haematologica
Journal of the Ferrata Storti Foundation

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Received: February 4, 2024.
Accepted: August 26, 2024.

Citation: Ningjing Lin, Xiuhua Sun, Hui Zhou, Liqun Zou, Keshu Zhou, Lihong Liu, Haiyan Yang, Kai Hu, Qingqing Cai, Yao Liu, Jie Jin, Liling Zhang, Wenyu Li, Ye Guo, Wei Yang, Feng Luo, Zhenguang Wang, Rong Zhu, Lei Yang, Dan Song, Yuqin Song, and Jun Zhu. Loncastuximab tesirine in Chinese patients with relapsed or refractory diffuse large B-cell lymphoma: a multicenter, open-label, single-arm, phase II trial.
Haematologica. 2024 Sept 5. doi: 10.3324/haematol.2024.284973 [Epub ahead of print]

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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Running title: Loncastuximab tesirine in Chinese R/R DLBCL

Word count: abstract, 250 words; main text (= introduction + methods + results + discussion): 3661 words, 2 figures, 3 tables

Trial registration: *Chinese Clinical Trial Registry identifier: ChiCTR2300072058.*

Disclosures

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

Funding

This study is funded by ADC Therapeutics SA and Overland Pharmaceuticals.

Authors' contributions

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

Acknowledgements

We thank the participating patients and their families, and the investigators, research

nurses, study coordinators, and operations staff.

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.

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 2 LOTIS-2 study. In the China bridging pivotal phase 2 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 with Lonca every 3 week with 150 μg/kg for 2 cycles; then 75 μg/kg for subsequent cycles (up to 1 year). The primary endpoint was overall response rate (ORR) assessed by 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 to 17]). The median number of prior lines of therapies was 3.0 (range: 2 to 12). The ORR was 51.6% (95% CI: 38.7% to 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 (TEAEs), in which increased gamma glutamyltransferase (25.0%), and hypokalaemia (18.8%) also were reported. Serious TEAEs were reported in 35 of 64 patients with 4 fatal TEAEs. 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 T cells (CAR-T) 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, 13, 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 1 study

(NCT02669017) and a pivotal phase 2 LOTIS-2 study in R/R DLBCL (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 of Asian patients were enrolled in the LOTIS-2 study, therefore a pivotal phase 2 OL-ADCT-402-001 study was conducted to further evaluate the safety and efficacy of Lonca in Chinese patients with R/R DLBCL 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 2 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 ≥1.0×10^3/μL; platelet count ≥75×10^3/μL; 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 AEs and SAEs, changes from baseline of safety laboratory values, vital signs, ECOG performance status, and 12-lead electrocardiograms (ECGs);

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 assessment 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 had did not take prohibited concomitant treatments, nor had other protocol deviations which have major impact on efficacy results) with at least 1 pre- (C1D1) and 1 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 [50.8%] of 59 patients).

Overall, 63 (98.4%) of 64 patients had DLBCL not otherwise specified, 1 patient had high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. Twelve patients (18.8%) had transformed DLBCL, of whom 9 patients had transformation from follicular lymphoma. The median age of the patients was 60 years (range: 26 to 81), there were 23 patients (37.5%) aged ≥65 years old. Patients had received a median of 3 (range: 2 to 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 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 to 379), and the relative dose intensity was 94.9% (54.9%-104.4%). The median number of treatment cycles was 4.0 (range: 1 to 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 3 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 to 14.6), 33 patients (51.6%; 95% 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% to 71.5%) (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 to 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 to 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, 7 (46.7%) of 15 patients with CR still maintained CR at data-cutoff with no additional treatment, 2 patients had ongoing CR at the 1-year follow-up, and 3 patients maintained response for at least 6 months after EOT (Online Supplementary Figure S2). Median PFS was 4.96 months (95% CI: 2.99 to 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 CRs, 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 ORRs 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 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 Table S4-5). Sixty-one patients (95.3%) had at least one grade ≥3 TEAE (Table 3 and 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 TEAEs, including decreased platelet count (34.4%), decreased neutrophil count (28.1%), decreased white blood cell count (28.1%), anaemia (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 TEAEs were grades 3; in which, increased gamma-glutamyltransferase (GGT) was the most common (25%), followed by hypokalaemia (18.8%). A summary of TEAEs by age group is shown in Online Supplementary Table S6, suggesting the TEAEs 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 TEAEs (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 TEAEs, except from clinical symptoms related to the respiratory system, were abnormalities of clinical laboratory values as opposed to other clinical symptoms. Most serious TEAEs were generally reversible.

