Loncastuximab tesirine in Chinese patients with relapsed or refractory diffuse large B-cell lymphoma: a multicenter, open-label, single-arm, phase II trial

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Abstract

Patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) have a poor prognosis. Loncastuximab tesirine (Lonca), an antibody conjugate targeting CD19, has demonstrated significant clinical benefit in R/R DLBCL in a global phase II LOTIS-2 study. In the China bridging pivotal phase II OL-ADCT-402-001 study, eligible patients aged ≥18 years with R/R DLBCL who had failed ≥2 lines of systemic therapies were enrolled and treated every 3 weeks with 150 μg/kg Lonca for two cycles; then 75 μg/kg for subsequent cycles (up to 1 year). The primary endpoint was overall response rate (ORR) assessed by an independent review committee. Primary analyses for efficacy and safety were performed on the patients who received at least one treatment and had at least 6 months of follow-up following an initial documented response. As of data cutoff, 64 patients received Lonca (median 4.0 cycles; range, 1-17). The median number of prior lines of therapies was 3.0 (range, 2-12). The ORR was 51.6% (95% confidence interval [CI]: 38.7-64.2), and the complete response rate was 23.4%. Hematological events accounted for the majority of the most common (≥15%) grade ≥3 treatment-emergent adverse events (TEAE), in which increased γ-glutamyltransferase (25.0%), and hypokalaemia (18.8%) also were reported. Serious TEAE were reported in 35 of 64 patients with four fatal TEAE. In conclusion, Lonca monotherapy demonstrated clinically meaningful efficacy and was well-tolerated in heavily pretreated Chinese patients with R/R DLBCL, which was consistent with the results of the LOTIS-2 study in Caucasian patients.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently occurring subtype of non-Hodgkin lymphoma (NHL) and accounted for 40.8% of all NHL in China.[1] In 2019, there were estimated 91,954 new cases, 44,310 deaths, and 410,380 existing cases of NHL in China.[2] DLBCL can be effectively treated with the current standard first-line chemoimmunotherapy, however, approximately 30-50% of DLBCL patients still progress to relapsed or refractory (R/R) disease.[3] High-dose chemotherapy (HDT) followed by autologous stem cell transplantation (ASCT) is typically used for patients with chemotherapy-sensitive R/R disease with a cure rate ranging from 25% to 35%.[3] However, about 50% of patients with R/R DLBCL are considered HDT/ASCT-ineligible.[4] The prognosis is poor for HDT/ASCT-ineligible patients, patients who have early relapse after HD-ASCT, and patients who failed ≥2 lines of prior therapies. A recent analysis showed only 27% of DLBCL patients responded to the third-line therapy, with an overall response rate (ORR) of 21.2% in refractory patients,[5] highlighting a significant unmet medical need. In the recent era, several new therapies were approved, including anti-CD79b antibody-drug conjugate (ADC) polatuzumab plus rituximab and bendamustine (pola-BR),[6,7] anti-CD19 chimeric antigen receptor (CAR) T cells such as axicabtagene ciloleucel[8] and relmacabtagene autoleucel,[9] and a bispecific antibody-glofitamab[10,11] for Chinese patients with R/R DLBCL. Even with those novel therapies, the current unmet medical need was not truly addressed as only partial DLBCL patients can benefit in ≥3 line settings. Furthermore, the affordability of CAR T-cell therapy is still a significant issue for the majority of patients in China.[8]

Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]) is a novel ADC comprising a humanized anti-CD19 monoclonal antibody stochastically conjugated through a cathepsin-cleavable linker to a potent pyrrolobenzodiazepine (PBD) dimer alkylating cytotoxin, SG3199.[12-14] Upon binding to the CD19 antigen, Lonca is internalized by cells expressing CD19, the linker is cleaved, and the PBD dimer induces interstrand DNA crosslinks that lead to cell death.[14,15] Clinical data of Lonca from the phase I study (*clincaltrials gov. Identifier: NCT02669017*) and a pivotal phase II LOTIS-2 study in R/R DLBCL (*clincaltrials gov. Identifier: NCT03589469*) demonstrated substantial clinical activity of Lonca with an acceptable safety profile in Caucasian patients with R/R DLBCL.[12,13,16,17] However, only very few Asian patients were enrolled in the LOTIS-2 study, therefore a pivotal phase II OL-ADCT-402-001 study was conducted to further evaluate the safety and efficacy of Lonca in Chinese patients with R/R DLBCL and to understand the impact of racial differences. Here we present results from the OL-ADCT-402-001 study in Chinese patients with R/R DLBCL.

Methods

Study design and participants

We conducted a multicenter, open-label, single-arm phase II study (*Chictr.org.cn identifier: ChiCTR2300072058*) of Lonca monotherapy in adult Chinese patients with R/R DLBCL. This study enrolled patients from 15 hospitals in China. The clinical study protocol and amendments were approved by the institutional review boards at each study site and was undertaken in accordance with the International Conference on Harmonization good clinical practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent.

