Mistry et al Case Study: Photosensitivity rash associated with ZYNLONTA® (loncastuximab tesirine-lpyl)

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]
    - Grade ≥3 skin and subcutaneous tissue disorders included exfoliative rash, photosensitivity reaction and rash (n=1, 0.5% each).
- 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 relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) following >2 lines of prior systemic therapy.[2]
    - In LOTIS-2, treatment-emergent adverse event of photosensitivity reaction occurred in 12 patients (8%) (Grade 1-2) and 3 patients (2%) (Grade 3).
    - Grade ≥3 photosensitivity typically occurred within the first 2 treatment cycles, with a median onset of 32 days, and a median duration of 38 days.
- In the pooled safety population, serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.[4]
    - The pooled safety population 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 studies.
- An independent case study by Mistry H.E et al at the University of Texas MD Anderson Cancer Center, on photosensitivity rash associated with ZYNLONTA highlighted two unique patients who experienced grade 3 photosensitivity rash associated with ZYNLONTA within the first two cycles of therapy for R/R DLBCL.[3]
    - The first patient developed a severe rash to sun- exposed areas (bilateral forearms, neck, and ears). Patient responded with improvement to clobetasol cream, cetirizine, famotidine, and l-lysine within a few days.
    - The patient continued with treatment, achieving a complete response that lasted for a total of 9 cycles.
    - The second patient responded with improvement to clobetasol cream, cetirizine, famotidine, and l-lysine within 2 days, thereby allowing her to continue ZYNLONTA treatment without delay.
- The underlying mechanism regarding the incidence of dermatologic rash in relation to antibody drug conjugate therapy ZYNLONTA, is related to the cytotoxic payload, tesirine, which may have off-target effect on cutaneous DNA, leading to increasing susceptibility to UV radiation.[3]
    - Histamine 1 (H1), (H2) blocker, and corticosteroids diminish the immune response thereby mitigating and managing photosensitivity skin reactions.
- Please consider consultation with a dermatologist and defer to your clinical judgement when managing photosensitivity reactions.
- ADC Therapeutics does not make recommendations regarding the specific duration of time a patient is required to remain out of sunlight, nor does ADC Therapeutics make

recommendations for the management of photosensitivity reactions outside of what is contained in the Prescribing Information.

Independent Case Report

Case Report 1[3]

- Patient was a 72-year-old Caucasian man with non-germinal center (GCB) DLBCL, who presented with stage IV disease cutaneous lesions, a right testicular mass, retroperitoneal nodal involvement, innumerable bone marrow, liver lesions, pituitary, and leptomeningeal disease on MRI (confirmed via cerebral spinal fluid). He received R-CHP without vincristine (rituximab, cyclophosphamide, doxorubicin, prednisone), tafasitamab lenalidomide, and ZYNLONTA.
    - Within the first two cycles of ZYNLONTA, the patient developed a severe rash to sun-exposed areas (bilateral forearms, neck, and ears). Patient responded with improvement within a few days to clobetasol cream, cetirizine, famotidine, and l-lysine.
    - The patient continued with treatment, achieving a complete response that lasted for a total of 9 cycles.

Case Report 2[3]

- Patient was a 55-year-old woman with biopsy proven stage IV DLBCL, non-GCB subtype, originally transformed from follicular lymphoma (FL), that received bendamustine rituximab, spinal radiation, polatuzumab plus R-CHP and ZYNLONTA.
    - Patient had photosensitivity rash within the first two cycles of ZYNLONTA, which she responded with improvement to clobetasol cream, cetirizine, famotidine, and l-lysine within 2 days, thereby allowing her to continue ZYNLONTA treatment without delay.

Management of Photosensitivity Reactions[3]

- Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions.
    - Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution to Grade 1 or less.
    - Patients should be advised to minimize or avoid exposure to direct natural or artificial sunlight and to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products.
    - Patients should be advised to minimize or avoid peeling open skin wounds to decrease the risk of skin infections.
    - If a skin reaction or rash develops, topical steroids, H1 blocker, + H2 blocker, and dermatologic consultation should be considered.
- Topical treatments (including topical steroids or other agents), as well as oral antipruritic agents were permitted in clinical trials. However, the efficacy of these supportive treatment options in managing and treating cutaneous reactions associated with ZYNLONTA treatment has not been established. Please consider consultation with a dermatologist and defer to your clinical judgement when managing photosensitivity reactions.

Literature Search

- A PubMed biomedical literature search conducted on August 8, 2025, yielded no further relevant data regarding photosensitivity rash associated with ZYNLONTA.

Relevant Prescribing Information

Section 2: Dosage and Administration[4]

2.3: Dose Delays and Modifications

Table 4: Dose Delays and Modifications. Adapted from Prescribing Information.

Adverse Reactions	Severity[a]	Dosage Modification
Nonhematologic Adverse Reactions		
Other Adverse Reactions [*see Warnings and Precautions (5.3), (5.4), Adverse Reactions (6.1)*]	Grade 3[a] or higher	Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less

[a] National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

- 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.
- 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.

Section 5: Warnings and Precautions[4]

5.4: Cutaneous Reactions

- Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema.
- Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution.
- Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered.

Section 6: Adverse Reactions[4]

6.1: Clinical Trials Experience
Relapsed or Refractory Diffuse Large B-Cell Lymphoma

- All-grade rash, pruritis, and photosensitivity reaction occurred in 30%, 12%, and 10% of patients, respectively, while Grade 3 rash and Grade 3 photosensitivity reaction occurred in 2% of patients each.
- Hyperpigmentation (4%) was included as a clinically relevant adverse reactions in <10% of patients (all grades) who received ZYNLONTA.

6.2: Postmarketing Experience

- The following adverse reactions have been identified during post approval use of ZYNLONTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
    - **Skin and Subcutaneous Tissue Disorders:** telangiectasia, blister, rash vesicular.

Section 12: Clinical Pharmacology[4]

12.2: Pharmacodynamics

- Higher loncastuximab tesirine-lpyl exposure in Cycle 1 was associated with higher incidence of some Grade ≥2 adverse reactions, including skin and nail reactions, liver function test abnormalities and increased gamma-glutamyltransferase.
- Lower loncastuximab tesirine-lpyl exposure in Cycle 1 was associated with lower efficacy over the dose range of 0.015-0.2 mg/kg (0.1 to 1.33 times the maximum recommended dose).

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] 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. Haematologica. 2024;109:1184-1193

[3] Mistry HE, Ahmed S. et al. Case study: Photosensitivity rash associated with loncastuximab tesirine. The University of Texas MD Anderson Cancer Center. Houston, TX, USA

[4] 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.