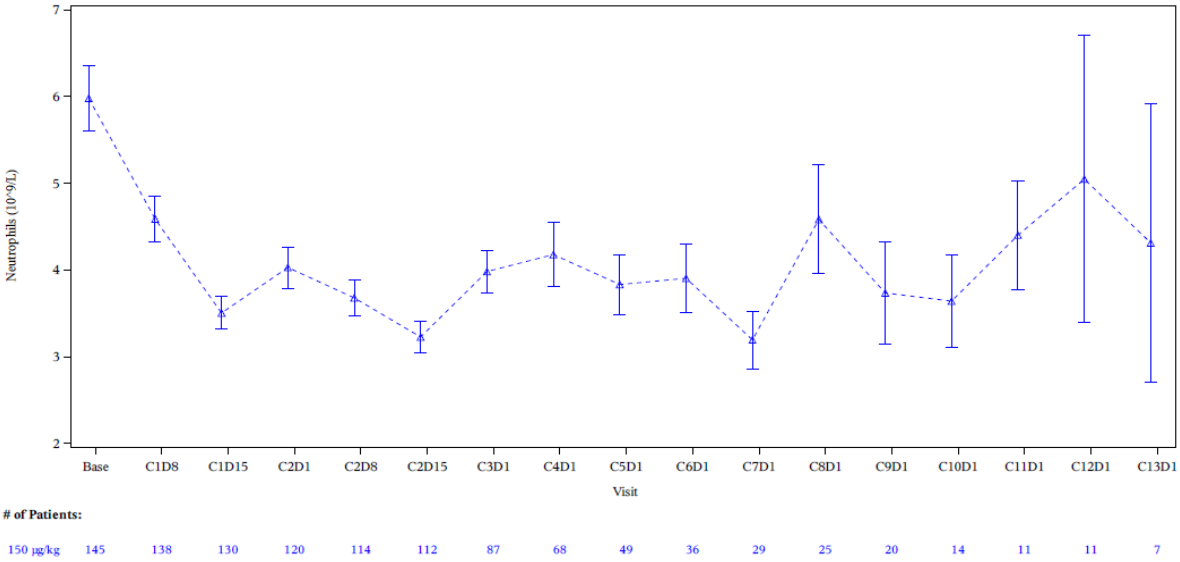
LOTIS-2 (Phase 2)

- In LOTIS-2, patients received ZYNLONTA 150 µg/kg (0.15 mg/kg) every 3 weeks (Q3W) for the first 2 cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles.[4]

- The median number of treatment cycles in LOTIS-2 was 3.0 (interquartile range [IQR]: 2.0–4.0]).

- Mean neutrophil values were variable across cycles. A general decrease in neutrophil count was observed from baseline to Cycle 1, Day 8. At Cycle 2, Day 1, neutrophils were still decreasing and continued to decrease at Cycle 2, Day 15 with a slight increase by Cycle 3, Day 1.[2]
- Please see **Figure 1** below for mean neutrophil values throughout treatment.

Figure 1: Mean (SE) Plot of Neutrophils ($10^{x}9/L$) All-Treated Population. Adopted from Data on File. ADC Therapeutics.[2]



Baseline is defined as the last non-missing value before the initial administration of ADCT-402. Visits with less than 5 assessments of a lab test are not displayed.

- Febrile neutropenia was reported in 5 patients (3.4%) at data cut-off, March 01, 2021.[5]
- In the long-term efficacy and safety report from LOTIS-2 study Grade ≥3 neutropenia was reported in 38 patients (26.2%), all grade neutropenia was observed in 58 of 145 patients (40%).[8.]
    - Grade ≥3 neutropenia in CR patients was observed in 10(27.8%), all grade neutropenia in CR patients was observed in 15 (41.7%).
- There were 16 patients with CR, event-free ≥1 year and 11 patients with CR, event-free ≥2 years.[8]
    - Neutropenia occurred in 6 patients (37.5%) that were event-free ≥ 1 year, and in 4 patients (36.4%) that were event-free ≥2 years.
- Neutropenia led to dose delays and drug withdrawal in 18 patients (12.4%) and in 1 patient (0.7%), respectively.[2,4]

Pooled Data Analysis

- The pooled safety population (N=215) reflects patients with DLBCL who received ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in LOTIS-1 and LOTIS-2 and includes 145 patients from LOTIS-2 treated with 0.15 mg/kg for 2 cycles, followed by 0.075 mg/kg for subsequent cycles.[4,6,7]

- Among patients in the pooled safety population, the median number of ZYNLONTA cycles was 3 (range 1 to 15), with 30% receiving 5 or more cycles.
- Grade 3 or 4 neutropenia occurred in 32% of patients, while Grade 4 neutropenia occurred in 21% of patients.
- Febrile neutropenia was reported in 3% of patients.

