Long-Term Responses With Loncastuximab Tesirine: Updated Results From LOTIS-2, the Pivotal Phase 2 Study of Patients With Relapsed/Refractory Diffuse Large B-cell Lymphoma

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INTRODUCTION

- Patients with diffuse large B-cell lymphoma (DLBCL) who relapse after stem cell transplant (SCT) or chimeric antig refractory to second-line therapy have a poor prognosis and few treatment options^{1,2}
- There is an unmet need for accessible therapies with manageable toxicity profiles that have demonstrated long-t relapsed/refractory (R/R) DLBCL
- Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]), an anti-CD19 antibody conjugated to a pyrrolobenz single-agent antitumor activity in LOTIS-2, the pivotal phase 2 study, in heavily pretreated patients with R/R DLBC - Lonca monotherapy was approved in the US in 2021 and in Europe in 2022^{5,6}
- A follow-up analysis (data cutoff: March 1, 2021), at a median (range) of 7.8 (0.3 to 31.0) months, showed a similar overall response rate (ORR) to the primary analysis, with a complete response (CR) rate of 24.8% and a median duration of response (DOR) of 13.4 months⁷

OBJECTIVE

• To present updated long-term efficacy and safety results from patients with R/R DLBCL treated with Lonca in the phase 2 LOTIS-2 study (NCT03589469), including for subgroups of patients with durable CR

METHODS

Study Design

- LOTIS-2 was a multicenter, open-label, single-arm, phase 2 study of Lonca monotherapy in patients with R/R DLBCL after ≥2 prior systemic therapies, with measurable disease (2014 Lugano criteria⁸) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2⁴
- Intravenous Lonca was administered every 3 weeks on day 1 of each 21-day cycle at a dose of 0.15 mg/kg for 2 cycles followed by 0.075 mg/kg for subsequent cycles
- Follow-up was every 12 weeks for up to 3 years after the end of treatment

Efficacy and Safety Outcomes

- The primary endpoint was the ORR (2014 Lugano criteria⁸)
- Secondary endpoints included the CR rate, DOR, progression-free survival (PFS), and overall survival (OS)
- Safety endpoints included the frequency and severity of treatment-emergent adverse events (TEAEs)

Statistical Analysis

- The data cutoff for this analysis was September 15, 2022
- Efficacy and safety analyses were performed for the following:
- All-treated patients
- Patients with a CR
- Patients with a CR who were event-free (defined as no progressive disease or death) for ≥1 year from day 1 of cycle 1 - Patients with a CR who were event-free for ≥ 2 years from day 1 of cycle 1

RESULTS

Patient Population

- The median (range) follow-up was 7.8 (0.3 to 42.6) months, and 145 patients had received at least 1 dose of Lonca
- In patients with a CR, the median (range) duration of follow-up was 35.0 (4.4 to 42.6) months • The baseline patient demographics and disease characteristics, both in the all-treated population and in subgroups of patients with a long-term
- response, are shown in **Table 1**
- The median (range) number of treatment cycles was 3.0 (1 to 26) in the all-treated population, 8.0 (1 to 26) in patients with a CR, 12.5 (1 to 26) in patients with a CR who were event free for ≥1 year, and 13.0 (1 to 22) in patients with a CR who were event free for ≥2 years

Efficacy Outcomes

- The ORR was 48.3% (70/145), with a CR rate of 24.8% (36/145)
- Among patients with a CR, 44% (16/36) and 31% (11/36) were event-free for ≥ 1 and ≥ 2 years, respectively
- All 11 patients with a CR who were event-free for ≥2 years were censored due to patient discontinuation of the study
- The median (range) time to response was 41.0 (35 to 247) days for all responders and 42.0 (36 to 247) days for patients with a CR • The median (95% CI) DOR was 13.37 (6.87, –) months in the all-treated population and was not reached among patients with a CR (Figure 1) • The median (95% CI) PFS (4.93 months [2.89 to 8.3]) and OS (9.53 months [6.7 to 11.5]) in the all-treated population and in patients with a CR (not
- reached for both PFS and OS) are shown in **Figures 2A** and **2B** • Additional efficacy outcomes for the all-treated population and the subset of patients with CR are summarized in **Table 2**

the LOTIS-2 study
All-treated population (N = 145)
100%
11 (31%) patients were event-free for ≥2 years
ents with CR lian OS: not reached lian PFS: not reached
fied during the long-term follow-up
nses and an
tigen receptor T-cell therapy or are
g-term disease control in patients with
nzodiazepine dimer, demonstrated CL ^{3,4}

