Real-world clinical effectiveness of loncastuximab tesirine monotherapy for the treatment of relapsed/refractory diffuse large B-cell lymphoma following chimeric antigen T cell therapy in the US

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INTRODUCTION

- CD19-directed chimeric antigen receptor modified T-cell (CAR-T) therapy is a potentially curative option for patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) however, the outcomes are poor for those who progress following CAR-T.
- Loncastuximab tesirine (lonca) monotherapy is the first and only single agent CD19-directed antibody drug conjugate approved for treating adult patients with R/R DLBCL after two or more lines (2L+) of systemic therapy. Accelerated and conditional approval for lonca was granted by the United States Food and Drug Administration and the European Medicines Agency in 2021 and 2022, respectively, following positive results from the phase 2 open-label single-arm (LOTIS-2) study on the efficacy and safety of lonca monotherapy in patients with R/R DLBCL. [1]
- In LOTIS-2, 13 patients received lonca monotherapy after progressing following CAR-T therapy, with an overall response rate (ORR) of 46%.[2] However, the sample size in the LOTIS-2 study was low, and all patients received CAR-T therapy in the 3L+ setting. Furthermore, there are limited real-world data describing the effectiveness of lonca in DLBCL patients where prior treatment with CAR-T therapy failed [3], and there are no studies to our knowledge that examined lonca outcomes among patients who received CAR-T in the second line (2L) setting.

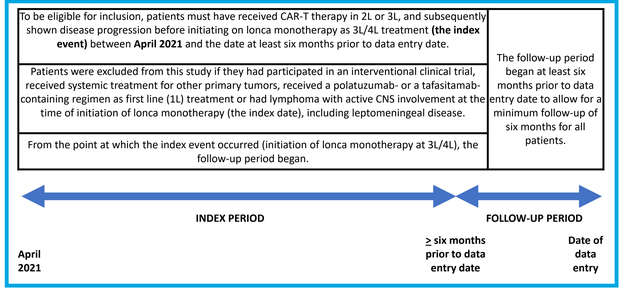
STUDY OBJECTIVES

- The aim of this study was to examine the real-world use and outcomes of lonca monotherapy in the treatment of R/R DLBCL when administered following CAR-T therapy received at 2L or third line (3L) in the United States.

METHODS

- In this non-site based, online, retrospective chart review, physicians specialised in oncology/haematology followed a random selection process to identify adult patients with R/R DLBCL (DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, or high-grade B-cell lymphoma) who initiated lonca monotherapy as the next treatment following commercial CAR-T therapy received at 2L or 3L between April 2021 and the date six months prior to data entry. **Figure 1** illustrates the study design.

Figure 1. Design of study



CART-T, CD19-directed chimeric antigen receptor modified T-cell; CNS, central nervous system; lonca, loncastuximab tesirine; 1L, first line therapy; 2L, second line therapy; 3L, third line therapy; 4L, fourth line therapy.

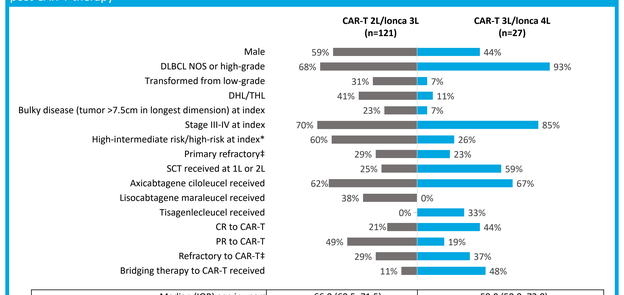
- Physicians completed an electronic case report form (eCRF) for each patient, reporting patient demographics, clinical characteristics, treatment history, lonca treatment patterns and outcomes.
- Outcomes of lonca monotherapy post-CAR-T therapy included ORR, proportion of patients with complete response [CR] or partial response [PR], duration of response (DOR; time from initial response for patients with CR or PR until progression or death), progression-free survival (PFS; time from index to recurrence/disease progression or death) and overall survival (OS; time from index until death). Time to event endpoints (such as time to CR/PR, time to disease progression or death) were evaluated by the Kaplan-Meier method.
- Verification checks were conducted after each eCRF was completed to check for consistency in responses provided. Any eCRF where inconsistencies were found during these checks were excluded from all analyses. Where possible, queries were raised and resolved with physicians regarding incomplete or unexpected datapoints.