To be eligible for the enrollment, patients had to be ≥18 years, with histologically confirmed DLBCL including: DLBCL not otherwise specified, DLBCL transformed from indolent lymphoma, and high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit or triple-hit); have R/R disease following ≥2 multi-agent systemic treatment regimens (including rituximab and anthracycline); have measurable disease as defined by the 2014 Lugano Classification, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and adequate organ function (defined as: absolute neutrophil count ≥1.0×10^9/L; platelet count ≥75×10^9/L; hemoglobin ≥80 g/L etc.). Biopsy-proven CD19 expression was required for patients with previous CD19-directed therapy. Key exclusion criteria included: bulky disease (tumor ≥10 cm in longest dimension); diagnosis of Burkitt lymphoma; history of hypersensitivity to a CD19 antibody; autologous hematopoietic stem-cell transplantation (HSCT) within 30 days, allogeneic HSCT within 60 days, active central nervous system lymphoma; or significant comorbidities. Complete eligibility criteria are available in the *Online Supplementary Appendix*.

Procedures

Please see details in the *Online Supplementary Appendix*.

Outcomes

The primary efficacy endpoint was ORR. Secondary efficacy endpoints included duration of response (DOR), complete response rate (CRR), time to response (TTR), relapse-free survival (RFS), progression-free survival (PFS) and overall survival (OS); safety endpoints included frequency and severity of AE and SAE, changes from baseline of safety laboratory values, vital signs, ECOG performance status, and 12-lead electrocardiograms (ECG); other secondary endpoints included the serum concentrations and PK parameters of Lonca total antibody, PBD-conjugated antibody, and unconjugated warhead SG3199; anti-Lonca ADA titers.

More details are available in the *Online Supplementary Appendix*.

Statistical analysis

The primary hypothesis is that the ORR based on IRC assess-

ment for patients treated with Lonca is significantly greater than 20%. With the null hypothesis that the true ORR is 20%, and the alternative hypothesis that the true ORR is 40%, a sample size of 64 patients provides 90% power to detect a significant difference of the ORR in Chinese patients greater than 20% with a type I error of 0.025 (1-sided significance).

Primary analyses of anti-tumor activity and safety were done on the All-Treated Population (all patients who received at least one dose of Lonca when all responding patients had at least 6 months of follow-up after initial documented response). PK analysis was performed on the Per-Protocol Population (all patients in the All-Treated Population who met the inclusion/exclusion criteria, neither received prohibited concomitant treatments, nor had other protocol deviations which have major impact on efficacy results) with at least one pre- (C1D1) and one post-dose valid PK assessments. More details are available in the *Online Supplementary Appendix*.

Results

Patients

From September 15, 2021, to May 26, 2022, 92 patients were screened, 64 (69.6%) were enrolled and received at least one dose of Lonca, and were evaluated for anti-tumor activity and safety (Figure 1). At the data cut-off date (Jan 11, 2023) for the pre-planned primary analysis, 59 (92.2%) of 64 patients had treatment discontinuation, the most common reason for which was disease progression (30/59 [50.8%] patients).

Overall, 63 (98.4%) of 64 patients had DLBCL not otherwise specified, one patient had high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. Twelve patients (18.8%) had transformed DLBCL, of whom nine patients had transformation from follicular lymphoma. The median age of the patients was 60 years (range, 26-81), there were 23 patients (37.5%) aged ≥65 years old. Patients had received a median of three (range, 2-12) lines of prior systemic therapy, with a total of 67.2% of the patients had ≥3 lines of previous therapies, and 6.3% had prior CAR T-cell therapy. The majority of patients had refractory disease (67.2% to the first-line therapy, 87.5% to the most recent line therapy, 62.5% to all prior lines of therapy), and advanced disease (Ann Arbor stage III or IV disease in 82.8%). Detailed baseline demographic and clinical characteristics are shown in Table 1.

The median treatment duration was 77.5 days (range, 1-379), and the relative dose intensity was 94.9% (range, 54.9-104.4).

