ZYNLONTA® (loncastuximab tesirine-lpyl) – Incidence and Management of Dermatologic Reactions

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]
    - Of the total population, skin- or nail-related toxicities were reported in 98 patients (53.6%) and were most commonly rash (45 patients, 24.6%), erythema (21 patients, 11.5%), pruritus (20 patients, 10.9%) and maculopapular rash (19 patients, 10.4%).[1]
    - Grade ≥3 treatment emergent skin and subcutaneous tissue disorders occurred in 1 patient receiving Lonca 120 µg/kg and in 2 patients receiving Lonca 150 µg/kg.[3]
    - Grade ≥3 skin and subcutaneous tissue disorders included exfoliative rash, photosensitivity reaction and rash (n=1, 0.5% each).[3]
    - In the diffuse large B-cell lymphoma (DLBCL) subset (n=139), a total of 77 patients (55.4%) experienced all grade skin and subcutaneous tissue disorders.[3]
    - Rash was most common in sun-exposed areas and most affected patients continued treatment as planned.[1]
    - A small proportion of patients were managed with dose delays (1.6% each of patients with rash and maculopapular rash) and 2 patients (1.1%) discontinued treatment.[1]
- LOTIS-2 was a pivotal Phase 2, open-label, single-arm, multicenter study that 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.[2]
    - Skin- or nail-related treatment-emergent adverse events (TEAEs) occurred in 63 patients (43.4%) and were considered likely to be related to the pyrrolobenzodiazepine (PBD) payload.[2,4]
    - 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.[5]
    - Clinically relevant hyperpigmentation (all grades) occurred in 4% of patients. [5]
- 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.[9]
    - 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.
- Telangiectasia, blister, rash vesicular 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.[9]
- The underlying mechanism regarding the incidence of dermatologic rash in relation to antibody drug conjugate therapy loncastuximab tesirine (ZYNLONTA), is related to the cytotoxic payload, tesirine, which may have off-target effect on cutaneous DNA, leading to increasing susceptibility to UV radiation.[5,6]
    - Patients who receive immunotherapy have an increased histamine and histamine receptor (H1) within the tumor microenvironment.

    - H1 blocker, H2 blocker, and corticosteroids have been used to 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 dermatologic reactions.[5,7]
- 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 dermatologic reactions outside of what is contained in the Prescribing Information.
- See **Prevention and Management of Dermatologic Reactions**, as well as **Relevant Prescribing Information** for additional information regarding the management of skin reactions with ZYNLONTA therapy.

Background

- 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. The study was conducted in two parts, dose-escalation (Part 1), followed by dose-expansion (Part 2).[1]
- LOTIS-2 was a Phase 2, open-label, single-arm, multicenter study that 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.[2]

Clinical Data

LOTIS-1

- In Part 1 of the LOTIS-1 study, 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, while 69 patients received Lonca 150 µg/kg Q3W, with some patients in the 150 µg/kg dose cohort reducing their 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]
- Of the overall population (N=183), 102 patients (55.7%) experienced all grade treatment emergent skin and subcutaneous tissue disorders.[3]
    - Of the total population, skin- or nail-related toxicities were reported in 98 patients (53.6%) and were most commonly rash (45 patients, 24.6%), erythema (21 patients, 11.5%), pruritus (20 patients, 10.9%) and maculopapular rash (19 patients, 10.4%).[1]
    - Grade ≥3 treatment emergent skin and subcutaneous tissue disorders occurred in 1 patient receiving Lonca 120 µg/kg and in 2 patients receiving Lonca 150 µg/kg.
        - Grade ≥3 skin and subcutaneous tissue disorders included Grade 3 exfoliative rash, photosensitivity reaction and rash (n=1, 0.5% each).[3]
    - Rash was most common in sun-exposed areas and most affected patients continued treatment as planned.[1]
    - A small proportion of patients were managed with dose delays (1.6% each of patients with rash and maculopapular rash), while 2 patients (1.1%) discontinued treatment.[1]
- **Table 1** contains additional information regarding reports of treatment-emergent skin and subcutaneous reactions across all dosage cohorts in LOTIS-1.