RESULTS

Patient characteristics and treatment history

- Data were reported by 27 physicians, of which 44% were in academia.
- Data were reported on 148 patients who progressed after receiving CAR-T therapy. Among these, 121 received lonca monotherapy at 3L following CAR-T therapy at 2L (subsequently referred to as 2L CAR-T/3L lonca patients), 27 received lonca monotherapy at 4L following CAR-T therapy at 3L (subsequently referred to as 3L CAR-T/4L lonca patients). Patient demographics and clinical characteristics are outlined in **Figure 2**.
- Among 2L CAR-T/3L lonca patients, 70% were stage III-IV at index versus 85% of 3L CAR-T/4L lonca patients (according to Ann Arbor staging) and 41% had double hit lymphoma (DHL)/triple hit lymphoma (THL) at diagnosis versus 11% of 3L CAR-T/4L lonca patients.
- The most common CAR-T therapy received by both groups was axicabtagene ciloleucel.
- There were 70% and 63% of patients who responded to 2L and 3L CAR-T therapy, respectively.

Figure 2. Demographics and clinical characteristics of patients who received loncastuximab tesirine monotherapy post CAR-T therapy



Median (IQR) age in years	66.0 (60.5, 71.5)	59.0 (50.0, 72.0)
Most common 1L treatment received, n (%)	R-CHOP: 58 (48)	R-CHOP: 18 (67)
Most common 2L treatment received, n (%)	-	BR: 6(22) R-ICE: 6 (22)

BR, bendamustine and rituximab; CAR-T, CD19-directed chimeric antigen receptor T-cell; CR, complete response; DHL, double hit lymphoma; DLBCL, diffuse large B-cell lymphoma; IQR, Interquartile range; lonca, loncastuximab tesirine; NOS, not otherwise specified; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-ICE, rituximab with ifosfamide, carboplatin and etoposide; THL, triple hit lymphoma; 2L, second line therapy. *Based on International Prognostic Index risk classification (R-IPI) at index (initiation of lonca monotherapy) of high-intermediate risk (3 points)/high-risk (4 - 5 points). ‡Refractory to CAR-T therapy is defined as patients who had no response (i.e., stable disease or progressive disease) to treatment. Best response to 2L CAR-T therapy was unknown for three patients. Complete response and partial response are reported for the best response to CAR-T therapy.

Treatment patterns of loncastuximab tesirine monotherapy

- Treatment patterns of lonca monotherapy are detailed in **Table 1**.
- Median (interquartile range; IQR) duration of lonca monotherapy was approximately eight months (7.9) in both groups. Patients who were on 2L CAR-T/3L lonca monotherapy received a median (IQR) of 5.0 (3.0, 7.0) cycles, while a median (IQR) of 6.0 (6.0, 11.0) cycles was received by patients on 3L CAR-T/4L lonca monotherapy.
- Treatment discontinuations and treatment interruptions due to adverse events (AEs) were low in the overall sample (7%). The main AEs leading to treatment discontinuations were neutropenia (50%) and thrombocytopenia (40%).

