ZYNLONTA® (loncastuximab tesirine-lpyl) – Renal Safety and Use in Post-Transplant Lymphoproliferative Disorder (PTLD)

Summary

- LOTIS-1 was the first-in-human Phase 1, open-label, single-arm, multicenter study that evaluated the safety and tolerability of ZYNLONTA in 183 patients (>18 years of age) with relapsed or refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL).[1,4]
    - In LOTIS-1 trial, 24 out of 183 patients (13.1%) reported renal and urinary disorders, with 7 patients (3.8%) experiencing Grade ≥3 events.
- LOTIS-2 was a Phase 2, open-label, single-arm, multicenter study which evaluated the efficacy and safety of ZYNLONTA monotherapy in patients with R/R diffuse large B-cell lymphoma (DLBCL) following >2 lines of prior systemic therapy.[2,5]
    - In LOTIS-2 trial, 14 out of 144 patients (9.7%) experienced renal-related treatment-emergent adverse events (TEAEs), including 4 patients (2.8%) with Grade 3 and 1 patient (0.7%) with a Grade 5 event.
- An independent case report demonstrated clinical benefit of ZYNLONTA in a patient with Post-Transplant Lymphoproliferative Disorder (PTLD) and severe renal dysfunction, with no evidence of treatment-related renal deterioration.[3]

Background

- ZYNLONTA is an antibody drug conjugate (ADC) comprised of a humanized anti-CD19 monoclonal antibody (Ab) conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin.[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's Lymphoma (B-NHL).[1]
    - LOTIS-2 was a pivotal Phase 2, open-label, single-arm, multicenter study that evaluates the efficacy and safety of ZYNLONTA monotherapy in adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) following ≥2 lines of prior systemic therapy.[2]
- PTLD is a severe complication of solid organ transplantation, often associated with prolonged immunosuppression. DLBCL is the most common subtype.[3]

Clinical Data

LOTIS-1 (Phase 1)[1]

- All grade renal and urinary disorders were reported in 24 patients (13.1%), Grade ≥3 events occurred in 7 patients (3.8%), including: Acute kidney injury: 6 patients (3.3%), Hematuria: 1 patient (0.5%), Oliguria: 1 patient (0.5%), Anuria: 1 patient (0.5%).

LOTIS-2 (Phase 2)

- All grade renal-related TEAEs were reported in 14 patients (9.7%), Grade 3 events occurred in 4 patients (2.8%), and Grade 5 events in 1 patient (0.7%).[2,5]
    - Events included: Acute kidney injury: 4 patients (2.8%), Hydronephrosis: 2 patients (1.4%). Other renal TEAEs included dysuria 2 patients (1.4%), pollakiuria 2 patients (1.4%), nocturia 1 patient (0.7%), urinary incontinence 1 patient (0.7%) and ureterolithiasis 1 patient (0.7%).

- Acute kidney injury reported as a TEAE leading to a fatal outcome in one patient was not considered related to ZYNLONTA therapy.[5]
- There was no cumulative renal function decline, and mean creatinine levels remained stable throughout cycles.[5]

Independent Case Report: Use of ZYNLONTA in PTLD[3]

- Alshemmari et al. (2025) reported a case involving a 41-year-old female kidney transplant recipient with DLBCL-type PTLD. After relapse following R-CHOP and polatuzumab-based therapy, she presented with cervical lymphadenopathy and tonsillar involvement.
  - The patient had severe renal dysfunction, serum creatinine 633 µmol/L, eGFR <10 mL/min/1.73 m².
  - She received 4 cycles of ZYNLONTA, 0.15 mg/kg for cycles 1–2 and 0.075 mg/kg for cycles 3–4.
    - PET scan after 4 cycles demonstrated complete metabolic response. A 5th cycle was administered without renal deterioration.

Tables

Table 1. Renal-Related TEAEs by System Organ Class in LOTIS-1 (Safety Analysis Set)[4]

TEAE, n (%)	Dose (µg/kg)				
	≤90*	120	150	200	
	Part 1 (N=17)	Part 1+2 (N = 42)	Part 1+2 (N = 88)	Part 1 (N = 36)	Total (N=183)
Renal and Urinary Disorders	1 (25.0)	9 (21.4)	10 (11.4)	4 (11.1)	24 (13.1)
Acute Kidney Injury	-	2 (4.8)	3 (3.4)	1 (2.8)	6 (3.3)
Dysuria	-	1 (2.4)	2 (2.3)	1 (2.8)	4 (2.2)
Hematuria	-	1 (2.4)	2 (2.3)	-	3 (1.6)
Pollakiuria	-	1 (2.4)	2 (2.3)	-	3 (1.6)
Proteinuria	-	1 (2.4)	1 (1.1)	-	2 (1.1)
Urinary incontinence	-	-	2 (2.3)	-	2 (1.1)
Urinary retention	1 (5.9)**	1 (2.4)	-	-	2 (1.1)
Anuria	-	-	-	1 (2.8)	1 (0.5)
Bladder Spasm	1 (5.9)**	-	-	-	1 (0.5)
Hydronephrosis	-	1 (2.4)	-	-	1 (0.5)
Nocturia	-	-	-	1 (2.8)	1 (0.5)
Oliguria	-	1 (2.4)	-	-	1 (0.5)
Renal failure	-	1 (2.4)	--	-	1 (0.5)

Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion
*No renal-related adverse events were reported in 30 µg/kg, 60 µg/kg, or 90 µg/kg treatment groups. **15 µg/kg treatment arm

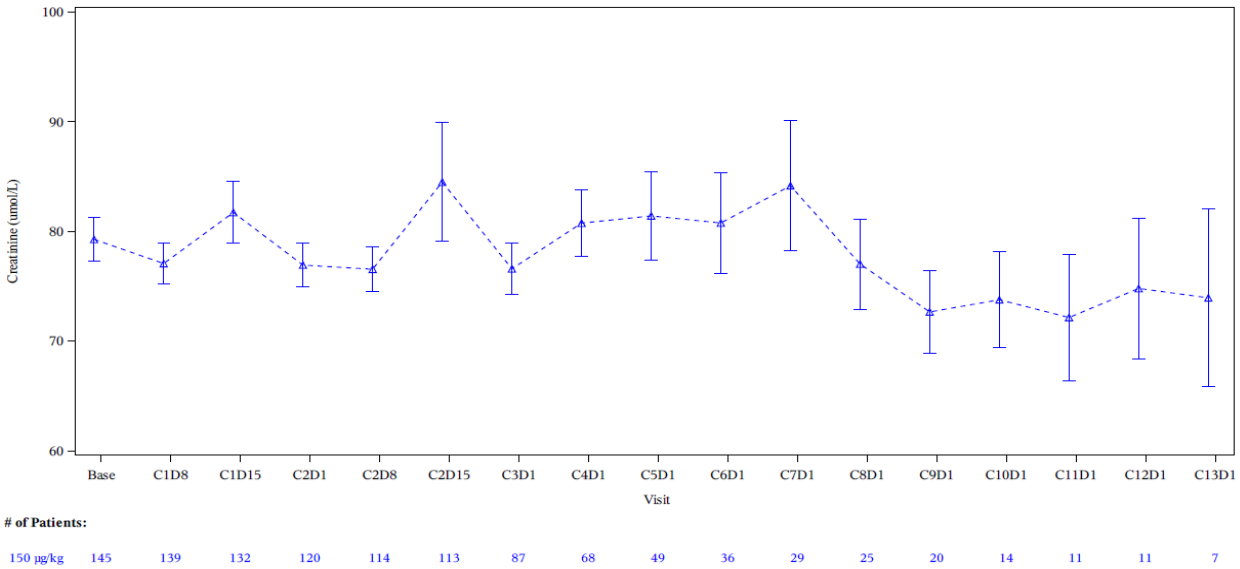
Table 2. Renal-Related TEAEs in LOTIS-2 (All-Treated Population) Adapted from Data on File ADC Therapeutics[5]

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
Renal and Urinary Disorders	9 (6.2)	0	4 (2.8)	0	1 (0.7)	14 (9.7)
Acute Kidney Injury	2 (1.4)	0	1 (0.7)	0	1 (0.7)	4 (2.8)
Dysuria	2 (1.4)	0	0	0	0	2 (1.4)
Hydronephrosis	0	0	2 (1.4)	0	0	2 (1.4)
Pollakiuria	2 (1.4)	0	0	0	0	2 (1.4)

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)
Bladder Hypertrophy	1 (0.7)	0	0	0	0	1 (0.7)
Bladder Spasm	0	1 (0.7)	0	0	0	1 (0.7)
Nocturia	1 (0.7)	0	0	0	0	1 (0.7)
Ureterolithiasis	0	0	1 (0.7)	0	0	1 (0.7)
Urinary incontinence	1 (0.7)	0	0	0	0	1 (0.7)
Urinary retention	0	1 (0.7)	0	0	0	1 (0.7)

Patients received ZYNLONTA intravenously on Day 1 of each 21-day cycle, at 150 µg/kg for 2 cycles, then 75 µg/kg thereafter.

Figure 1: Mean (SE) Plot of Creatinine (umol/L) All-Treated Population. Adopted from Data on File. ADC Therapeutics.[5]



Note: 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. C-cycle. D-day.

Literature Search

- A PubMed biomedical literature search conducted on May 28, 2025, yielded an independent case report on use of ZYNLONTA in the management of DLBCL as PTLD in a kidney transplant recipient.

Relevant Prescribing Information

Section 12: Pharmacokinetics[6]

Section 12.3: Specific Populations

- No clinically significant differences in the pharmacokinetics of loncastuximab tesirine-lpyl were observed based on age (20-94 years), sex, race (White vs. Black), body weight (42.1 to 160.5 kg), ECOG status (0 to 2) or mild to moderate renal impairment (CLcr 30 to <90 mL/min using the Cockcroft-Gault equation).
- The effect of severe renal impairment (CLcr 15 to 29 mL/min), and end-stage renal disease with or without hemodialysis on loncastuximab tesirine-lpyl pharmacokinetics is unknown.

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]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
[3]Alshemmari S, et al. *Management of Diffuse Large B-Cell Lymphoma as PTLD in a Kidney Transplant Recipient: A Case Report.* Hematol Rep. 2025;17(3):22. doi: 10.3390/hematolrep17030022
[4]Data on File, LOTIS 1 Clinical Study Report. ADC Therapeutics.
[5]Data on File, LOTIS 2 Clinical Study Report. ADC Therapeutics.
[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.