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Abstract

Therapies that demonstrate durable, long-term responses with manageable safety and tolerability are needed for patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]), an anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine dimer, demonstrated single-agent antitumor activity in the pivotal phase II LOTIS-2 study in heavily pretreated patients with R/R DLBCL. Here we present updated efficacy and safety analyses from LOTIS-2, performed for all patients and in subsets of patients with a complete response (CR), including patients with CR who were event-free (no progressive disease or death) for ≥1 year and ≥2 years from cycle 1, day 1 of treatment. Lonca was administered every 3 weeks (0.15 mg/kg for 2 cycles; 0.075 mg/kg for subsequent cycles). As of the final data cutoff (September 15, 2022; median follow-up: 7.8 months [range, 0.3-42.6]), 70 of 145 (48.3%) patients achieved an overall response. Thirty-six (24.8%) patients achieved CR, of which 16 (44%) and 11 (31%) were event-free for ≥1 year and ≥2 years, respectively. In the all-treated population, the median overall survival was 9.5 months; the median progression-free survival was 4.9 months. Among patients with CR, median overall survival and progression-free survival were not reached, with 24-month overall and progression-free survival rates of 68.2% (95% CI: 50.0-81.0) and 72.5% (95% CI: 48.2-86.8), respectively. No new safety concerns were detected. With additional follow-up, Lonca continued to demonstrate durable, long-term responses with manageable safety and tolerability in patients with CR (*clinicaltrials gov. Identifier: NCT03589469*).

Introduction

In newly diagnosed diffuse large B-cell lymphoma (DLBCL), frontline therapy is potentially curative for approximately 60% of patients.[1] Further, patients with newly diagnosed DLBCL who achieved event-free survival (defined as no disease progression, relapse, new anticancer treatment, or death) for 24 months after the initial first-line immunochemotherapy were found to have an overall survival (OS) equivalent to that of the age- and sex-matched general population, suggesting that long-term responses can indicate positive outcomes for patients with DLBCL.[1] However, up to 40% of patients do not respond to frontline therapy or relapse.[1] Patients with relapsed/refractory (R/R) DLBCL after stem cell

transplant (SCT) or chimeric antigen receptor T-cell (CAR T) therapy or who are refractory to second-line therapy have a poor prognosis and limited treatment options.[2,3] While the number of treatment options for R/R DLBCL is increasing, not all patients are eligible for, able to access easily, or able to tolerate many of these therapies.[4,5] There remains a medical need for effective and accessible therapies with manageable safety and tolerability that have demonstrated the potential for long-term disease control in R/R DLBCL.

Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated through a cleavable linker to a potent pyrrolobenzodiazepine (PBD) dimer alkylating cytotoxin, SG3199.[6] Upon binding to the CD19 antigen, Lonca is internalized, the linker is cleaved, and PBD dimers are rapidly released.[6] The PBD dimer forms persistent DNA crosslinks in the DNA minor groove, leading to tumor cell apoptosis.[7] In April 2021, Lonca received accelerated approval from the US Food and Drug Administration as a single agent for the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma (HGBCL).[8] Subsequently, Lonca received European Medicines Agency conditional approval in December 2022 for the same indication.[9]

In the primary analysis of the pivotal phase II LOTIS-2 study (data cutoff: April 6, 2020; median follow-up: 7.3 months [range, 0.3-20.2][8]), Lonca demonstrated single-agent antitumor activity and had an acceptable safety profile in heavily pretreated patients with R/R DLBCL with an overall response rate (ORR) of 48.3% and a complete response (CR) rate of 24.1%.[10] In a previously presented follow-up analysis (data cutoff: March 1, 2021; median follow-up: 7.8 months [range, 0.3-31.0]), the ORR was the same as in the primary analysis, and one patient with a partial response (PR) converted to CR for a final CR rate of 24.8%. Durable responses to Lonca were observed, with a median duration of response (DOR) of 13.4 months and a median DOR in patients with CR not reached; no new safety signals were detected.[11]

Here we present updated long-term efficacy and safety data in patients with R/R DLBCL treated with Lonca in the phase II LOTIS-2 study, including analyses of subsets of patients with durable CR.

Methods

Study design and patients

The multicenter, open-label, single-arm phase II LOTIS-2 study (*clinicaltrials gov. Identifier: NCT03589469*) design and methodology were previously described.[10] Briefly, key eligibility criteria included patients aged ≥18 years, investigator-defined R/R DLBCL (including DLBCL not otherwise specified, HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements, and primary mediastinal B-cell lymphoma) after two or more prior systemic therapies, measurable disease (2014 Lugano criteria), and an Eastern Cooperative Oncology Group performance status of 0 to 2.

Lonca was administered on an outpatient basis intravenously over 30 minutes once every 3 weeks on day 1 of each 21-day cycle at a dose of 0.15 mg/kg for the first two cycles followed by 0.075 mg/kg for subsequent cycles for up to 1 year or until disease relapse or progression. Patients with clinical benefit could continue treatment beyond 1 year upon sponsor approval. Patients received dexamethasone premedication to reduce the incidence and severity of PBD-related adverse events (AE; i.e., edema, effusion, and skin-related events).

This study was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and ethical principles of the Declaration of Helsinki. All participants provided written informed consent. The study protocol and amendments were approved by all relevant ethics committees.