A total of 26 patients (40.6%) died during the study including 8 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 TEAEs. There were total of 4 patients (6.3%) with fatal TEAEs, and 3 patients (4.7%) had a treatment-related fatal TEAE by the investigator assessment. The four fatal TEAEs 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 AEs reported (multiple organ dysfunction syndrome, metabolic acidosis) and the cause of death was considered as disease progression. One patient had a nontreatment-emergent AE leading to death. This event, reported as unexplained death after this patient started CAR-T 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 TEAEs included treatment discontinuation in 11 (17.2%) of 64 patients, dose reduction in 10 (15.6%) patients, and dose delay in 47 (73.4%) patients, which were used to manage non-hematologic and hematologic AEs. 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 TEAEs 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 TEAEs accounted for the remaining most common reasons for dose delay (Online Supplementary Table S7) and dose reduction (followed by decreased platelet count in 4 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 (std: 24.71) at baseline to the maximum of 112.8 U/L (std: 60.69) 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 ECGs.

Pharmacokinetics

There was moderate inter-patient variability of Lonca PK exposure as determined by maximum observed concentration (Cmax) 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 timepoint. 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 two 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 ORRs were observed in patients with high-risk features such as transformed disease (ORR of 50%), previous treatment with anti-CD19 CAR-T therapy (ORR of 50%), In particular, promising ORRs (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 1 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 abovementioned 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 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. 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 10 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 vs 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 vs 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 on 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 for evaluating the combination of Lonca with CD20×CD3 T-cell engaging antibodies[22] and the early clinical readout is encouraging and highlighted 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 TEAEs 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 TEAEs (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, 7, 8] were not observed in the current study. Overall, Lonca is generally well-tolerated in the current study population and its AEs 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 noncytotoxic therapies for older patients. Lonca has a safety profile that differs from that of conventional chemotherapeutics.[13, 17] Furthermore, no increase in AEs 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 chemo-free combinations). The updated results from the safety run-in of the phase 3 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 or HSCT for patients with DLBCL.

References

1. Li XQ, Li GD, Gao ZF, Zhou XG, Zhu XZ. Distribution pattern of lymphoma subtypes in China: A nationwide multicenter study of 10002 cases. J Diagn Concepts Pract. 2012;11(02):111-115.

2. Liu W, Liu J, Song Y, et al. Burden of lymphoma in China, 1990-2019: an analysis of the global burden of diseases, injuries, and risk factors study 2019. Aging (Albany NY). 2022;14(7):3175-3190.

3. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med. 2021;384(9):842-858.

4. Nastoupil LJ, Bartlett NL. Navigating the Evolving Treatment Landscape of Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2023;41(4):903-913.

5. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-1808.

6. Sehn LH, Hertzberg M, Opat S, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Blood Adv. 2022;6(2):533-543.

7. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155-165.

8. Sun W, Liang AB, Huang H, Huang XJ. Strategies to optimize chimeric antigen receptor T-cell therapy in hematologic malignancies: Chinese experience. Haematologica. 2023;108(8):2011-2028.

9. Ying Z, Yang H, Guo Y, et al. Relmacabtagene autoleucel (relma-cel) CD19 CAR-T therapy for adults with heavily pretreated relapsed/refractory large B-cell lymphoma in China. Cancer Med. 2021;10(3):999-1011.

10. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231.

11. Song YQ, Zhang HL, Huang HQ, et al. Glofitamab monotherapy induces high

complete response rates and manageable safety in Chinese patients with heavily pretreated relapsed or refractory diffuse large B-cell lymphoma. Haematologica. 2024;109(4):1269-1273.

12. Kahl BS, Hamadani M, Radford J, et al. A Phase I Study of ADCT-402 (Loncastuximab Tesirine), a Novel Pyrrolobenzodiazepine-Based Antibody-Drug Conjugate, in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma. Clin Cancer Res. 2019;25(23):6986-6994.

13. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790-800.

14. Zammarchi F, Corbett S, Adams L, et al. ADCT-402, a PBD dimer-containing antibody drug conjugate targeting CD19-expressing malignancies. Blood. 2018;131(10):1094-1105.

15. Furqan F, Hamadani M. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma: a review of clinical data. Ther Adv Hematol. 2022;13:20406207221087511.

16. Caimi PF, Ai WZ, Alderuccio JP, et al. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase II LOTIS-2 study. Haematologica. 2024;109(4):1184-1193.

17. Hamadani M, Radford J, Carlo-Stella C, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood. 2021;137(19):2634-2645.