Table 1. Treatment patterns of loncastuximab tesirine monotherapy

	CAR-T in 2L n=121	CAR-T in 3L n=27
Treatment patterns of lonca monotherapy		
Median (IQR) time from CAR-T infusion to lonca monotherapy initiation, months*	6.5 (3.0, 8.9)	9.8 (7.1, 11.8)
Median (IQR) follow-up duration, months‡	8.8 (6.6, 15.3)	12.0 (10.1, 13.7)
Median (IQR) number of cycles of lonca monotherapy	5.0 (3.0, 7.0)	6.0 (6.0, 11.0)
Occurrence of treatment interruptions or discontinuations due to adverse events		
Treatment interruptions, n (%)	10 (8)	0 (0)
Treatment discontinuations, n (%)	9 (7)	1 (4)

IQR, Interquartile range. *The base size for time from CAR-T infusion to loncastuximab tesirine (lonca) monotherapy initiation was n=87, due to the date of CAR-T infusion being unknown for n=61 patients (n=43 2L CAR-T patients and n= 18 3L CAR-T patients). ‡Follow-up time is the time from index to last clinical evaluation date or date of death.

Treatment outcomes

- Best response to lonca monotherapy received at 3L and 4L post CAR-T therapy is shown in **Figure 3**.
- For 2L CAR-T/3L lonca patients, ORR was 73% (CR = 34%, PR = 39%; **Figure 3A**). Median (IQR) DOR, PFS and OS were not reached.
- For 3L CAR-T/4L lonca patients, ORR was 78% and the percentage of patients who had a CR was 17% (PR = 61%; **Figure 3A**). Median DOR was 7.6 months, median PFS was 12.0 months, and median OS was not met.
- Those 2L CAR-T/3L lonca patients defined as having responded to CAR-T therapy (CR or PR) had an ORR to lonca monotherapy of 82% and those who were refractory (stable disease or progression) had an ORR of 52% (**Figure 3B**).
- ORR to lonca monotherapy in 3L CAR-T/4L lonca patients who responded to CAR-T therapy was 83% and was 67% in those who were refractory **(Figure 3C)**.
- For patients who received 2L CAR-T/3L lonca, in those who had DHL/THL, ORR to lonca monotherapy was 61% (CR = 42%), and in those who had high-grade lymphoma, ORR to lonca monotherapy was 63% (CR = 26%), while in the patients who had DLBCL arising from low-grade lymphoma, ORR was 84% (CR = 38%).

Figure 3. Best response to loncastuximab tesirine monotherapy received at 3L and 4L post CAR-T therapy

Figure 3A: Best response for lonca monotherapy received at 3L and 4L post CAR-T therapy

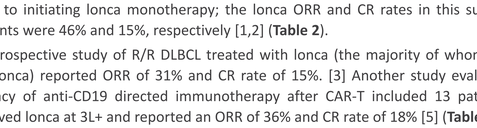


Figure 3B: Best response in 2L CAR-T/3L lonca patients who responded to CAR-T therapy compared to those who were refractory

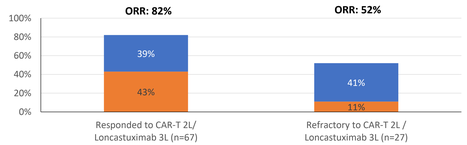
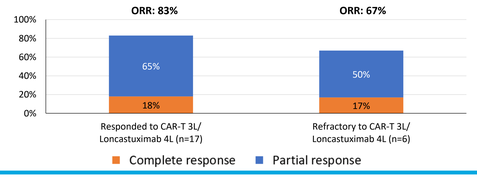


Figure 3C: Best response in 3L CAR-T/4L lonca patients who responded to CAR-T therapy compared to those who were refractory



CAR-T, CD19-directed chimeric antigen receptor modified T-cell; lonca, loncastuximab tesirine monotherapy; ORR, overall response rate; 1L, first line; 2L, second line; 3L, third line; 4L fourth line.
Percentages based on patients where best overall response to treatment was known (response to lonca monotherapy unknown for n=26 patients that received lonca at 3L, n=4 patients that received lonca at 4L). Figure 3B.1: Percentages based on patients where best overall response to treatment was known (response to CAR-T therapy unknown for n=17 patients at 2L, n=7 patients that were refractory to CAR-T received at 2L). Figure 3B.2: Percentages based on patients where best overall response to treatment was known (response to CAR-T therapy unknown n=4 patients that were refractory to CAR-T received at 3L).