Table 1: Baseline patient demographics and disease characteristics					
	All-treated N = 145	Best response of CR at any time n = 36	Patients with CR who were event-free ≥1 year n = 16	Patients with CR who were event-free ≥2 years n = 11	
Sex, n (%) Female	60 (41.4)	22 (61.1)	13 (81.3)	9 (81.8)	
Age Median, years (range)	66.0 (23, 94)	67.5 (45, 94)	71.0 (53, 84)	70.0 (53, 82)	
ECOG score, n (%) 0 1 2	58 (40.0) 78 (53.8) 9 (6.2)	19 (52.8) 14 (38.9) 3 (8.2)	9 (56.3) 6 (37.5) 1 (6.3)	7 (63.6) 3 (27.3) 1 (9.1)	
Histology, ^a n (%) DLBCL, NOS HGBCL ^b Primary mediastinal DLBCL	128 (88.3) 10 (6.9) 7 (4.8)	31 (86.1) 5 (13.9) 0	11 (68.8) 5 (31.3) 0	8 (72.7) 3 (27.3) 0	
Transformed DLBCL, n (%)	30 (20.7)	7 (19.4)	4 (25.0)	2 (18.2)	
Double/triple hit, n (%) Double hit Triple hit	12 (8.3) 3 (2.1)	5 (13.9) 0	5 (31.3) 0	3 (27.3) 0	
Stage, n (%) I-II III-IV	33 (22.8) 112 (77.2)	9 (25.0) 27 (75.0)	3 (18.8) 13 (81.3)	2 (18.2) 9 (81.8)	
Prior systemic therapies Median (range)	3.0 (2, 7)	3.0 (2, 7)	2.0 (2, 7)	2.0 (2, 7)	
Primary refractory, n (%)	29 (20.0)	5 (13.9)	2 (12.5)	0	
Refractory to last line of therapy	89 (61.4)	11 (30.6)	5 (31.3)	4 (36.4)	
Prior stem cell transplant, n (%)	24 (16.6)	8 (22.2)	1 (6.3)	1 (9.1)	
Prior CAR-T therapy, n (%)	14 (9.7)	3 (8.3)	2 (12.5)	0	

CAR-T, chimeric antigen receptor T-cell; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBCL, high-grade B-cell lymphoma; NOS, not otherwise specified. ^aRelapsed/refractory DLBCL was classified according to the 2016 WHO classification. ^bThe primary analyses reported HGBCL in 11 patients.

Figure 1. Kaplan–Meier curve of the DOR in the all-treated population and the subset of patients with a CR



0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 Time, months

Patients at risk All-treated population CR, complete response; DOR, duration of response

70 63 42 38 33 29 25 22 21 20 18 17 17 16 15 15 15 15 13 11 11 11 11 11 11 11 11 7 6 5 2 2 2 2 2 2 2 1 1 0 Subset of patients with CR 36 35 30 29 25 22 20 18 18 17 17 16 16 15 14 14 14 14 12 11 11 11 11 11 11 11 11 11 7 6 5 2 2 2 2 2 2 2 1 1 0

Figure 2. Kaplan–Meier curves of the (A) PFS in the all-treated population (N = 145) and the subset of patients with a best response of a CR (n = 36), and (B) OS in the all-treated population and the subset of patients with a best response of a CR (n = 36)



	Median (95% CI) months: not reached	
	Number of events: 23	
-1	Median (95% Cl) months: 13.37 (6.87, –)	

Number of events: 6 Median (95% CI) months: not reached Number of events: 73 Median (95% CI) months: 4.93 (2.89, 8.31) 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 Time, months

5 124 85 56 46 37 34 29 <mark>27 24 21 2</mark>0 18 18 18 16 15 15 15 15 11 11 11 11 11 11 11 11 10 7 7 4 4 3 3 3 3 1 1 0

Number of events: 12 Median (95% CI) months: not reached

Number of events: 97 Median (95% CI) months: 9.53 (6.74, 11.47) ──┤───<u>┤</u>──┤<u>┤</u>┤╢╫╫┼┼┼╫╫┼┼┤╶┼┼┼╶┼╫┼╶┼

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 Time, months

98 89 78 72 68 63 56 51 48 47 45 44 42 42 40 38 38 37 37 36 36 36 36 36 36 35 35 34 34 32 29 24 20 14 9 7 5 3 0

Table 2: Summary of efficacy outcomes

Median DOR, months (95% CI) Probability of maintaining response at 1 Probability of maintaining response at 2 Median PFS, months (95% CI) Probability of maintaining PFS at 1 year Probability of maintaining PFS at 2 years

Median OS, months (95% CI) Probability of maintaining OS at 1 year Probability of maintaining OS at 2 years

CR, complete response; DOR, duration of response; NR, not reached; OS, overall survival; PFS, progression-free survival.

