A Pooled Safety Analysis of Loncastuximab Tesirine in R/R DLBCL in the LOTIS Clinical Trial Program: Incidence, Onset, and Management of Myelosuppression

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INTRODUCTION

- Although there are numerous therapeutic options available for the treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), an optimal treatment regimen has not been established due to the substantial toxicities associated with these treatments.[1-4]
- Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca) is an FDA-approved antibody-drug conjugate (ADC) comprised of an anti-CD19 antibody conjugated to the alkylating agent SG3199, a pyrrolobenzodiazepine dimer cytotoxin, designed to target and kill CD19-expressing malignant B-cells.[5]
- Lonca is indicated for the treatment of adult patients with R/R large B-cell lymphoma after ≥2 prior systemic therapies, including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.[5]
- The antitumor activity and safety of Lonca as a single agent has been evaluated in patients with R/R B-cell non-Hodgkin lymphoma in the phase 1 trial (LOTIS-1; NCT02669017) and in patients with R/R DLBCL in the phase 2 trial (LOTIS-2; NCT03589469).[6,7]
  - A pooled analysis of myelosuppression events in LOTIS-1 and LOTIS-2 (data cutoff: August 6, 2020) showed a moderate incidence of grade ≥3 myelosuppression events with single-agent Lonca treatment, which were manageable with dose delays and did not typically result in dose reductions.[8]

OBJECTIVE

- To present the results of an updated analysis, characterizing the incidence, time to onset, and management of grade ≥3 myelosuppression from a pooled safety analysis of patients treated with Lonca for patients with R/R DLBCL in LOTIS-1 and LOTIS-2 (data cutoff: March 1, 2021).

METHODS

Study Design

- Patients with R/R DLBCL in the completed phase 1 LOTIS-1 (NCT02669017) and the ongoing phase 2 LOTIS-2 (NCT03589469; World Health Organization 2016 classification; data cutoff: March 1, 2021) trials received Lonca every 3 weeks intravenously.
  - LOTIS-1: doses ranged from 0.015 to 0.2 mg/kg; however, only patients treated at the initial dose of 0.15 mg/kg were included in this pooled analysis.
  - LOTIS-2: approved dose of 0.15 mg/kg for 2 cycles followed by 0.075 mg/kg for subsequent cycles.
- Growth factors were permitted according to ASCO guidelines in both trials.
- Laboratory values were monitored at least weekly for the first 2 cycles and every 3 weeks thereafter.

Myelosuppression Events (Neutropenia, Thrombocytopenia, Anemia)

- Incidence of grade 3/4 adverse events (AEs) based on laboratory abnormalities (**Table 1**)
- Time to onset of AEs
- Dose delay due to AEs
- Dose reduction due to AEs
- Treatment discontinuation due to AEs

Table 1. Myelosuppression event definitions

Neutropenia	
Grade 3	1.0 – 0.5 × 10^9/L
Grade 4	<0.5 × 10^9/L
Thrombocytopenia	
Grade 3	50.0 – 25.0 × 10^9/L
Grade 4	<25.0 × 10^9/L
Anemia	
Grade 3	Hemoglobin <80 g/L or transfusion indicated
Grade 4	Life-threatening consequences or urgent intervention

Statistical Analysis

- Safety analyses were conducted in the all-treated population, who received ≥1 dose of Lonca.
- Time to event analyses were performed for grade 3/4 neutropenia, thrombocytopenia, and anemia.
  - Analyses were performed if a minimum of 20 patients had an event in at least one dose group.
  - Analyses assessed time to first onset of grade 3/4 anemia, neutropenia, and thrombocytopenia.
- The incidence of hematologic abnormalities was based on laboratory reporting, whereas dose modification was based on adverse event reporting.
- Myelosuppression events were graded according to the Common Terminology Criteria for Adverse Events version 4.0.

RESULTS

Patient Population

- In total, 215 patients received at least one dose of Lonca (0.15 mg/kg) in LOTIS-1 (n=70) or LOTIS-2 (n=145) and were included in this analysis (**Table 2**).

Table 2. Lonca administration and extent of exposure in patients with R/R DLBCL

	Lonca 0.15 mg/kg (N=215)
Total Lonca cycles, n (range)	3 (1, 26)
Duration of treatment, days	45 (1, 569)
Total dose administered, mg	30 (7.5, 112.5)
Total weight-adjusted dose, mg/kg	0.376 (0.122, 2.061)
Average dose per cycle, mg	9.4 (3, 22.2)
Average weight-adjusted dose per cycle, mg/kg	0.126 (0.049, 0.161)