Efficacy and safety outcomes

The primary efficacy endpoint was the ORR (defined as the proportion of patients with a CR or PR according to the 2014 Lugano classification,[12] determined by independent central review). Patient disease assessment and follow-up were previously described.[10] Secondary efficacy endpoints included the DOR (time from first response [CR or PR] to disease progression or death), CR rate (the proportion of patients with a CR as determined by an independent central review), relapse-free survival (RFS; the time from CR to disease progression or death), progression-free survival (PFS; the time from the start of treatment to disease progression or death), and OS (the time from the start of treatment to death from any cause).

Safety endpoints included frequency and severity of AE and serious AE, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0.

Statistical analyses

The primary analysis of the LOTIS-2 study was previously published (data cutoff: April 6, 2020).[10] The follow-up efficacy and safety analyses reported here (data cutoff: September 15, 2022) were performed for all patients who received ≥1 dose of Lonca, in a subset of patients who achieved a best response of CR, and in subsets of patients with a best response of CR who were event-free (events defined as progressive disease or death) for ≥1 year or ≥2 years starting from cycle 1, day 1 of Lonca treatment.

Analysis of primary and secondary endpoints was previously described[10] (see the *Online Supplementary Appendix 1*). The duration of time patients remained treatment-free post-Lonca was defined as the interval from the last dose of Lonca until the end of study for patients who did not receive subsequent anticancer therapy or the start of subsequent

anticancer therapy for patients who received subsequent anticancer therapy. All statistical analyses were conducted using SAS, version 9.4.

Results

Patients

As of the final data cutoff of September 15, 2022 (median follow-up, all-treated population: 7.8 months [range, 0.3-42.6]), a total of 145 patients received at least one dose of Lonca and were evaluable for efficacy and safety. Baseline characteristics and demographics are summarized in Table 1. Briefly, the median age was 66.0 years, 58.6% of patients were male, 6.9% of patients had HGBCL, the median number of prior therapies was 3.0, 20.0% of patients had primary refractory disease, 61.4% had disease refractory to the last prior systemic therapy, 9.7% of patients had prior CAR T therapy, and 16.6% had prior SCT.

Patient subsets of interest included patients with CR (36 [24.8%]; median follow-up: 35.0 months) and patients with CR who were event-free for ≥1 year (16 [11.0%]; median follow-up: 37.2 months) and ≥2 years (11 [7.6%]; median follow-up: 37.5 months). Among the subset of patients with CR (n=36), 38.9% were male, 13.9% had HGBCL, 13.9% had double-hit disease, 13.9% had primary refractory disease,

Table 1. Patient baseline characteristics and demographics.

	All-treated N=145	Best response of CR 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 in years, N (%)				
Median (range)	66.0 (23-94)	67.5 (45-94)	71.0 (53-84)	70.0 (53-82)
<65	65 (44.8)	13 (36.1)	3 (18.8)	3 (27.3)
≥65 to <75	59 (40.7)	15 (41.7)	7 (43.8)	5 (45.5)
≥75	21 (14.5)	8 (22.2)	6 (37.5)	3 (27.3)
Race, N (%)				
White	130 (89.7)	34 (94.4)	15 (93.8)	11 (100)
Black or African American	5 (3.4)	1 (2.8)	0	0
Asian	3 (2.1)	0	0	0
Other	7 (4.8)	1 (2.8)	1 (6.3)	0
ECOG score, N (%)				
0	58 (40.0)	19 (52.8)	9 (56.3)	7 (63.6)
1	78 (53.8)	14 (38.9)	6 (37.5)	3 (27.3)
2	9 (6.2)	3 (8.3)	1 (6.3)	1 (9.1)
Histology,[a] N (%)				
DLBCL, NOS	128 (88.3)	31 (86.1)	11 (68.8)	8 (72.7)
HGBCL[b]	10 (6.9)	5 (13.9)	5 (31.3)	3 (27.3)
Primary mediastinal DLBCL	7 (4.8)	0	0	0
Transformed DLBCL, N (%)	30 (20.7)	7 (19.4)	4 (25.0)	2 (18.2)
Double/triple hit, N (%)				
Double hit	12 (8.3)	5 (13.9)	5 (31.3)	3 (27.3)
Triple hit	3 (2.1)	0	0	0
Stage, N (%)				
I-II	33 (22.8)	9 (25.0)	3 (18.8)	2 (18.2)
III-IV	112 (77.2)	27 (75.0)	13 (81.3)	9 (81.8)
Prior systemic therapies, N (%)				
Median (range)	3.0 (2-7)	3.0 (2-7)	2.0 (2-7)	2.0 (2-7)
2 prior lines	63 (43.4)	15 (41.7)	10 (62.5)	8 (72.7)
3 prior lines	34 (23.4)	5 (13.9)	2 (12.5)	1 (9.1)
>3 prior lines	48 (33.1)	16 (44.4)	4 (25.0)	2 (18.2)
Refractory, N (%)				
Primary refractory	29 (20.0)	5 (13.9)	2 (12.5)	0
Refractory to last therapy	89 (61.4)	11 (30.6)	5 (31.3)	4 (36.4)
Prior SCT, 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

[a]R/R DLBCL was classified according to the 2016 World Health Organization classification. [b]The primary analysis reported high-grade B-cell lymphoma (HGBCL) in 11 patients. CAR T: chimeric antigen receptor T cell; CR: complete response; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; NOS: not otherwise specified; R/R: relapsed/refractory; SCT: stem cell transplant.

and 30.6% had disease refractory to the last prior systemic therapy. In the subset of patients with CR who were event-free for ≥1 year (n=16), 18.8% were male, 31.3% had HGBCL, 31.3% had double-hit disease, 12.5% had primary refractory disease, and 31.3% had disease refractory to the last prior systemic therapy. In the subset of patients with CR who were event-free for ≥2 years (n=11), 18.2% were male, 27.3% had HGBCL, 27.3% had double-hit disease, 0% had primary refractory disease, and 36.4% had disease refractory to the last prior systemic therapy.