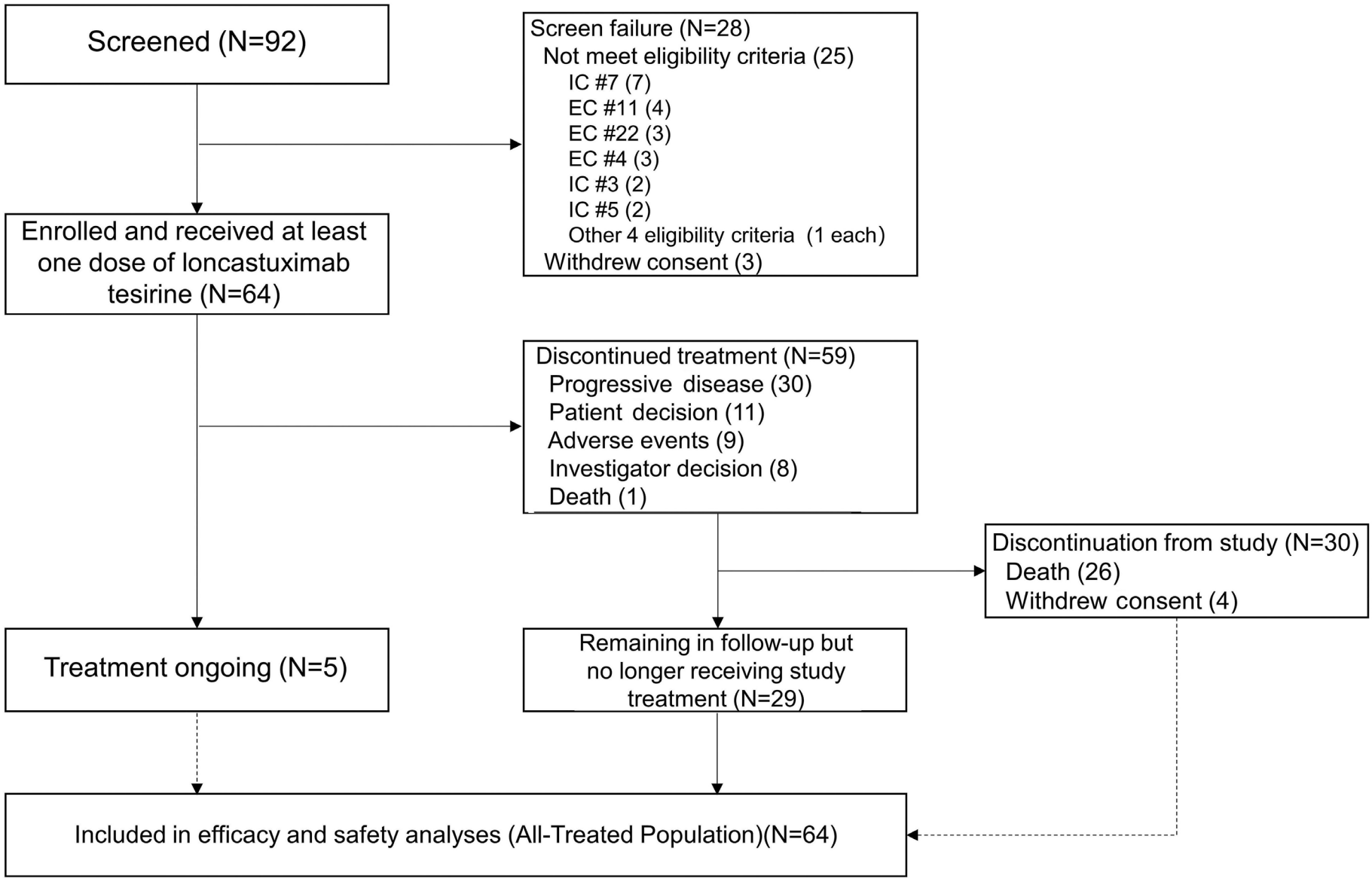

Figure 1. Consort flow diagram. IC: inclusion criteria; EC: exclusion criteria.

Table 1. Demographic and clinical characteristics of the patients in the All-Treated Population at baseline.

Characteristic	All-Treated Population N=64
Sex	
Female	22 (34.4)
Male	42 (65.6)
Age in years	
Median (range)	60 (26-81)
<65 years	40 (62.5)
≥65 - <75 years	19 (29.7)
≥75 years	5 (7.8)
ECOG performance status score*	
0	23 (35.9)
1	36 (56.3)
2	5 (7.8)
Histology	
DLBCL, not otherwise specified	63 (98.4)
HGBCL	1 (1.6)
GCB or ABC DLBCL[†]	
GCB	20 (31.3)
ABC	6 (9.4)
Double-hit or triple-hit DLBCL[‡]	1 (1.6)
Double-expressor or triple expressor DLBCL	11 (17.2)
Transformed DLBCL	12 (18.8)
Ann Arbor stage at time of study entry	
I	4 (6.3)
II	7 (10.9)
III	15 (23.4)
IV	38 (59.4)
Previous lines of therapy	
Median number of lines (range)	3 (2-12)
2 prior lines	21 (32.8)
3 prior lines	23 (35.9)
>3 prior lines	20 (31.3)
Previous therapy for lymphoma	
Anti-CD20 antibody	64 (100.0)
Anthracycline	64 (100.0)
CAR T-cell therapy	4 (6.3)
Prior autologous HSCT	3 (4.7)
Response to first-line systemic therapy	
Relapse[§]	21 (32.8)
Refractory[¶]	43 (67.2)
Response to last line systemic therapy	
Relapse[§]	8 (12.5)
Refractory[¶]	56 (87.5)
Refractory to all previous therapies	
Relapse[§]	8 (12.5)
Refractory[¶]	56 (87.5)