18. Alderuccio JP, Ai WZ, Radford J, et al. Loncastuximab tesirine in relapsed/refractory high-grade B-cell lymphoma: a subgroup analysis from the LOTIS-2 study. Blood Adv. 2022;6(16):4736-4739.

19. Salles G, Duell J, Gonzalez Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020;21(7):978-988.

20. Epperla N, Lucero M, Bailey T, et al. 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. Transplant Cell Ther. 2024;30(2):S353.

21. Thapa B, Caimi PF, Ardeshna KM, et al. CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy. Blood Adv. 2020;4(16):3850-3852.

22. Hess BT, Solh MM, Gandhi M, et al. Phase 1b open-label study of loncastuximab tesirine in combination with other anticancer agents in patients with relapsed/refractory B-cell non-Hodgkin lymphoma (LOTIS-7). J Clin oncol. 2023;41(16_suppl):TPS7581.

23. ADC Therapeutics Announces Updates on LOTIS-7 Clinical Trial Evaluating ZYNLONTA® in Combination with Glofitamab or Mosunetuzumab in Patients with Relapsed/Refractory B-cell Non-Hodgkin Lymphoma [press release]. Accessed April 04, 2024. https://ir.adctherapeutics.com/press-releases/press-release-details/2024/ADC-Therapeutics-Announces-Updates-on-LOTIS-7-Clinical-Trial-Evaluating-ZYNLONTA-in-Combination-with-Glofitamab-or-Mosunetuzumab-in-Patients-with-RelapsedRefractory-B-cell-Non-Hodgkin-Lymphoma/default.aspx.

24. Kwiatek M, Grosicki S, Jiménez JL, et al. ABCL-515 Updated Results of the Safety Run-In of the Phase 3 LOTIS-5 Trial: Novel Combination of Loncastuximab Tesirine With Rituximab (Lonca-R) Versus Immunochemotherapy in Patients With R/R DLBCL. Clin Lymphoma Myeloma Leuk. 2023;23:S439-S440.

Tables

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, 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)

Characteristic	All-Treated Population (N=64)
>3 prior lines	20 (31.3)
Previous therapy for lymphoma	
Anti-CD20 antibody	64 (100.0)
Anthracycline	64 (100.0)
CAR-T 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-T=chimeric antigen receptor T cell. HSCT=haematopoietic 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.

Table 2. Best overall responses and overall response rate

	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 to 64.2)
95% CI for CR	(13.8 to 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 timepoint was considered not evaluable for response if no assessment after this timepoint 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.

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 TEAEs				
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)
Anaemia	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 TEAEs				
Gamma-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.

Figure legends

Figure 1. Consort flow diagram

IC, inclusion criteria; EC, exclusion criteria.

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.