Most baseline characteristics were similar between the all-treated population, the subset of patients with a CR, and the subsets of patients with CR who were event-free for ≥1 year and ≥2 years. The median age, the percentage of female patients, and the percentage of patients with HGBCL were higher in the subsets of patients with CR who were event-free for ≥1 year and ≥2 years than in the all-treated population. The percentage of primary refractory patients was lower among the subset of patients with CR who were event-free for ≥1 year, and substantially lower (0% *vs*. 20%) in the subset of patients with CR who were event-free for ≥2 years, than in the all-treated population.

Lonca exposure and patient disposition

Lonca administration and exposure are summarized in the *Online Supplementary Table S1*. In the all-treated population, the median number of treatment cycles was 3.0 (range, 1-26). Among patients with CR, the median number of treatment cycles was 8.0 (range, 1-26). Among patients with CR who were event-free for ≥1 year and ≥2 years, the median numbers of treatment cycles were 12.5 and 13.0, respectively.

Efficacy outcomes

As of the final data cutoff, the ORR was 48.3% (70/145), with a CR rate of 24.8% (36/145). Among patients with CR, 44% (16/36) and 31% (11/36) were event-free for ≥1 year and ≥2 years, respectively. The median time to response for all responders was 41.0 days (range, 35-247). Among the subset of patients with CR, the median time to response was 42.0 days (range, 36-247).

Efficacy outcomes for the all-treated population and the subset of patients with CR are summarized in Table 2. The median DOR was 13.4 months (95% confidence interval [CI]: 6.9- not estimated [NE]) in the all-treated population and was not reached among patients with CR (Figure 1). Of the 36 patients with CR, it is estimated (Kaplan–Meier approach) that 82.8% (95% CI: 59.9-93.3) of patients would maintain response for 1 year, and 72.4% (95% CI: 48.1-86.8) would maintain the response for 2 years. The median PFS was 4.9 months (95% CI: 2.9-8.3) in the all-treated population and was not reached in patients with CR (Figure 2A). Of the 36 patients with CR, it is estimated (Kaplan–Meier approach) that 82.9% (95% CI: 60.0-93.3) of patients would be progression-free for 1 year, and 72.5% (95% CI: 48.2-86.8) would be progression-free for 2 years. The median OS was 9.5 months (95% CI: 6.7-11.5) in the all-treated population and was not reached in patients with CR. Of the 36 patients with CR, 12 OS events were reported, and it is estimated (Kaplan–Meier approach) that 77.1% (95% CI: 59.4-87.9) of patients would maintain survival for 1 year, and 68.2% (95% CI: 50.0-81.0) of patients would maintain survival for 2 years (Figure 2B). Among the 36 patients with CR, the median RFS was not reached (Figure 2C), and it is estimated (Kaplan–Meier approach) that 83.2% (95% CI: 60.5-93.5) and 72.8% (95% CI: 48.5-87.0) of patients would be relapse-free for 1 and 2 years, respectively.

Among patients with CR, the median duration of time patients remained treatment-free post-Lonca was 6.1 months (range, 1.0-37.5). In the subsets of patients who were event-

Table 2. Summary of efficacy.

	All-treated population N=145 (95% CI)	Best response of CR N=36 (95% CI)
Median DOR in months	13.4 (6.9-NR)	NR
Probability % of maintaining response at 12 months	54.7 (37.9-68.8)	82.8 (59.9-93.3)
Probability % of maintaining response at 24 months	44.6 (27.9-60.0)	72.4 (48.1-86.8)
Median DOR in months	4.9 (2.9-8.3)	NR
Probability % of maintaining PFS at 12 months	33.5 (23.3-44.0)	82.9 (60.0-93.3)
Probability % of maintaining PFS at 24 months	25.9 (16.2-36.7)	72.5 (48.2-86.8)
Median DOR in months	9.5 (6.7-11.5)	NR
Probability % of maintaining OS at 12 months	39.0 (30.7-47.1)	77.1 (59.4-87.9)
Probability % of maintaining OS at 24 months	29.5 (22.0-37.4)	68.2 (50.0-81.0)
Median DOR in months	-	NR
Probability % of maintaining RFS at 12 months	-	83.2 (60.5-93.5)
Probability % of maintaining RFS at 24 months	-	72.8 (48.5-87.0)

CI: confidence interval; CR: complete response; DOR: duration of response; NR: not reached; OS: overall survival; PFS: progression-free survival; RFS: relapse-free survival.

free for ≥1 year and ≥2 years, the median duration of time patients remained treatment-free post-Lonca was 24.8 months (range, 3.4-37.5) and 27.7 months (range, 20.7-37.5), respectively (Figure 3). None of the 11 patients with CR who were event-free for ≥2 years received new anticancer therapy; all 11 patients were censored due to patient discontinuation of the study. The most common reason for the censoring of patients with CR was study discontinuation in 15 (41.7%) patients, followed by transplant in ten (27.8%) patients. Five (13.9%) patients were censored for the start of new anticancer therapy other than transplant. Three (8.3%) patients each experienced progressive disease and death. Among the 14 (9.7%) patients in the all-treated population who were previously treated with CAR T therapy, the ORR was 42.9%. Following treatment with Lonca, 16 (11.0%) patients in the all-treated population received CAR T therapy, and 12 (8.3%) received SCT. As assessed by principal investigators, four of the five patients with a record of response achieved CR after SCT.