Data are N (%) unless otherwise stated. GCB: germinal center B cell; ABC: activated B cell; DLBCL: diffuse large B-cell lymphoma; HGBCL: high-grade B-cell lymphoma with double-hit or triple-hit; CAR: chimeric antigen receptor; HSCT: hematopoietic stem cell transplantation. *Eastern Cooperative Oncology Group (ECOG) performance-status scores are on a 5-point scale, with higher numbers indicating greater disability. [†]ABC and GCB were investigator-reported without independent testing. [‡]Double/triple-hit status is not known or negative in the remaining 63 patients. [§]Relapsed disease defined as progression of disease (PD) at least 6 months after having achieved complete response (CR) or partial response (PR) with adequate prior anti-DLBCL therapy. [¶]Refractory disease defined as failure to achieve CR or PR or experienced PD within 6 months after having achieved CR or PR, after adequate prior anti-DLBCL therapy.

The median number of treatment cycles was 4.0 (range, 1-17) while patients with CR or PR had a greater number of median treatment cycles (7.0 cycles).

Thirty-five patients (54.7%) received subsequent therapy after Lonca treatment, including three patients (4.7%) with subsequent CAR T-cell therapy. No patient received subsequent SCT.

Efficacy

At the time of data cutoff, the patients were followed with a median follow-up of 8.5 months (range, 0.7-14.6), 33 patients (51.6%; 95% confidence interval [CI]: 38.7-64.2) achieved radiographic responses as determined by IRC, including 15 (23.4%; 95% CI: 13.8-35.7) with a CR and 18 (28.1%) with a PR (Table 2). The lower limit of 95% CI of ORR (38.7%) was significantly greater than the threshold for the null hypothesis (20%). Individual patient response is shown by the best percentage change in tumor size from baseline (*Online Supplementary Figure S1*). The ORR by Investigator assessment was 59.4% (38/64 patients; 95% CI: 46.4-71.5) (*Online Supplementary Table S1*). Evaluation of ORR in Per-Protocol Population is shown in the *Online Supplementary Table S2*.

The median time to first objective response was 41.0 days (range, 26-89), which is associated with the first planned response assessment at approximately 6 weeks after C1D1. Three patients with PR at the first response assessment exhibited a CR in the subsequent assessment. Of the 33 patients who achieved CR or PR, the median DOR was 6.37 months (95% CI: 3.61-10.22). The mDOR was 10.22 months for patients with CR, 6.08 months for patients with PR (Figure 2A). The proportions of patients maintaining response at 3, 6, 9, and 12 months were 72.7%, 36.4%, 18.2% and not reached, respectively (*Online Supplementary Table S3*). Notably, seven (46.7%) of 15 patients with CR still maintained CR at data cutoff with no additional treatment, two patients had ongoing CR at the 1-year follow-up, and three patients maintained response for at least 6 months after EOT (*Online Supplementary Figure S2*). Median PFS was 4.96 months (95% CI: 2.99-7.66) (Figure 2B), median OS was 9.33 months (95% CI: 7.66 to not estimable) (Figure 2C), and median RFS was 6.37 months (95% CI: 3.55 to not estimable).

Subgroup analyses of ORR showed treatment anti-tumor activity across prespecified subgroups (*Online Supplementary Figure S3*). Responses, including CR, were observed in several high-risk subgroups: ORR was 54.7% in patients with

advanced stage disease (stage III/IV) and 50.0% in patients with transformed disease. Patients who were refractory to first-line therapy, to the most recent therapy, or to all prior therapies experienced ORR of 44.2%, 51.8% and 42.5%, respectively. Three patients who had received a prior SCT had an ORR of 100%. Lonca was also effective in elderly patients ≥65 years (ORR of 45.8%) and in patients who had received prior CD19 CAR T-cell therapy (ORR of 50%).

Safety

Sixty-four patients (100%) had at least one treatment-emergent adverse event (TEAE), and 63 patients (98.4%) had at least one TEAE related to Lonca by the investigator assessment (*Online Supplementary Tables S4, S5*). Sixty-one patients (95.3%) had at least one grade ≥3 TEAE (Table 3; *Online Supplementary Table S4*), and 58 patients (90.6%) had at least one treatment-related TEAE of grade ≥3 by the investigator assessment. Hematologic toxic effects were the most common grade ≥3 TEAE, including decreased platelet count (34.4%), decreased neutrophil count (28.1%), decreased white blood cell count (28.1%), anemia (18.8%), neutropenia (17.2%), decreased lymphocyte count (15.6%). The majority of these observed events are expected adverse effects previously associated with Lonca. The majority of non-hematological grade ≥3 TEAE were grades 3; in which, increased γ-glutamyltransferase (GGT) was the most common (25%), followed by hypokalaemia (18.8%). A summary of TEAE by age group is shown in *Online Supplementary Table S6*, suggesting the TEAE were similar across age groups. Two patients (3.1%) had infusion-related reactions.