Figure 1

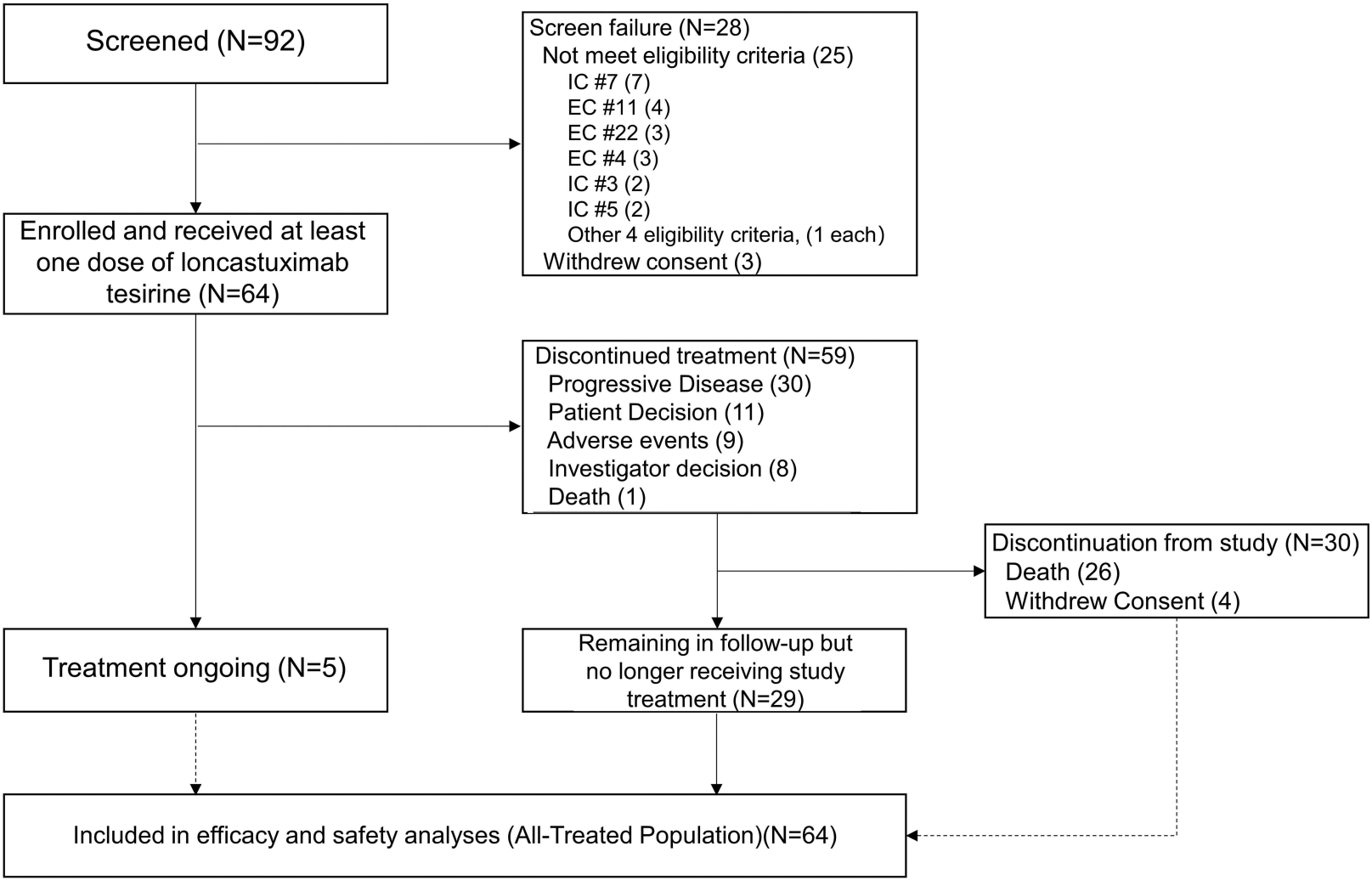
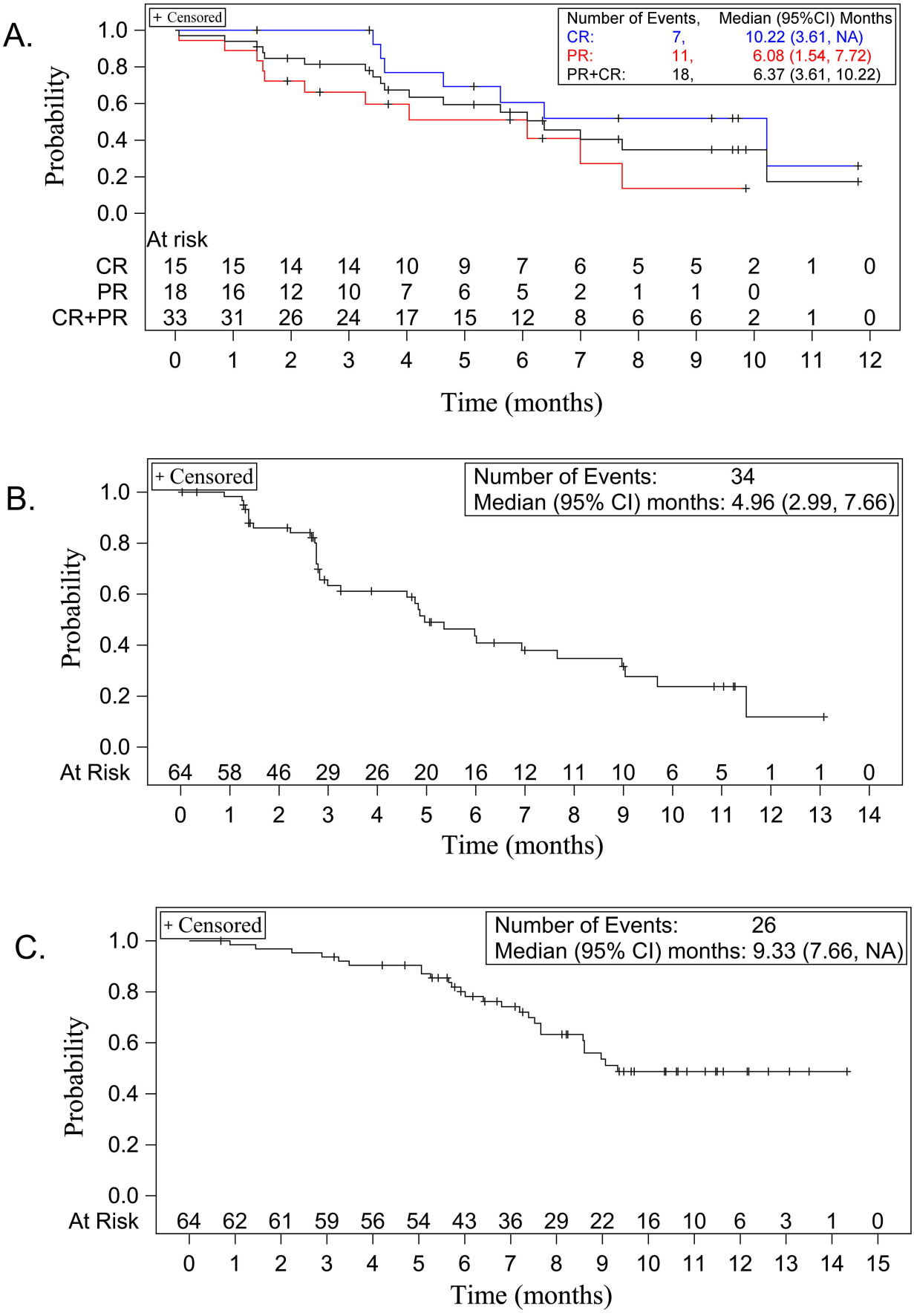