Safety outcomes

No new safety signals were identified during the long-term follow-up. All-grade treatment-emergent adverse events (TEAE; occurring in ≥10% of all-treated patients) and grade ≥3 TEAE are summarized in Table 3. All-grade TEAE occurred in 98.6% of patients in the all-treated population. TEAE occurring in ≥30% of the all-treated population were increased γ-glutamyl transferase (GGT; 42%), neutropenia (40%), and thrombocytopenia (33%). Grade ≥3 TEAE were reported in 73.8% of patients. Grade ≥3 TEAE in ≥10% of the all-treated population were neutropenia (26%), thrombocytopenia (18%), increased GGT (17%), and anemia (10%). No cases of secondary malignancy or myelodysplastic syndrome were reported. No deaths due to TEAE were considered to be related to Lonca.

TEAE were similar between the all-treated population and the subset of patients with CR. All-grade TEAE occurred in 100% of patients with CR. TEAE occurring in ≥30% of patients with CR were increased GGT (50%), neutropenia (42%), anemia (36%), thrombocytopenia (36%), peripheral edema (33%), and nausea (31%). Grade ≥3 TEAE were reported in 75% of patients with CR; grade ≥3 TEAE occurring in ≥10% of patients with CR were neutropenia (28%), increased GGT (19%), thrombocytopenia (19%), leukopenia (14%), and hypophosphatemia (11%). All-grade and grade ≥3 TEAE in patients with CR who were event-free for ≥1 year and ≥2 years were generally similar to those of the overall population (*Online Supplementary Table S2*).

In the all-treated population, 40% of patients had dose withdrawal before cycle 3, meaning that those patients did not reach the scheduled dose reduction before discontinuing treatment with Lonca. TEAE leading to treatment discontinuation occurred in 24.8% of patients in the all-treated population. The most common TEAE leading to treatment discontinuation in the all-treated population were increased GGT (12.4%), peripheral edema (2.8%), localized edema (2.1%), and pleural effusion (2.1%). Among the subset of patients with CR, TEAE leading to treatment discontinuation occurred in 41.7% of patients. The most common TEAE leading to discontinuation in patients with CR were increased GGT (19.4%), peripheral edema (8.3%), localized edema (5.6%), and pericardial effusion (5.6%).

