Incidence, onset, and management of edema and effusion in patients treated with loncastuximab tesirine for R/R DLBCL in the LOTIS clinical trial program

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BACKGROUND

- Loncastuximab tesirine (loncastuximab tesirine-lpyl; Lonca), an anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine (PBD) dimer cytotoxin, is an FDA-approved antibody drug conjugate, indicated for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) after ≥2 lines of systemic therapy.[1]
- Lonca demonstrated substantial single-agent anti-cancer activity in the pivotal phase 2 clinical trial in patients with R/R DLBCL.[2]
  - The ORR was 48.3% and the CR was 24.1%.[2]
- Any-Grade and Grade ≥3 treatment emergent adverse events (TEAEs) were reported in 98.6% (n=143) and 72.4% (n=105) of patients in LOTIS-2, respectively.[2]
- Although the incidence of peripheral edema, localized edema, and pleural effusions was low, they were among the most common adverse events leading to treatment discontinuation.[2]
- Several TEAEs, including edema and effusions, appear to be PBD-related as these toxicities have been seen with other PBD compounds.[3,4]

OBJECTIVE

- To further characterize edema and effusion by assessing the time to onset, duration, and management in the pivotal LOTIS-2 clinical trial.

METHODS

Study Design

- In the open-label, single-arm, phase 2 LOTIS-2 trial (NCT03589469), Lonca was administered intravenously over 30 minutes once every 3 weeks at the labeled dose of 0.15 mg/kg for 2 doses followed by 0.075 mg/kg for subsequent doses in patients with relapsed/refractory DLBCL after ≥2 prior systemic therapies.
- Per study protocol, dexamethasone premedication (4 mg, PO BID) was administered the day before Lonca administration (if possible), the day of Lonca administration, and the day after Lonca administration unless contraindicated.
  - Dexamethasone premedication was administered to reduce the risk of PBD-related toxicities, based on outcomes from the phase 1 dose-finding study (LOTIS-1; NCT02669017).[5]
- Per study protocol, patients with weight gain of more than 1 kg from day 1 of cycle 1, new or worsening edema, and/or new or worsening pleural effusion received standard doses of spironolactone.
- Per study protocol, Lonca was held for any patient that experienced Grade ≥2 edema or effusion until toxicity resolved to Grade ≤1.

Edema and Effusion Events

- Incidence of edema and/or effusion (any Grade and Grade ≥3).
- Time to onset of edema and effusion.
- Duration of edema and effusion.
- Presenting symptoms for edema and effusion.
- Dose delay and treatment discontinuation due to edema and effusion events.
- Rechallenge with Lonca following edema and effusion.

Statistical Analyses

- Safety analyses were conducted in the all-treated population, who received ≥1 dose of Lonca, (April 6, 2020 data cutoff date).
- Missing AE end dates were imputed using the date of new anticancer therapy (NAT), the end of study (EOS) or data cutoff. Partial AE end dates were imputed using the last month or last day of the month bounded by EOS/data cutoff (when EOS is not reached) or NAT date. All AE start dates are complete or partial, with day imputed to the first day of the month, bounded by first dose date.
  - After AE start/end date imputation, duration was calculated at patient level. If patients experienced multiple Preferred Terms (PTs), all PTs with overlap were combined and the duration was calculated from first start date to last end date.

RESULTS

Patient population

- In total, 145 patients received at least one dose of Lonca and were included in the safety analysis.

Edema and Effusion Incidence, Onset, and Duration

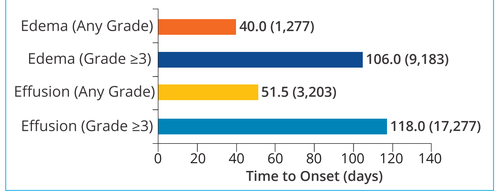
- Any Grade and Grade ≥3 edema occurred in 27.6% and 3.4% of patients, respectively, and any Grade and Grade ≥3 effusion occurred in 11.0% and 2.8% of patients, respectively (**Table 1**).
  - Edema includes edema, face edema, generalized edema, peripheral edema, ascites, fluid overload, peripheral swelling, swelling, and swelling face.

Table 1. Incidence of edema and effusion

	LOTIS-2 (N=145)
Edema, any Grade, n (%)	40 (27.6)
Edema, Grade ≥3	5 (3.4)
Effusion, any Grade	16 (11.0)
Effusion, Grade ≥3	4 (2.8)

- Any Grade edema and effusion typically developed within the first 3 treatment cycles, while Grade ≥3 edema and effusion typically developed within the first 6 treatment cycles (**Figure 1**).

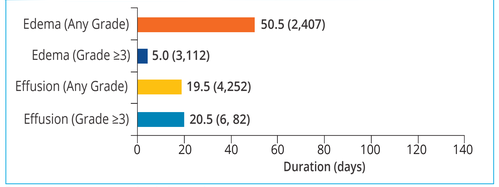
Figure 1. Median time to onset of any Grade and Grade ≥3 edema and effusion



Data labels represent median (min, max).