Thirty-five patients (54.7%) experienced at least one serious TEAE, and 31 patients (48.4%) had at least one treatment-related serious TEAE by the investigator assessment. The most frequently reported serious TEAE (in ≥2 patients) were pneumonia (10.9%), increased GGT (9.4%), decreased platelet count (9.4%), pleural effusion (7.8%), anaemia (6.3%), thrombocytopenia (6.3%), neutropenia (4.7%), pneumonia bacterial (4.7%), upper respiratory tract infection (4.7%), febrile neutropenia (3.1%), neutrophil count decreased (3.1%), and leukopenia (3.1%). The most frequently reported serious TEAE, except from clinical symptoms related to the respiratory system, were abnormalities of clinical laboratory values as opposed to other clinical symptoms. Most serious TEAE were generally reversible.

A total of 26 patients (40.6%) died during the study including eight deaths within 15 weeks of the last dose (AE reporting period). Most deaths (21 [81%] of 26) were due to disease progression; three (11.5%) of 26 patients died due to pulmonary embolism, lymphoma cachexia, and COVID-19 each which all happened after receiving new anti-cancer therapy, and two (7.7%) of 26 patients died from fatal TEAE. There were total of four patients (6.3%) with fatal TEAE, and three patients (4.7%) had a treatment-related fatal TEAE by the investigator assessment. The four fatal TEAE included multiple organ dysfunction syndrome, pneumonia, septic shock, and metabolic acidosis in one patient each. Of those, metabolic acidosis was considered unrelated to Lonca by the investigator's assessment. Two patients had fatal AE reported (multiple organ dysfunction syndrome, metabolic acidosis) and the cause of death was considered as disease progression. One patient had a non-treatment-emergent AE leading to death. This event, reported as unexplained death after this patient started CAR T-cell treatment, occurred 113 days after the last dose of Lonca and was considered by the investigator to be unrelated to Lonca.

Dose modifications due to TEAE included treatment discontinuation in 11 (17.2%) of 64 patients, dose reduction in ten (15.6%) patients, and dose delay in 47 (73.4%) patients, which were used to manage non-hematologic and hematologic AE. No patient had infusion interruption due to AE. The estimated time to first AE leading to dose modification is shown in the *Online Supplementary Figure S4*. The most frequently reported TEAE leading to treatment discontinuation were increased GGT (6.3%) and pneumonia (3.1%). Increased GGT was also the most common reason for dose reduction (6.3%) and dose delay (32.8%). Beyond increased GGT, hematologic TEAE accounted for the remaining most common reasons for dose delay (*Online Supplementary Table S7*) and dose reduction followed by decreased platelet count in four patients (6.3%); decreased neutrophil count, decreased white blood cell count in one patient each (1.6%). In addition, herpes zoster led to dose reduction in one patient. Increased GGT from a mean of 36.2 U/L (standard: 24.71) at baseline to the maximum of 112.8 U/L (standard: 60.69)

Table 2. Best overall responses and overall response rate.

Response	All-Treated Population N=64
Best overall response	
Complete response	15 (23.4)
Partial response	18 (28.1)
Stable disease	19 (29.7)
Not evaluable*	5 (7.8)
Progressive disease	7 (10.9)
ORR (CR + PR)	33 (51.6)
95% CI for ORR	38.7-64.2
95% CI for CR	13.8-35.7

Data are N (%). Response was assessed by central independent review. A best overall response of stable disease could only be achieved after the patient was on the study for a minimum of 35 days following the first dose of loncastuximab tesirine. Any disease assessment indicating stable disease before this time point was considered not evaluable for response if no assessment after this time point was available. *Patients without any scan available to the independent reviewer or patients whose scan was determined to be not evaluable by the independent reviewer. ORR: overall response rate; CR: complete reponse; PR: partial response; CI: confidence interval.

at cycle 8 day 1 suggested a possible cumulative effect, which also was observed with alkaline phosphatase (*Online Supplementary Figure S5*). Other biochemistry parameters exhibited no evidence of a cumulative effect. No Hy's law cases were observed. Hematologic parameters were affected by treatment and tended to recover to some extent between cycles (*Online Supplementary Figure S5*). There was no evidence of a consistent or clinically meaningful change from baseline for vital signs, ECOG performance status, and 12-lead ECG.