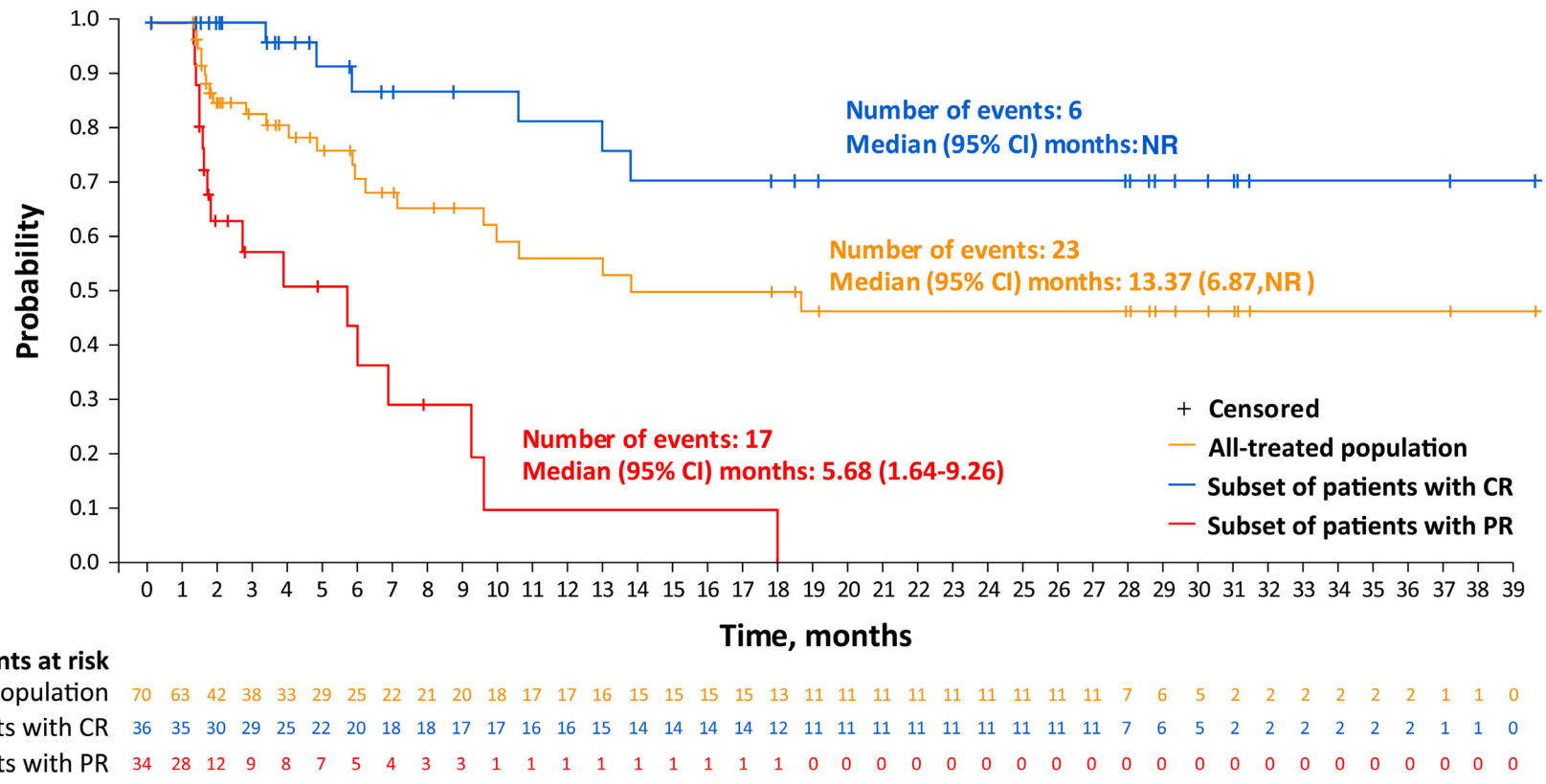

Figure 1. Duration of response. Duration of response curve for the all-treated population (N=145) and the subsets of patients with a best response of complete response (CR) (N=36) and partial response (PR) (N=34). Reasons for censor included stem cell transplant. CI: confidence interval; NR: not reached.

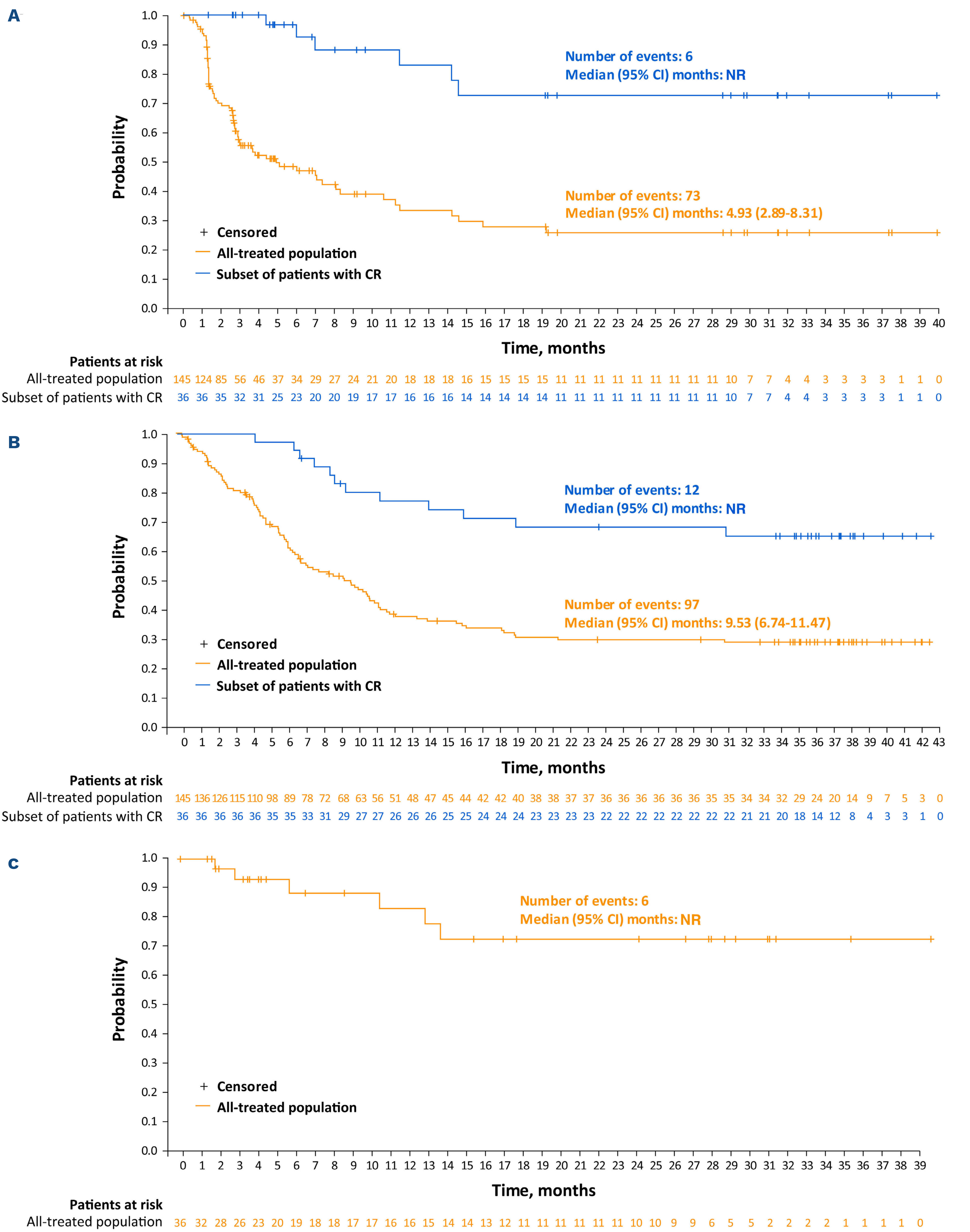

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Figure 2. Kaplan–Meier curve. (A) Progression-free survival curve of the all-treated population (N=145) and the subset of patients with a best response of complete response (CR) (N=36). (B) Overall survival curve of the all-treated population and the subset of patients with a best response of CR. (C) Relapse-free survival curve of patients with a best response of CR. Reasons for censor in progression-free survival and relapse-free survival analyses included stem cell transplant. CI: confidence interval; NR: not reached.