- The median duration of any Grade edema and effusion was 50.5 and 19.5 days, respectively, and the median duration of Grade ≥3 edema and effusion was 5.0 days and 20.5 days, respectively (**Figure 2**).

Figure 2. Median duration of any Grade and Grade ≥3 edema and effusion



Data labels represent median (min, max).

- Patients with effusions were more likely to have edema.
- No predisposing factors (including medical history, concomitant medications, or reported incidence of hypoalbuminemia) were identified between patients with reported adverse events of edema or effusion and those without.
  - However, other potential causes for effusion, including infection and disease progression, were seen in some patients.

Edema and Effusion Dose Modification

- Dose delay was reported in 8 (5.5%) patients due to edema and 2 (1.4%) patients due to effusion.
- Only 1 (0.7%) patient had dose reduction due to edema and no patients had dose reduction due to effusion.
- Edema and effusion resulted in treatment discontinuation in 4 (2.8%) and 4 (2.8%) patients, respectively.

Edema and Effusion Presentation

- Most patients with edema presented with peripheral edema (72.5%); facial edema was the second most common presentation (17.5%).
- Presenting symptoms were typical for pleural effusion including dyspnea (31.3%), cough (31.3%), and musculoskeletal chest pain (18.8%).

Edema and Effusion Rechallenge

- Among patients who experienced a dose delay due to edema-related events (any grade), 5 patients were able to undergo rechallenge with Lonca.
  - Diuretic therapy was commonly used to manage edema in patients who underwent rechallenge.
- Among patients who experienced a dose delay due to effusion related events (any Grade), 1 patient was able to undergo rechallenge with Lonca.

Edema and Effusion Treatment

- Diuretic therapy (bumetanide, furosemide, or spironolactone) was administered to 20 (50%) of the patients with edema. The median time from the first dose of Lonca to the start of diuretic therapy for edema was 93 days (min, max: 1, 204).
- Diuretic therapy for the treatment of effusion was administered to 7 (43.8%) of the patients with effusion. The median time from the first dose of Lonca to the start of diuretic therapy for effusion was 87 days (min, max: 17, 277).

CONCLUSIONS

- With dexamethasone premedication, edema and effusions in LOTIS-2 were generally reversible and manageable with standard spironolactone, dose delays, and/or dose modifications, as was recommended for Grade ≥2 events.
- Most patients were able to continue therapy with Lonca following an edema- or effusion-related event.
- Grade ≥3 edema or effusion was uncommon and typically developed later in therapy.
- No predisposing factors were identified for the development of edema or effusion.
- While the mechanism is uncertain, edema and effusion appear to be an effect of the of the PDB cytotoxin.

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Disclosures

JP Alderuccio reports consultancy/advisory roles for ADC Therapeutics (self), Agios Pharmaceuticals (immediate family member), Forma Therapeutics (immediate family member), Foundation Medicine (immediate family member), Inovio Pharmaceuticals (immediate family member), and Puma Biotechnology (immediate family member); receipt of research funding from ADC Therapeutics (self); and receipt of honoraria from OncLive and OncInfo (self). K Ardeshna consultancy/advisory roles for and receipt of honoraria from Gilead, Beigene, Celgene, Novartis, and Roche; and receipt of research funding from Novartis, Bristol Myers Squibb, Autolus Therapeutics, ADC Therapeutics, Pharmocyclics, and Janssen. B Hess reports consultancy/advisory roles for ADC Therapeutics, Bristol Myers Squibb, and AstraZeneca. J Radford reports consultancy/advisory roles for ADC Therapeutics, Bristol Myers Squibb, Kite Pharma, and Takeda; stock ownership of ADC Therapeutics (self) and AstraZeneca (spouse); receipt of research funding from Takeda; and receipt of honoraria from ADC Therapeutics, Bristol Myers Squibb, and Takeda. M Lunning reports financial relationships with Beigene, Karyopharm, Gilead/Kite Pharma, Daiichi Sankyo, Novartis, Kyowa Kirin, AbbVie, Celgene, Verastem, Janssen, Myeloid Therapeutics, AstraZeneca, Acrotech, ADC Therapeutics, Legend, Spectrum, Morphosys, and TG Therapeutics. D Ungar reports employment for ADC Therapeutics and stock ownership for ADC Therapeutics. M. Burke reports employment for ADC Therapeutics. L Wang reports employment for ADC Therapeutics and stock ownership for ADC Therapeutics. M Solh reports consultancy/advisory roles for Abbvie, Amgen, Bristol Myers Squibb, and GlaxoSmithKline; and receipt of research funding from Partner Therapeutics and ADC Therapeutics.

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SCAN ME

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