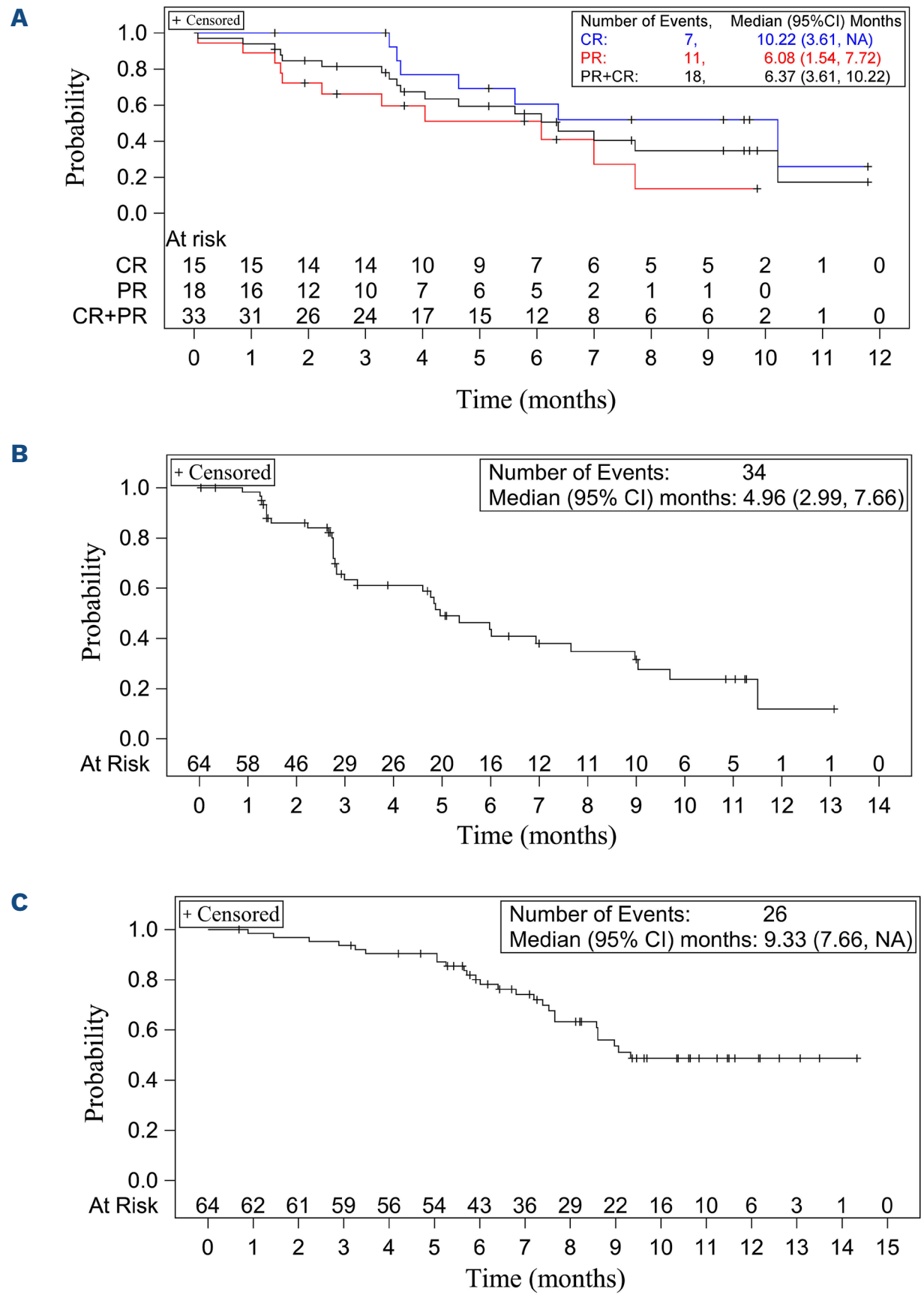

Figure 2. Kaplan-Meier plots. (A) Duration of response by best overall response. Based on independent reviewer data, including death as event. (B) Progression-free survival. Based on independent reviewer data, including death as event. (C) Overall survival. Patients with events after the start of subsequent anticancer therapy or procedure, or progression-free and alive at data cutoff, or who had unknown status were censored at the last valid tumor assessment on or before the start of subsequent anticancer therapy or procedure or data cutoff; this included patients who had early progression before disease assessment and patients who started subsequent therapy due to investigator-assessed progressive disease before independent assessment. Patients with no disease assessment after baseline were censored on day 1. CI: confidence interval; NA: not applicable; CR: complete response; PR: partial response.

Table 3. Grade ≥3 treatment-emergent adverse events reported in ≥2% of patients.

Preferred term	Grade 3	Grade 4	Grade 5	Grade 3-5
Patients with any TEAE of grade ≥3	35 (54.7)	22 (34.4)	4 (6.3)	61 (95.3)
Hematologic TEAE				
Platelet count decreased	16 (25.0)	6 (9.4)	0	22 (34.4)
Neutrophil count decreased	11 (17.2)	7 (10.9)	0	18 (28.1)
White blood cell count decreased	16 (25.0)	2 (3.1)	0	18 (28.1)
Anemia	12 (18.8)	0	0	12 (18.8)
Neutropenia	4 (6.3)	7 (10.9)	0	11 (17.2)
Lymphocyte count decreased	9 (14.1)	1 (1.6)	0	10 (15.6)
Leukopenia	4 (6.3)	4 (6.3)	0	8 (12.5)
Thrombocytopenia	7 (10.9)	1 (1.6)	0	8 (12.5)
CD4 lymphocytes decreased	1 (1.6)	2 (3.1)	0	3 (4.7)
Febrile neutropenia	0	2 (3.1)	0	2 (3.1)
Lymphopenia	1 (1.6)	1 (1.6)	0	2 (3.1)
Non-hematologic TEAE				
γ-glutamyltransferase increased	16 (25.0)	0	0	16 (25.0)
Hypokalaemia	11 (17.2)	1 (1.6)	0	12 (18.8)
Pneumonia	8 (12.5)	0	1 (1.6)	9 (14.1)
Upper respiratory tract infection	4 (6.3)	0	0	4 (6.3)
Pneumonia bacterial	3 (4.7)	0	0	3 (4.7)
Aspartate aminotransferase increased	3 (4.7)	0	0	3 (4.7)
Hyponatraemia	3 (4.7)	0	0	3 (4.7)
Malaise	2 (3.1)	0	0	2 (3.1)
C-reactive protein increased	2 (3.1)	0	0	2 (3.1)
Hypertriglyceridaemia	2 (3.1)	0	0	2 (3.1)
Hyperuricaemia	0	2 (3.1)	0	2 (3.1)
Hypophosphataemia	2 (3.1)	0	0	2 (3.1)