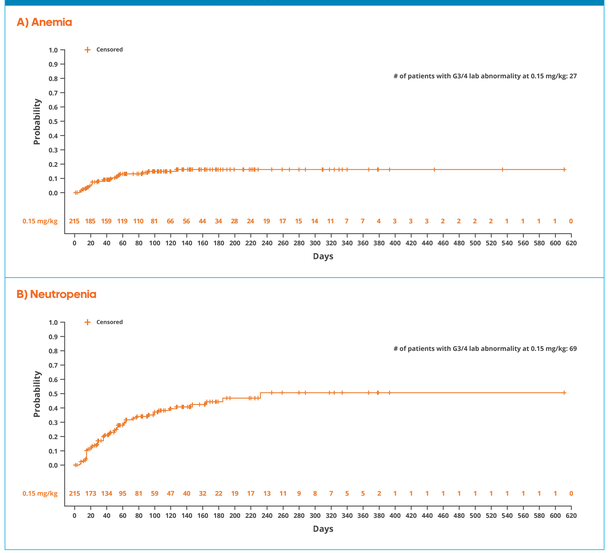
Data are median (min, max).

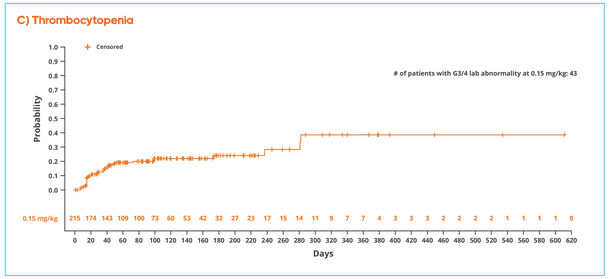
- Neutrophil growth factors were administered to 33.5% (n=72) of patients. They were administered prophylactically to 15.3% (n=33) of patients and as treatment in 26.0% (n=56) of patients.

Myelosuppression Events

- Grade ≥3 neutropenia, thrombocytopenia, and anemia occurred in 32.1% (n=69), 20% (n=43), and 12.6% (n=27) of patients, respectively.
  - Febrile neutropenia occurred in 3.3% (n=7) of patients.
- The time to onset for each myelosuppression event is shown in **Figure 1**.
  - Most patients with grade 3/4 neutropenia experienced onset in the first 4 months.
  - Most patients with grade 3/4 thrombocytopenia or anemia experienced onset in the first 2 months.

Figure 1. Time to first onset of grade 3/4 anemia, neutropenia, and thrombocytopenia in patients who received at least one dose of Lonca (0.15 mg/kg)





- More than half of patients who developed grade ≥3 thrombocytopenia or anemia had grade 1 or 2 thrombocytopenia or anemia at baseline, whereas <10% of patients who developed grade ≥3 neutropenia had neutropenia at baseline (**Table 3**).

Table 3. Incidence of grade ≥3 myelosuppression based on baseline myelosuppression

		0.15 mg/kg (N=215)
	Baseline	Patients With a Maximum Post-Baseline of Grade ≥3 Myelosuppression
Neutropenia	Grade 0, n (%)	63 (29.3)
	Grade 1, n (%)	3 (1.4)
	Grade 2, n (%)	3 (1.4)
	Grade 3, n (%)	0 (0)
	Grade 4, n (%)	0 (0)
Thrombocytopenia	Grade 0, n (%)	17 (7.9)
	Grade 1, n (%)	22 (10.2)
	Grade 2, n (%)	2 (0.9)
	Grade 3, n (%)	1 (0.5)
	Grade 4, n (%)	1 (0.5)
Anemia	Grade 0, n (%)	2 (0.9)
	Grade 1, n (%)	11 (5.1)
	Grade 2, n (%)	14 (6.5)
	Grade 3, n (%)	0 (0)
	Grade 4, n (%)	0 (0)

Values represent the shift summary of hematology results by maximum CTCAE v4.0 grade.

- Dose delays occurred due to grade ≥3 neutropenia, thrombocytopenia, anemia, and febrile neutropenia in 10.2% (n=22), 8.4% (n=18), 1.4% (n=3), and 0.5% (n=1) of patients, respectively.
- Dose reductions due to grade ≥3 neutropenia and thrombocytopenia occurred in 0.5% (n=1) and 0.5% (n=1) of patients, respectively.
- Treatment discontinuation occurred due to grade ≥3 thrombocytopenia and neutropenia in 2.3% (n=5) and 0.5% (n=1) of patients, respectively.
- No dose reductions or treatment discontinuations occurred due to anemia or febrile neutropenia.

CONCLUSIONS

- The incidences of grade ≥3 neutropenia, thrombocytopenia, and anemia were <35%, and the incidence of febrile neutropenia was low (3.3%; data cutoff: March 1, 2021).
- While grade 3/4 neutropenia and thrombocytopenia were among the leading causes of dose delays, most myelosuppression was manageable with dose delays.
- Most grade ≥3 anemia or thrombocytopenia developed in the first 2 months of treatment, and most grade ≥3 neutropenia developed within the first 4 months.
- This extension of previously reported results[8] shows no new safety signals regarding single-agent Lonca treatment in patients with R/R DLBCL.

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Disclosures

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