Table 1. Proportion of Patients Experiencing All-Grade Skin and Subcutaneous TEAEs in LOTIS-1. (Safety Analysis Set) Adapted from Hamadani et al. *Blood* 2020 and Data on File, LOTIS-1 Clinical Study Report. ADC Therapeutics.[1,3]

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)	
Skin and Subcutaneous Tissue Disorders[a]	8 (47.1)	25 (59.5)	47 (53.4)	22 (61.1)	102 (55.7)
Rash[b]	2 (11.8)	7 (16.7)	27 (30.7)	9 (25.0)	45 (24.6)
Erythema[b]	1 (5.9)	5 (11.9)	11 (12.5)	4 (11.1)	21 (11.5)
Pruritis[b]	2 (11.8)	4 (9.5)	7 (8.0)	7 (19.4)	20 (10.9)
Rash maculopapular[b]	3 (17.6)	4 (9.5)	7 (8.0)	5 (13.9)	19 (10.4)
Skin hyperpigmentation[b]	1 (6.0)	3 (7.1)	5 (5.7)	4 (11.1)	13 (7.1)
Photosensitivity reaction[b]	0 (0.0)	4 (9.5)	3 (3.4)	3 (8.3)	10 (5.5)

Values are n (%); TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion. [a]Occurring in ≥5% of patients. [b]Occurring in ≥ 10% of patients.

DLBCL Patient Subset

- In the DLBCL subset, a total of 77 patients (55.4%) experienced all grade skin and subcutaneous tissue disorders. Table 2 contains additional information regarding reports of skin reactions and nail disorders.[3]
- **Table 2** provides additional information regarding the proportion of patients with DLBCL experiencing dermatologic-related TEAEs.

Table 2. Proportion of DLCBL Patients Experiencing Skin and Subcutaneous TEAEs in LOTIS 1(Safety Analysis Set). Adapted Data on File, LOTIS-1 Clinical Study Report. ADC Therapeutics.[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)	
Skin and Subcutaneous Disorders[a]	5 (50.0)	18 (56.3)	38 (54.3)	16 (59.3)	77 (55.4)
Rash	1 (10.0)	5 (15.6)	25 (35.7)	5 (18.5)	36 (25.9)
Pruritis	1 (10.0)	4 (12.5)	7 (10.0)	5 (18.5)	17 (12.2)
Rash maculopapular	3 (30.0)	3 (9.4)	4 (5.7)	4 (14.8)	14 (10.1)
Erythema	0 (0)	2 (6.3)	7 (10.0)	2 (7.4)	11 (7.9)
Skin hyperpigmentation	1 (10.0)	1 (3.1)	3 (4.3)	3 (11.1)	8 (5.8)

Values are n (%); DLBCL, diffuse large B-cell lymphoma; TEAE, treatment-emergent adverse event; Part 1, dose escalation; Part 2, dose expansion [a]Occurring in ≥5% patients.

LOTIS-2

- Skin- or nail-related TEAEs occurred in 63 patients (43.4%) and were considered likely to be related to the PBD payload.[2,4]
    - 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.[5]
- Clinically relevant hyperpigmentation (all grades) occurred in 4% of patients.[5]

Pooled Data

- 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.[9]
    - 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.