Discussion

In the primary analysis of the LOTIS-2 study, Lonca demonstrated antitumor activity with an ORR of 48.3%, a CR rate of 24.1%, and durable responses (median DOR, 10.3 months) in patients with heavily pretreated R/R DLBCL.[10] In this longer-term follow-up analysis, with a median follow-up of 35.0 months in patients with CR, these durable responses were maintained. The ORR was consistent with the primary analysis at 48.3%, and one PR was converted to a CR for a final CR rate of 24.8%. In the all-treated population, the median DOR extended to 13.4 months. The median OS and median PFS were consistent with the primary analysis at 9.5 months and 4.9 months, respectively. Further, in this LOTIS-2 long-term follow-up analysis, 44% and 31% of the 36 patients with CR were event-free for ≥1 year and ≥2 years, respectively. In a previous study, patients with newly diagnosed DLBCL who achieved event-free survival for ≥2 years after initial therapy were found to have an OS similar to that of an age- and sex-matched general population.[1] For patients with R/R DLBCL, it remains to be seen whether achieving event-free survival for ≥2 years may also translate to a comparable effect on OS and disease-specific mortality. Among the subset of patients with CR who were event-free for ≥1 year or ≥2 years, the median duration of time patients remained treatment-free post-Lonca was greater than 24 months, with one patient remaining treatment-free as long as 37 months. Achievement of these long treatment-free intervals is likely to translate into improved measures of quality of life, as patients with non-Hodgkin lymphoma who are off treatment and disease-free have been shown to have improved quality of life compared with patients with active disease.[13]

Baseline characteristics were compared between the all-treated patient population and the subsets of patients with durable responses to identify potential factors predictive of long-term response to Lonca. Overall, no trends have emerged, as baseline characteristics were generally similar between the all-treated population and the subsets of patients with durable responses; however, there was a notable difference in the proportion of patients who were primary refractory in the all-treated population (20%) and the subset of patients with CR who were event-free for ≥2 years (0%), as well as a difference between the proportion of patients with HGBCL in the all-treated population (6.9%) and the subsets of patients with CR who were event-free for ≥1 year (31.3%) and ≥2 years (27.3%). Further studies are needed to expand our understanding of subgroups that