Data are N (%). TEAE: treatment-emergent adverse event.

Pharmacokinetics

There was moderate inter-patient variability of Lonca PK exposure as determined by maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) for the total antibody and PBD-conjugated antibody. The PK exposure of total antibody was slightly higher than PBD-conjugated antibody, and the PK profile at the terminal phase was similar between the PBD-conjugated antibody and total antibody, consistent with a relative stable amount of Lonca in the circulation (*Online Supplementary Figure S6*). An apparent longer T_{half} of 13.0 days for PBD-conjugated antibody in cycle 2 compared to 8.25 days in cycle 1 was observed. The mean accumulation index in cycle 2 was 1.51 and 1.49 for Lonca PBD-conjugated antibody and total antibody, respectively (*Online Supplementary Table S8*). The levels of SG3199 varied, largely due to the limited number of available patients providing measurable levels of SG3199 for PK assessment and the majority of patients with serum concentration below the lower limit of quantification (LLOQ) (*Online Supplementary Figure S7*). No patient exhibited a confirmed positive ADA at any post-dose time point. Overall, the PK and ADA results were similar in Chinese patients in comparison with the Caucasian patients.[13]

Discussion

In the current study, Lonca monotherapy demonstrated a clinically meaningful ORR of 51.6% with a CRR of 23.4% in heavily pretreated (more than two-thirds of patients receiving ≥3 lines of prior therapies) Chinese patients with R/R DLBCL. Responses to Lonca were rapid and usually occurred at the first scheduled postbaseline response assessment 6 weeks after treatment started (after 2 cycles). Responses were durable with a median DOR of 6.37 months. Notably, responses extended beyond the EOT, especially for patients with CR. Overall, the efficacy is clinically meaningful and consistent with that of LOTIS-2 study, indicating that Lonca monotherapy is effective in patients with R/R DLBCL in both Caucasian and Chinese patients.

The population of our study reflects broad and representative DLBCL patients seen in clinics. Impressive ORR were observed in patients with high-risk features such as transformed disease (ORR of 50%), previous treatment with anti-CD19 CAR T-cell therapy (ORR of 50%), In particular, promising ORR (42.5-51.8%) were also observed in the refractory disease setting in patients refractory to first-line therapy, to most recent line therapy, or to all prior systemic therapies. Only one patient with double/triple-hit disease

was enrolled in our study, but the clinical activity of this subgroup population was shown in LOTIS-2 study with an ORR of 33.3% with all responders being CR.[13,18] These subgroup analyses not only highlight the effectiveness of Lonca monotherapy in ≥3 line DLBCL within this clinical trial, but also imply the efficacy of Lonca monotherapy in a real-world setting where difficult-to-treat populations are common. It is worth mentioning that notable differences in the patient population were seen in clinical studies of recently approved therapies for R/R DLBCL. For example, patients with transformed disease were excluded and patients with double/triple-hit disease were not enrolled in the randomized portion of the pivotal study of pola-BR in ≥2 line DLBCL patients.[6,7] In the pivotal study of tafasitamab plus lenalidomide in ≥2 line DLBCL, patients with primary refractory, double/triple-hit disease, or >3 previous systemic therapies were excluded from the trial.[19] Although those combination regimens such as pola-BR and tafasitamab plus lenalidomide have shown higher ORR with 56.6% and 60% in the above-mentioned two studies,[6,19] respectively, as compared with the 51.6% ORR for Lonca monotherapy in our study, cross-trial comparisons as always need to be interpreted with caution given the trial design and patient populations are different.