Case Series

- A case series at one site describes 6 patients (age range, 30–80 years) who received loncastuximab tesirine or rovalpituzumab tesirine; each patient experienced a progressive telangiectatic rash that developed over the upper and lower extremities of the body.[6]
    - Patients were diagnosed with mantle cell lymphoma, follicular lymphoma, or DLCBL.
    - A total of 5 patients received loncastuximab, in LOTIS- 2, with cycles ranging from 3 to 9.
    - The timing of the onset of rash was described as follows: occurring during treatment for 2 patients receiving ZYNLONTA; occurring during the last month of treatment for one patient receiving rovalpituzumab tesirine; and occurring 3 months after therapy, 4 months after treatment, and 16 months following therapy (one patient each, all receiving loncastuximab). None of these events were reported to ADC Therapeutics as adverse events during the conduct of the trial.[7]
    - None of the patients experienced an improvement in rash during the follow up periods ranging from 8 months to 2 years.[7]
    - One patient received treatment for rash which consisted of methylprednisolone and hydrocortisone 1% ointment. Additional information regarding management of rash in this patient was not available.[6]
    - In all cases, rash persisted months to years after discontinuation of antibody drug conjugate therapy. Based on these findings, authors suggested patient counseling that rash may be permanent in certain individuals who are receiving antibody drug conjugate therapy containing the cytotoxic payload, tesirine. Authors also suggested tesirine could lead to off-target cutaneous DNA damage and potentially increase susceptibility to UV radiation.[6]
- Another independent case study, highlighted two unique patients who experienced grade 3 photosensitivity rash associated with ZYNLONTA within the first two cycles of therapy for R/R DLBCL.[5]
    - 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.

Report of Spontaneous Post marketing Cases[7,8]

- In an independent case study by the American Medical Association, blistering lesions associated with ZYNLONTA were presented.[8]
  - Two adult patients with DLBCL presented with similar vesicular lesions (small, tense blisters) after receiving cycles 3 and 4 cycles of treatment with ZYNLONTA.
  - Patient 1 was an 89-year-old female and patient 2 was a 68-year-old male.
  - Both patients had a recent history of a photodistributed eruption that appeared within weeks of initiating treatment with ZYNLONTA, along with concurrent bilateral lower extremity edema.
  - In both patients, 2-mm to 4-mm vesicles were filled with clear fluid and surrounded by mild erythema.
  - These 2 cases suggest that there is a novel association between ZYNLONTA and bullous dermatitis.
  - Both patients were treated with supportive management, the lesions in patient 1 resolved following discontinuation of ZYNLONTA treatment and there has been no reoccurrence till date. Patient 2 died before able to access course of lesions.
  - Table 3 provides additional information about the 2 patients demographic characteristics, oncologic history, and dermatological clinical and pathologic features.

Characteristic	Patient 1	Patient 2
Age, y	89	68
Sex	Female	Male
Oncologic diagnosis	MZL with transformation to DLBCL	FL with transformation to DLBCL
Prior therapies	RCHOP, BR, ibrutinib	RCHOP, R-GemOc, radiotherapy
Current therapy	ZYNLONTA monotherapy	ZYNLONTA monotherapy
No. of cycles before onset of vesicular rash	3 cycles (7 wk. after initiation)	4 cycles (12 wk after initiation)
Additional skin manifestations	Photodistributed rash involving other sites that preceded blisters; development of bilateral lower extremity edema with hydrostatic bullae and MSSA in association with edema/skin breakdown	Recent photodistributed rash on other sites that preceded blisters; worsening acute on chronic pitting edema of lower extremities with tense bullae and Enterococcus faecalis, Pseudomonas aeruginosa, and Klebsiella oxytoca in association with edema/skin breakdown
Lesion morphology	Scattered 2-mm to 4-mm vesicles with mild surrounding erythema	Scattered 2-mm to 3-mm vesicles with mild surrounding erythema
HSV PCR, VSV PCR, bacterial cultures from vesicular rash	Negative	Negative
Biopsy HE	Cell-poor subepidermal vesicular dermatitis without substantial dermal edema	Subepidermal vesicular dermatosis with interface dermatitis and epidermal dysmaturation without substantial dermal edema
Biopsy DIF	Fine granular IgA at the	Few grains of IgA along the

	basement membrane	basement membrane zone
Management	Supportive management	Supportive management
Course of lesions	Resolution following discontinuation of treatment with LT for other reasons, no recurrence to date	Unable to assess (patient died)