DISCUSSION

- The LOTIS-2 clinical trial was the first indication that lonca monotherapy would be an effective treatment among patients with prior CAR-T therapy. [2]
- Complete response rate at 4L lonca monotherapy in the current study was comparable to the CR rates in previous studies (**Table 2**).
- LOTIS-2 participants who received lonca post-CAR-T had a median of 3 lines of therapy prior to initiating lonca monotherapy; the lonca ORR and CR rates in this subgroup of patients were 46% and 15%, respectively [1,2] (**Table 2**).
- A retrospective study of R/R DLBCL treated with lonca (the majority of whom received 4L+ lonca) reported ORR of 31% and CR rate of 15%. [3] Another study evaluating the efficacy of anti-CD19 directed immunotherapy after CAR-T included 13 patients who received lonca at 3L+ and reported an ORR of 36% and CR rate of 18% [5] (**Table 2**).
- The differences in ORR between our study (78%) and the previous studies (**Table 2**) could be attributed to variation in the criteria used in the determination of PR.

Table 2. Published post CAR-T therapy and loncastuximab tesirine treatment outcomes[a]

	Caimi et al[1, 2]	Ayers et al[3]	Nastoupil et al[4]	Iqbal, et al[5]
	n=13	n=112	n=20	n=13
Study Type	Clinical trial	RWE study	RWE study	RWE study
Loncastuximab tesirine line of therapy	3-8+	2-12	3+	3-8+
Overall response rate, %	46	31	50	36
Complete response, %	15	15	20	18
Partial response, %	31	16	30	18
Duration of response, median (95% CI), months	8.0 (3.4, NR)	-	4.0	2.7 (0.7, 4.5)
Progression-free survival, median (95% CI), months	1.4 (0.7, NR)	2.0 (1.6, 2.7)	3.0 (2.0, 9.3)	1.4 (0.9, NR)
Overall survival, median (95% CI), months	8.2 (4.7, NR)	4.6 (3.2, 6.1)	4.7 (3.7, NR)	7.8 (2.1, NR)
Overall survival at 12 months, %	33.3%	-	-	-

CI, confidence intervals; NR, not reached; RWE, real-world evidence
[a]These data are provided for informational purposes only and are not meant to be compared side to side.

CONCLUSIONS

- This is the first study to our knowledge that examined the effectiveness of lonca monotherapy at 3L following 2L CAR-T.
- The findings suggest that prior CAR-T exposure does not prohibit a response to lonca monotherapy, suggesting that it may be an effective treatment option for patients who are resistant or progressed after CAR-T.
- The effective outcomes associated with lonca monotherapy in 4L following 3L CAR-T in the current study suggests that lonca monotherapy can also be considered in this setting.

LIMITATIONS

- Limitations inherent to using a retrospective study design include the lack of consistent baseline clinical data and standard clinical measures. Data quality was reliant on accurate and complete reporting by physicians in the eCRF and the availability of detailed, complete patient records.
- Although physicians were instructed to randomly select eligible patients for the medical chart review to minimize potential consecutive enrolment-associated selection bias, adherence to this methodology couldn't be verified and more recent patient charts may have been selected despite the randomization requirement.
- Given that physicians recruitment was voluntary, and the selection process may not be random, there is a risk of sampling bias. However, physicians were recruited from different settings across a diverse geographical spread to maximise representativeness.

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Disclosures

Narendranath Epperla provides consultancy, receives honoraria, and has membership on the Board of Directors or advisory committees for the following: ADC Therapeutics, Lilly, Merck, and Novartis. He is member of the Speakers Bureau for Novartis, Incyte, and Beigene. He also received research funding from Beigene. Tom Bailey, Laura Mirams, Jolenta Cheung, Mona Amet and Gary Milligan are employees of Adelphi Real World, who received funding from ADC Therapeutics for this work. Melanie Lucero and Lei Chen were employees of ADC Therapeutics at the time of the study and currently own stock in the company.

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