- Ten patients with a CR proceeded to SCT (**Figure 3**)

Each bar represents one patient in the study. Response was determined by an independent reviewer *Reasons for censoring included study discontinuation, new anticancer treatment started (excluding SCT), no valid post-baseline assessment, or transplant. CR, complete response; SCT, stem cell transplant.

Safety Outcomes

- No new safety signals were identified during the long-term follow-up

CONCLUSIONS

- safety profile

Acknowledgments

Disclosures

References

- Crump, M, et al. *Blood*. 2017;130:1800-1808.
- Chow, VA, et al. Am / Hematol. 2019;94:e209-213. Zammarchi, F, et al. *Blood*. 2018;131:1094-1105. Caimi, PF, et al. *Lancet Oncol*. 2021;22:790-800.
- ZYNLONTA[®] US prescribing information.
- Cheson, BD, et al. / *Clin Oncol*. 2014;32:3059-3068.

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	All-treated N = 145	Best response of CR n = 36
Vear	13.4 (6.9, -) 54 7% (37 9, 68 8)	NR 82.8% (59.9.93.3)
years	44.6% (27.9, 60.0)	72.4% (48.1, 86.8)
	4.9 (2.9, 8.3) 33.5% (23.3, 44.0) 25.9% (16.2, 36.7)	NR 82.9% (60.0, 93.3) 72.5% (48.2, 86.8)
	9.5 (6.7, 11.5) 39.0% (30.7, 47.1) 29.5% (22.0, 37.4)	NR 77.1% (59.4, 87.9) 68.2% (50.0, 81.0)

• Among patients with a CR (n = 36), the median (range) duration of time patients remained treatment-free post-Lonca was 6.1 (1.0 to 37.5) months

- In the subsets of patients who were event-free for ≥1 year and ≥2 years, the median (range) duration of time patients remained treatment-free post-Lonca was 24.8 (3.4 to 37.5) months and 27.7 (20.7 to 37.5) months, respectively

- As assessed by principal investigators, 4 of the 5 patients with a record of response achieved a CR after SCT; the remaining one patient had disease progression

Months since 1st dose

• All-grade TEAEs were reported in 98.6% of the all-treated population and 100% of patients with a CR

– All-grade TEAEs occurring in ≥30% of all patients were increased gamma-glutamyltransferase (GGT; 42%), neutropenia (40%), and thrombocytopenia (33%)

- All-grade TEAEs occurring in ≥30% of patients with a CR were increased GGT (50%), neutropenia (42%), anemia (36%), thrombocytopenia (36%), peripheral edema (33%), and nausea (31%) Grade ≥3 TEAEs were reported in 73.8% of patients and in 75% of patients with a CR

- Grade \geq 3 TEAEs occurring in \geq 10% of the all-treated population were neutropenia (26%), thrombocytopenia (18%), increased GGT (17%), and anemia (10%)

- Grade >3 TEAEs occurring in >10% of patients with a CR were neutropenia (28%), increased GGT (19%), thrombocytopenia (19%), leukopenia (14%), and hypophosphatemia (11%)

• Among heavily pretreated patients in the LOTIS-2 study, Lonca continued to demonstrate durable, long-term responses with a manageable

- Eleven of the 36 patients with a CR were event-free for ≥2 years with no evidence of disease and no new anticancer therapy post-Lonca - Patients with a CR maintained a median treatment-free period of 6.1 months from the last Lonca dose • Further study is needed to identify factors predictive of long-term response to Lonca

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Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761196s000lbl.pdf. Accessed April 12, 2023. ZYNLONTA[®] summary of product characteristics. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/zynlonta. Accessed April 12, 2023. Zinzani, PL, et al. Poster presented at: International Conference on Malignant Lymphoma Virtual Congress, June 18-22, 2021.