Screened (N=92)
Screen failure (N=28)
Not meet eligibility criteria (25)
IC #7 (7)
EC #11 (4)
EC #22 (3)
EC #4 (3)
IC #3 (2)
IC #5 (2)
Other 4 eligibility criteria, (1 each)
Withdrew consent (3)
Enrolled and received at least one dose of loncastuximab tesirine (N=64)
Discontinued treatment (N=59)
Progressive Disease (30)
Patient Decision (11)
Adverse events (9)
Investigator decision (8)
Death (1)
Discontinuation from study (N=30)
Death (26)
Withdrew Consent (4)
Treatment ongoing (N=5)
Remaining in follow-up but no longer receiving study treatment (N=29)
Included in efficacy and safety analyses (All-Treated Population)(N=64)

Figure 2


A.
+ Censored
Number of Events, Median (95%CI) Months
CR: 7, 10.22 (3.61, NA)
PR: 11, 6.08 (1.54, 7.72)
PR+CR: 18, 6.37 (3.61, 10.22)
Probability
1.0
0.8
0.6
0.4
0.2
0.0
At risk
CR 15 15 14 14 10 9 7 6 5 5 2 1 0
PR 18 16 12 10 7 6 5 2 1 1 0
CR+PR 33 31 26 24 17 15 12 8 6 6 2 1 0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (months)
B.
+ Censored
Number of Events: 34
Median (95% CI) months: 4.96 (2.99, 7.66)
Probability
1.0
0.8
0.6
0.4
0.2
0.0
At Risk
64 58 46 29 26 20 16 12 11 10 6 5 1 1 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time (months)
C.
+ Censored
Number of Events: 26
Median (95% CI) months: 9.33 (7.66, NA)
Probability
1.0
0.8
0.6
0.4
0.2
0.0
At Risk
64 62 61 59 56 54 43 36 29 22 16 10 6 3 1 0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (months)

Supplementary Data to the Manuscript Entitled

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

Contents

Supplementary methods

Complete eligibility criteria of OL-ADCT-402-001 study

Inclusion Criteria

1. Male or female patients aged 18 years or older who are current residents of mainland China with Chinese ancestry
2. Pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification, to include: DLBCL not otherwise specified, DLBCL transformed from indolent lymphoma, and high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
3. Relapsed or refractory disease following two or more multiagent systemic treatment regimens

   • Relapsed disease defined as progression of disease (PD) at least 6 months after having achieved CR or 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.

   • Adequate prior anti-DLBCL therapies defined as having received at least 4 cycles of multiagent systemic treatment regimens containing rituximab and anthracycline in 1L therapy and at least 2-cycle treatment regimen in 2L therapy, unless the patients are intolerant or had disease progression during the treatment. If disease progression occurred during the treatment period, then the disease is considered refractory irrespective of the number of treatment cycles received. Patients with transformed DLBCL are eligible if they have received at least two multi-agent systemic anti-lymphoma regimens as defined above, regardless of whether these treatments were given before or after histological transformation.
4. Patients who have received previous CD19-directed therapies must have a biopsy that shows CD19 protein expression after completion of the CD19-directed therapy
5. Measurable disease as defined by the 2014 Lugano Classification
6. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
7. Adequate organ function as defined by screening laboratory values within the following parameters:
   a) Absolute neutrophil count ≥1.0 × 10^3/μL (off growth factors at least 72 h)
   b) Platelet count ≥75 × 10^3/μL without transfusion in the prior 7 days
   c) Hemoglobin ≥80 g/L without transfusion in the prior 7 days

d) ALT, AST, and GGT ≤2.5 × the upper limit of normal (ULN)

e) Total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 × ULN)

f) Blood creatinine ≤1.5 × ULN or calculated creatinine clearance ≥60 mL/min by the Cockcroft and Gault equation

Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.