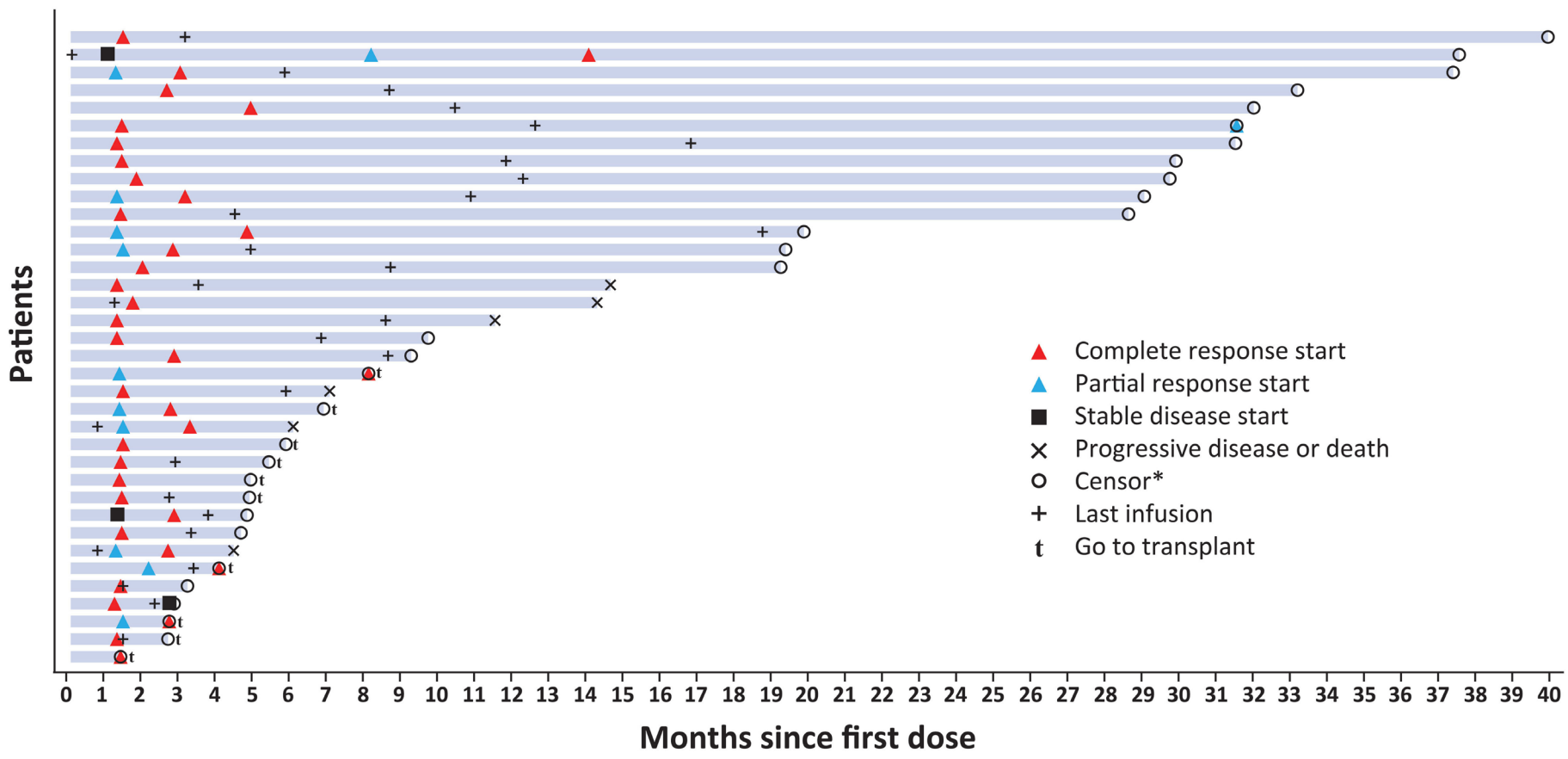

Figure 3. Swimmer plot of patients with complete response. Each bar represents 1 patient in the study. Response was determined by an independent review. SCT: stem cell transplant.

Table 3. Treatment-emergent adverse events occurring in ≥10% of the all-treated population.

	All-treated N=145		Best response of CR N=36	
	All grades N (%)	Grade ≥3 N (%)	All grades N (%)	Grade ≥3 N (%)
Any TEAE	143 (98.6)	107 (73.8)	36 (100)	27 (75.0)
Increased GGT	61 (42.1)	25 (17.2)	18 (50.0)	7 (19.4)
Neutropenia	58 (40.0)	38 (26.2)	15 (41.7)	10 (27.8)
Thrombocytopenia	48 (33.1)	26 (17.9)	13 (36.1)	7 (19.4)
Fatigue	40 (27.6)	2 (1.4)	8 (22.2)	-
Anemia	38 (26.2)	15 (10.3)	13 (36.1)	3 (8.3)
Nausea	34 (23.4)	-	11 (30.6)	-
Cough	33 (22.8)	1 (0.7)	8 (22.2)	-
Increased blood ALP	29 (20.0)	1 (0.7)	10 (27.8)	-
Peripheral edema	29 (20.0)	2 (1.4)	12 (33.3)	1 (2.8)
Pyrexia	28 (19.3)	2 (1.4)	6 (16.7)	-
Diarrhea	25 (17.2)	3 (2.1)	10 (27.8)	2 (5.6)
Increased AST	23 (15.9)	1 (0.7)	7 (19.4)	-
Hypokalemia	23 (15.9)	6 (4.1)	7 (19.4)	2 (5.6)
Hypophosphatemia	23 (15.9)	8 (5.5)	8 (22.2)	4 (11.1)
Increased ALT	22 (15.2)	4 (2.8)	5 (13.9)	1 (2.8)
Decreased appetite	22 (15.2)	-	6 (16.7)	-
Leukopenia	21 (14.5)	13 (9.0)	7 (19.4)	5 (13.9)
Hypomagnesemia	20 (13.8)	1 (0.7)	6 (16.7)	1 (2.8)
Pruritus	19 (13.1)	-	8 (22.2)	-
Rash	19 (13.1)	1 (0.7)	8 (22.2)	-
Vomiting	19 (13.1)	-	7 (19.4)	-
Abdominal pain	17 (11.7)	4 (2.8)	4 (11.1)	-
Constipation	17 (11.7)	-	6 (16.7)	-
Dyspnea	17 (11.7)	2 (1.4)	5 (13.9)	-
Insomnia	16 (11.0)	-	2 (5.6)	-
Pleural effusion	16 (11.0)	3 (2.1)	6 (16.7)	1 (2.8)
Erythema	15 (10.3)	1 (0.7)	7 (19.4)	1 (2.8)
Headache	15 (10.3)	1 (0.7)	3 (8.3)	-
Photosensitivity reaction	15 (10.3)	3 (2.1)	2 (5.6)	1 (2.8)

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate aminotransferase; CR: complete response; GGT: γ-glutamyl transferase; TEAE: treatment-emergent adverse event.

are predictive of durable response to Lonca. Preliminary biomarker studies suggest that response to treatment with Lonca is observed across a wide range of CD19 expression levels, including patients with very low levels.[14] The role of CD19 expression and response to Lonca is being further explored. Additional studies to investigate methods to overcome resistance to Lonca in subgroups such as chemorefractory patients, possibly through evaluation with combination therapies, are also needed.

One question that arises in practice is how best to sequence multiple CD19-directed therapies. In this study, patients had previously received CAR T therapy and achieved an ORR similar to that of the all-treated population. This finding is consistent with previous analyses and suggests that responses can be achieved with Lonca in patients who progressed after receiving CD19-targeted CAR T therapy.[15]

In this long-term follow-up analysis, the safety profile of Lonca remained consistent with previously reported safety data; no new safety concerns were detected.[10,11] With the use of dexamethasone premedication, standard spironolactone diuretics, and recommendations to minimize or avoid sun exposure, TEAE considered to be related to the PBD dimer cytotoxin—edema and effusion, skin-related AE, and liver enzyme abnormalities[16]—were consistent with previously reported safety data. PBD dimer cytotoxin-related AE continued to be manageable, with dose delays and/or modifications.[10] Increased GGT was the most common reason for treatment discontinuation, followed by edema and effusions. According to the LOTIS-2 study protocol, patients with recurrent grade ≥2 GGT elevation, after two dose reductions or dose delays >5 weeks due to GGT elevation, were discontinued from treatment with Lonca. However, treatment discontinuation due to elevated GGT does not reflect clinical practice, as elevated GGT

does not typically trigger the discontinuation of therapy in a patient whose disease is responding to anticancer therapy, especially without the presence of other elevated liver enzymes.[17] Further, patients with GGT elevations did not present with long-term liver toxicity of any grade.