Management of Neutropenia and Febrile Neutropenia

- Hematologic abnormalities such as neutropenia and febrile neutropenia were generally reversible and manageable in most patients with dose delays. Guidelines for dose delays and dose modifications are summarized below:[6,7]
- In LOTIS-1, Lonca could be delayed for up to 21 days in any patient experiencing toxicity, until recovery to Grade 1 or baseline grade.[6]
  - Investigators could resume Lonca with 50% dose reduction following assessment of the patient's clinical condition and presence of clinical benefit.
  - If the toxicity recurred in Part 1, treatment with Lonca was discontinued.
  - In Part 2, dose delays could be extended beyond 21 days, in consultation with the sponsor, for patients with toxicities. Lonca could be resumed with 50% dose reduction.
  - If the toxicity recurred, the dose could be reduced by a further 50%. If the toxicity occurred for a third time, the study treatment was permanently discontinued.
- In LOTIS-2, if ZYNLONTA dosing was delayed by more than 3 weeks and the toxicity was considered at least possibly related to ZYNLONTA, then subsequent doses of the drug were reduced by 50%. In addition, the investigator could reduce the dose of ZYNLONTA by 50% for any Grade ≥3 (≥2 for edema, effusion, or increased AST/ALT/GGT) toxicity that was possibly related to ZYNLONTA but did not result in dosing delay of more than 3 weeks if they concluded it was in the best interest of the patients.[7]
  - If toxicity requiring dose reduction as described above occurred following the second dose of ZYNLONTA (0.15 mg/kg), the patient received the per protocol-defined dose of 0.075 mg/kg for Cycle 3.
  - If toxicity as described above recurred at the reduced dose, subsequent doses of ZYNLONTA were reduced by an additional 50%.
  - If toxicity as described above recurred following a second dose reduction, ZYNLONTA was discontinued permanently.
  - If ZYNLONTA dosing was delayed by more than 5 weeks and the toxicity was considered at least possibly related to ZYNLONTA, treatment was permanently discontinued unless continued administration was approved by the Sponsor.

Literature Search

- A PubMed biomedical literature search conducted on November 3, 2025, yielded no further relevant data regarding the incidence of neutropenia with ZYNLONTA.

Relevant Prescribing Information

Section 2: Dosage and Administration[9]

2.3: Dosage Modifications and Delays[9]

Table 4: Recommended Dosage Modifications for Adverse Reactions. Adapted from Prescribing Information.[9]

Adverse Reactions	Severity[a]	Dosage Modification
Hematologic Adverse Reactions		
Neutropenia *[see Warnings and Precautions (5.2)]*	Absolute neturophil count less than 1 x 10^9/L	Withhold ZYNLONTA until neturophil counts returns to 1 x 10^9/L or higher
Thrombocytopenia *[see Warnings and Precautions (5.2)]*	Platelet count less than 50,000/mcL	Withhold ZYNLONTA until platelet count returns to 50,000/mcL or higher

Recommendations for Dosage Delays

- If dosing is delayed by more than 3 weeks due to toxicity related to ZYNLONTA, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation.[9]
- Note: If toxicity requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the dose of 0.075 mg/kg for Cycle 3.[9]

Section 5: Warnings and Precautions[9]

5.2: Myelosuppression[9]

- Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3%.
- Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony stimulating factor administration as applicable.

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 May 13;137(19):2634-2645. DOI: 10.1182/blood.2020007512.

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

[3] Data on File. LOTIS-1 Clinical Study Report. ADC Therapeutics.

[4] 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. *Lancet Oncol*. 2021 May 11;S1470-2045(21)00139-X. DOI: 10.1016/S1470-2045(21)00139-X.

[5] Kahl BS, Hamadani M, Caimi F, 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 Society of Hematologic Oncology (SOHO) Virtual Congress; September 8–11, 2021; Virtual.

[6] 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 [supplementary appendix]. Blood. 2021 May 13;137(19):2634-2645. DOI: 10.1182/blood.2020007512.

[7] 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; S1470-2045(21)00139-X. DOI: 10.1016/S1470-2045(21)00139-X.

[8] Caimi PF, Ai WZ, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, Kahl BS, Radford J, Solh M, Stathis A, Zinzani PL, Wang Y, Qin Y, Wang L, Xu ZC, Carlo-Stella C. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase 2 LOTIS-2 study. Hematologica; https://doi.org/10.3324/haematol.2023.283459 [Early view].

[9] 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.