8. Women of childbearing potential (WOCBP)* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 9 months after the last dose of loncastuximab tesirine. Men with female partners who are of childbearing potential must agree that they will use a highly effective method of contraception from the time of giving informed consent until at least 6 months after the patient receives his last dose of loncastuximab tesirine

* WOCBP are defined as sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Highly effective forms of birth control are methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include: hormonal contraceptives associated with inhibition of ovulation (oral, injectable, patch, a vaginal ring or implantable birth control), intrauterine devices and intrauterine hormone releasing systems, male partner sterilization (vasectomy), or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.

Note: The progesterone-only birth control pills which do not inhibit ovulation, barrier method (e.g., condoms, diaphragm, or cervical cap with or without spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not considered as highly effective methods of contraception.

Exclusion Criteria

1. Previous treatment with loncastuximab tesirine
2. Known history of hypersensitivity to or positive serum human anti-drug antibody (ADA) to a CD19 antibody
3. Pathologic diagnosis of Burkitt lymphoma
4. Bulky disease, defined as any tumor ≥10 cm in longest dimension
5. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agree and document should not be exclusionary
6. Autologous stem cell transplant within 30 days prior to start of study drug (Cycle 1 Day 1 [C1D1])
7. Allogeneic stem cell transplant within 60 days prior to start of study drug (C1D1)
8. Active graft-versus-host disease
9. Post-transplant lymphoproliferative disorders
10. Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other central nervous system (CNS) autoimmune disease
11. Seropositive for human immunodeficiency virus (HIV-1 and/or HIV-2 antibodies positive), serologic evidence of chronic hepatitis B virus (HBV) infection and unable or unwilling to receive standard prophylactic antiviral therapy or with detectable HBV viral load, or hepatitis C virus (HCV antibody positive or quantitative HCV RNA results greater than the lower limits of detection of the assay)
12. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
13. Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease
14. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
15. Breastfeeding or pregnant
16. Significant medical comorbidities, including but not limited to uncontrolled hypertension (blood pressure ≥160/100 mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or

ventricular cardiac arrhythmia, poorly controlled diabetes, severe chronic pulmonary disease, or active infections (including but not limited to tuberculosis)

17. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor
18. Use of any other experimental medication within 14 days prior to start of study drug (C1D1)
19. Planned live vaccine administration after starting study drug (C1D1)
20. Failure to recover to Grade ≤1 (Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]) from acute non-hematologic toxicity (except Grade ≤2 neuropathy or alopecia) due to previous therapy prior to screening
21. Congenital long QT syndrome or a corrected QTcF interval of >480 ms at screening (unless secondary to pacemaker or bundle branch block)
22. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk

Procedures

Lonca was administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle at a dose of 150 μg/kg every 3 weeks (Q3W) for 2 cycles, then at 75 μg/kg Q3W for the subsequent cycles, for up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria, patients still benefiting at 1 year could continue treatment.

Responses were assessed on PET-CT scans by the investigator as well as by the independent review committee (IRC) based on the 2014 Lugano classification criteria.[1] Adverse events (AEs) were assessed and graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. All AEs, including serious AEs (SAEs), were reported from the time of informed consent until 15 weeks after the last dose of the study drug or the start of subsequent new anti-cancer therapy.

Oral dexamethasone premedication as prophylaxis for infusion-related reactions was required unless contraindicated. In addition, spironolactone at standard doses was administered for patients with weight gain greater than 1 kg from day 1 of cycle one (C1D1) with new or worsening edema, and/ or new or worsening pleural effusion. Dose delay (≤5 weeks) and dose reduction (≤2 times) of loncastuximab tesirine were permitted to manage toxicity.

Imaging with positron-emission tomography (PET)–computed tomography (CT) and or CT was performed at screening; 6 weeks (prior to cycle 3) and 12 weeks (prior to cycle 5) after C1D1, then every 9 weeks until the end of treatment (EOT). During the follow-up period after EOT, for patients who discontinued the study drug for reasons other than disease progression or initiation of other anti-cancer therapy except SCT, imaging was performed approximately every 12 weeks for 1 year, then every 6 months until disease progression or up to 3 years from EOT.