Abbreviations: BR, bendamustine, rituximab; DIF, direct immunofluorescence; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HE, hematoxylin-eosin; HSV, herpes simplex virus; Ig, immunoglobulin; LT, loncastuximab tesirine; MZL, marginal zone lymphoma; PCR, polymerase chain reaction; RCHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; R-GemOx, gemcitabine-oxaliplatin plus rituximab; VSV, vesicular stomatitis virus

- The underlying mechanism regarding the incidence of dermatologic rash in relation to antibody drug conjugate therapy loncastuximab tesirine (ZYNLONTA), is related to the cytotoxic payload, tesirine, which may have off-target effect on cutaneous DNA, leading to increasing susceptibility to UV radiation.[6]

Independent case study - Cutaneous Collagenous Vasculopathy (CCV) associated with the use of ZYNLONTA.[9]

- The case study is completely independent of ADC therapeutics, further research is necessary to fully understand the underlying mechanism and strategies for management of CCV.
- It highlighted the importance of monitoring patients on ZYNLONTA for the development of vascular adverse events.
    - It is recommended to monitor patients on ZYNLONTA for signs of cutaneous vascular changes, particularly telangiectasias.
    - It is recommended to consider histopathological examination for persistent or progressive telangiectasia to rule out CCV.
- A female patient in her 60s with a history of untreated hypertension and DLBCL experienced a relapse 5 years after achieving remission with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). After disease progression on second-line therapy (R-DHAP: rituximab, dexamethasone, cytarabine, and cisplatin), she initiated on third-line treatment with ZYNLONTA.
    - The patient underwent 17 cycles of ZYNLONTA over one year, achieving complete remission. However, 3 months into treatment, she developed asymptomatic, progressive telangiectasias over her trunk and extremities, sparing the face, palms, soles, and mucous membranes. These lesions were persistent and widespread, involving both the flexor and extensor surfaces.
    - Dermatologic examination and histopathological analysis revealed dilated small vessels with thickened hyaline walls and perivascular hyalinization in the papillary and reticular dermis. Immunolabeling confirmed the presence of type IV collagen in the perivascular regions, consistent with a diagnosis of CCV.

Animal Studies

- In animal studies, black skin spots potentially related to phototoxicity were observed and were still present after the 12-week treatment-free period.[6]

Management of Dermatologic Reactions[5]

- Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions.[5]
    - 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 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 dermatologic reactions.[7]
- ADC Therapeutics does not make recommendations for the management of dermatologic reactions outside of what is contained in the Prescribing Information. Please defer to your clinical judgement when managing dermatologic reactions.

Literature Search

- A PubMed biomedical literature search conducted on August 12, 2025, yielded no further relevant data regarding the incidence and management of dermatologic reactions with ZYNLONTA.

Relevant Prescribing Information

Section 2: Dosage and Administration[10]

2.3: Dose Delays and Modifications

Table 4: Dose Delays and Modifications. Adapted from Prescribing Information.[10]

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
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
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[9]

- 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
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. Haematol. Published online August 31, 2023. doi: 110.3324/haematol.2023.283459

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

[4] 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.

[5] 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

[6] Sorensen EP, Thrush J, Bartlett NL, et al. Diffuse telangiectatic rash associated with novel antibody drug conjugate therapies. *JAMA Dermatol*. 2020 May 1;156(5):601-603.

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[8] Gociman S, Baron K, Hu B, Zussman J, Madigan LM. Blistering Lesions Associated with Loncastuximab Tesirine. JAMA Dermatol. 2022 May 18. doi: 10.1001/jamadermatol.2022.1389. Online ahead of print.

[9] Michelerio A, Cabutti F, Tomasini C. Cutaneous Collagenous Vasculopathy Associated With Antibody-Drug Conjugate Treatment. *JAMA Dermatol.* Published online August 21, 2024. doi:10.1001/jamadermatol.2024.2324.

[10] 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.