One limitation of this analysis was the small number of patients with long-term responses. Further study in a large patient population is needed to understand better the characteristics of patients with long-term response to treatment with Lonca. A strength of this analysis is that the LOTIS-2 patient population is representative of a real-world population of patients with R/R DLBCL who have received multiple prior lines of therapy, including similar median ages and proportions of sex, race, patients with transformed disease, and patients with double-/triple-hit disease.[18,19]

In conclusion, among heavily pretreated patients with R/R DLBCL in the pivotal LOTIS-2 study, Lonca continued to demonstrate durable responses with a manageable safety and tolerability profile in this long-term follow-up analysis. Further, a subset of 11 patients with CR remained event-free for ≥2 years with no evidence of disease, no new anticancer treatment, and a median treatment-free duration of 27.7 months post-Lonca treatment.

Disclosures

PFC served as a consultant/advisor for ADC Therapeutics, BMS/Celgene, Genentech, Genmab, Kite Pharma, MEI Pharma, Novartis, and Takeda. WZA participated in advisory boards for Acrotech Biopharma, ADC Therapeutics, BeiGene, Kymera Therapeutics, and Nurix Therapeutics; and received research funding from Nurix Therapeutics. JPA received honoraria from Oncinfo and OncLive; consultant and research funding from ADC Therapeutics and Genentech; and served as consultant for Genentech. An immediate family member of JPA served on the advisory boards for Agios Pharmaceuticals, Forma Therapeutics, Foundation Medicine, Inovio Pharmaceuticals, and Puma Biotechnology. KMA received honoraria from BMS, Gilead, and Novartis. MH served as a consultant for AbGenomics, ADC Therapeutics, Celgene, Incyte, Janssen R&D, Omeros, Pharmacyclics, TeneoBio, and Verastem; participated in speaker bureaus for AstraZeneca, BeiGene, and Sanofi Genzyme; and received research support from Astellas Pharma, Spectrum Pharmaceuticals, and Takeda. BH served as a consultant for ADC Therapeutics, AstraZeneca, and BMS; and participated in a speaker bureau for BMS. BSK served as consultant for AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Celgene/BMS, Eli Lilly, Epizyme, Genentech, Genmab, Hutchmed, Incyte, Kite, MEI Pharma, Molecular Templates, Pharmacyclics, Takeda, and T G Therapeutics; and received research funding from AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, and Genentech. JR served as consultant/advisor for ADC Therapeutics, BMS, Kite Pharma, Novartis, and Takeda; served as speaker for ADC Therapeutics, Seattle Genetics, and Takeda; owns stock in ADC Therapeutics and AstraZeneca (spouse); provided expert testimony for and received honoraria from ADC Therapeutics and Takeda; and received research funding from Takeda. MS served as consultant/advisor for ADC Therapeutics and Genentech; and served on speaker bureaus for BMS, GSK, and Sanofi. AS served as a consultant/advisor for AstraZeneca, Bayer, Eli Lilly, Janssen Oncology, Novartis, and Roche; and received research funding from AbbVie, ADC Therapeutics, Amgen, AstraZeneca, Bayer, Cellestia, Debiopharm Group, Eli Lilly, Incyte, Loxo, MEI Pharma, Merck/MSD, Novartis, Pfizer, Philogen, and Roche. PLZ served as a consultant for EUSA Pharma, MSD, Sanofi, and Verastem; participated in advisory committees for ADC Therapeutics and Sandoz; participated in speaker bureaus/advisory committees for BMS, Celltrion, EUSA Pharma, Gilead, Janssen-Cilag, Kyowa Kirin, MSD, Roche, Servier, Takeda, TG Therapeutics, and Verastem. YW is an employee of ADC Therapeutics with equity and stock options in the company; and has an immediate family member employed by/stock ownership in Johnson & Johnson. YQ is an employee of ADC Therapeutics with equity and stock options in the company. LW is an employee of ADC Therapeutics with equity and stock options in the company. ZX is an employee of ADC Therapeutics with equity and stock options in the company. CCS served as a consultant/advisor for ADC Therapeutics, Celgene/BMS, Karyopharm, MSD, Novartis, Roche, Sanofi, and Scenic Biotech; and received honoraria from AstraZeneca, Celgene, Incyte, Gilead Sciences, Janssen Oncology, MSD, and Roche.

Contributions

PFC, WZA, JPA, KMA, MH, BH, BSK, JR, MS, AS, PLZ, and CCS were principal investigators who contributed as follows: provision of patient care; data analysis and interpretation; development and critical revision of the manuscript; and provision of final approval of the submitted content. YW, YQ, LW, and ZX contributed as follows: data analysis and interpretation; statistical analyses; development and critical revision of the manuscript; and provision of final approval of the submitted content. All authors had full access to all data in the study and approved the decision to submit for publication.

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Data-sharing statement

Proposals requesting de-identified participant data collected for the study following publication can be sent to clinical.trials@adctherapeutics.com and will be evaluated on a case-by-case basis.

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