Intensive pharmacokinetic (PK) samples after the first 2 dose administrations were collected in 12 patients and sparse PK samples were collected for all patients. The concentration of loncastuximab tesirine (total antibody) in serum, PBD conjugated antibody, and unconjugated warhead SG3199 were assessed using validated methodology as used in LOTIS-2 study[2]. Anti- loncastuximab tesirine anti-drug antibody (ADA) titers were analyzed by validated bridging ECLIA assay.[2]

Definition of efficacy endpoints

1. Overall response rate (ORR) was defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR).
2. Duration of response (DOR) was defined as the time from first documented tumor response to disease progression or death.
3. Complete response rate (CRR) was defined as the percentage of treated patients with a BOR of CR
4. Time to response (TTR) was defined as the time from the first dose to the first documented response among patients who achieve either CR or PR as BOR.
5. Relapse-free survival (RFS) was defined as the time from the first documented CR to disease progression or death.
6. Overall survival (OS) was defined as the time between the start of treatment and death from any cause.

Statistical analysis

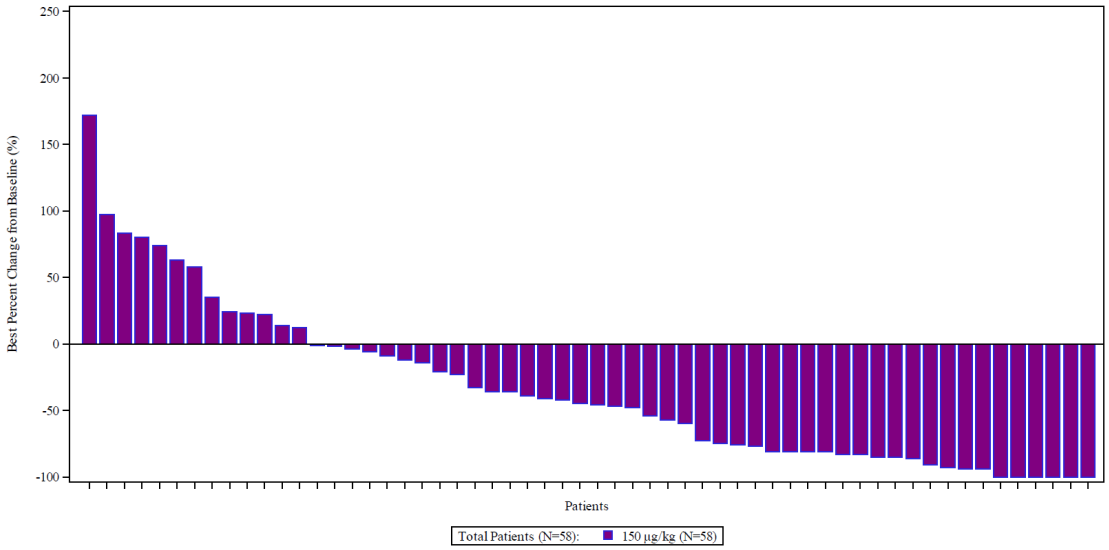
Response rates were reported as the percentage with associated 95% Clopper–Pearson (ie, exact binomial) CIs. Time-to-event endpoints, including DOR, RFS, PFS, and OS, were presented as median survival time estimated using Kaplan–Meier methodology with 95% Greenwood's CIs. Prespecified subgroup analyses of the efficacy variables, ORR, DOR, CRR, RFS, PFS, were performed.

Anti-tumor activity and safety data were analyzed with the use of SAS software, version 9.4 (SAS Institute),

and PK data was analyzed with the use of NONMEM version 7.4.