One of the current challenges in clinical practice is how best to sequence multiple CD19-directed therapies. In the current and LOTIS-2 study, patients with prior CAR T-cell therapy history (biopsy-proven CD19 expression was required at study entry) had similar ORR as compared to the overall study population.[13] Moreover, the effectiveness of Lonca for patients with R/R DLBCL following CAR T also was reported in the real world,[20] further demonstrated Lonca as a reasonable and effective treatment option for patients who received CAR T-cell therapy. On the other hand, in a retrospective analysis of 14 DLBCL patients with relapsed or progressive disease after treatment with Lonca and who subsequently underwent CD19-directed CAR T-cell therapy, favorable outcomes (ORR of 50%) to CAR T-cell therapy were also seen.[21] Furthermore, no CD19 antigen-negative relapses were noted in any of the ten patients who underwent reassessment of CD19 expression after relapse or progression on Lonca treatment. This provides preliminary suggestive evidence that prior treatment with Lonca in R/R DLBCL would not preclude subsequent sensitivity to anti-CD19 CAR T-cell therapies. Besides CD19-directed CAR T, how best to sequence Lonca *versus* other newer treatments, for example polatuzumab or CD20×CD3 T-cell engaging antibodies such as glofitamab, are also emerging as clinical practice challenges. However, there has not been adequate data regarding the optimal sequence of using Lonca *versus* CAR T or CD20×CD3 T-cell engaging antibodies and physician needs to decide the treatment sequence in their discretion which will generate more data to define the best treatment sequence. It is worth noting that from the mechanism of action perspective, the combination of Lonca and CD20×CD3 T-cell engaging antibodies can be more effective and a clinical study is currently ongoing to evaluate the combination of Lonca with CD20×CD3 T-cell engaging antibodies[22] and the early clinical readout is encouraging and highlights the potential of the combinations.[23]

No new safety signals were detected in the current study when compared with the LOTIS-2 study. Although grade ≥3 TEAE after Lonca occurred in 95.3% of the patients, these events were predominantly hematologic events reflecting laboratory abnormalities rather than clinical symptoms. Increased GGT was the most common non-hematologic grade ≥3 TEAE (25% of patients, and no grade 4 events), but was not associated with synthetic dysfunction or severe hepatic events, and no Hy's law cases were observed. The underlying mechanism of increased GGT after Lonca treatment remains unclear. Liver enzyme elevations other than GGT, rash and edema or effusion were considered likely related to PBD warhead, were mild-to-moderate in severity, and were generally manageable. Of note, encephalopathy, peripheral neuropathy, cytokine release syndrome and secondary malignancies which have been reported with other approved DLBCL treatments[6-8] were not observed in the current study. Overall, Lonca is generally well-tolerated in the current study population and its AE are generally reversible and manageable in most patients with dose delays/reductions and standard supportive care, making it an attractive treatment option for R/R DLBCL patients.

The median age of DLBCL at diagnosis is in the mid-60s, with over one-third of patients ≥75 years at diagnosis.[3] Older individuals carry a higher lymphoma burden.[2] However, this patient population typically faces treatment challenges such as comorbidities and poor tolerance to chemotherapy, especially in the setting of ≥3 line disease, highlighting the unmet need for non-cytotoxic therapies for older patients. Lonca has a safety profile that differs from that of conventional chemotherapeutics.[13,17] Furthermore, no increase in AE was observed in patients aged ≥65 years (37.5%) compared with younger patients. Our study also demonstrated Lonca's efficacy in elderly patients, with response rates comparable to those seen in a younger population, strongly suggesting Lonca as an attractive treatment option for elderly R/R DLBCL patients.

In conclusion, Lonca has consistent efficacy and safety profiles in Chinese patients as compared with LOTIS-2 study. Our study, together with other studies of Lonca monotherapy in R/R DLBCL including LOTIS-2, generated adequate clinical data supporting Lonca as a promising efficacious and safe monotherapy treatment for patients with R/R DLBCL. In the meantime, multiple ongoing clinical trials are evaluating its indications in DLBCL as combination with other chemoimmunotherapies (systemic chemotherapy-free combinations). The updated results from the safety run-in of the phase III LOTIS-5 study (Lonca plus rituximab in ≥2 line DLBCL patients ineligible for HSCT) has demonstrated encouraging anti-tumor activity without new safety signals.[24] In addition,

Lonca's promising single-agent activity and rapid response, even in high-risk populations, warrants its future clinical evaluation as the bridging therapy to potentially curative therapy measures including CAR T cell therapy or HSCT for patients with DLBCL.

Disclosures

FL, ZW, RZ, LY and DS are the employees of Overland Pharmaceuticals. All other authors have no conflicts of interest to disclose.

Contributions

Project administration, supervision, validation, investigation and article review by JZ and YS. Patient enrollment and data acquisition by NL, XS, HZ, LZ, KZ, LL, HY, KH, QC, YL, JJ, LZ, WL, YG and WY. Data analysis by NL, YS, JZ, FL, ZW, RZ, LY and DS. Original manuscript drafting by NL, ZW and FL. Critical revision of the manuscript by NL,YS and JZ, FL. All authors have read and approved the manuscript.

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Data-sharing statement

Individual patient data will not be made available in order to maintain health information privacy. The data that support the findings of this study will be shared upon reasonable request to the corresponding author.

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