Supplementary Figures

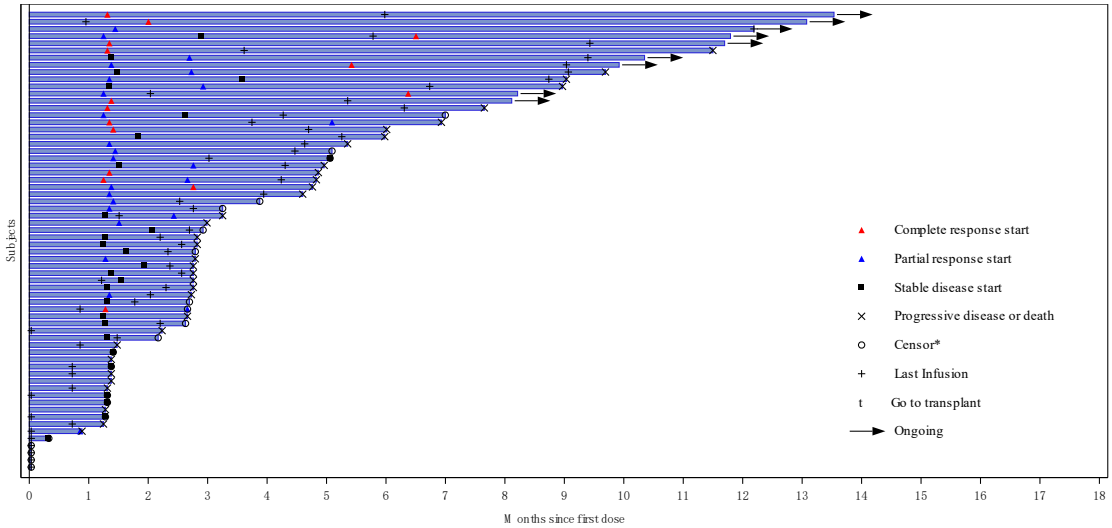
Supplementary Figure S1 Waterfall plot of best percent change from baseline in tumor size, as assessed by independent reviewer (All-Treated Population)



Bars represent individual patients. * Sum of the product of perpendicular diameters in multiple target lesions by independent reviewer is used.

The sum of the product of perpendicular diameters was NE for one patient and was missing for other 5 patients: three patients did not have target lesion; two patients did not have any post baseline assessment.

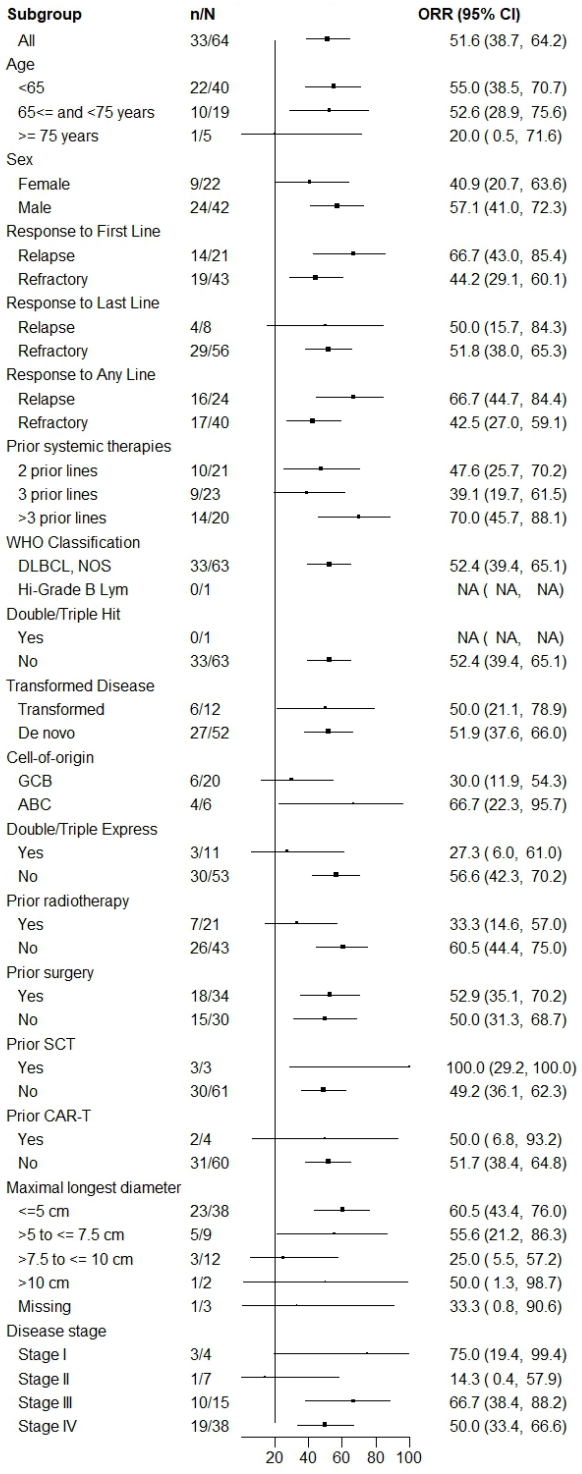
Supplementary Figure S2 Swimmer plot showing timing of response, as assessed by independent reviewer (All-Treated Population)



Each bar represents one patient in the study. Response is determined by independent reviewer

* Only for censored patients who discontinued trial due to reasons other than progression or who went onto a different anticancer treatment other than transplant.

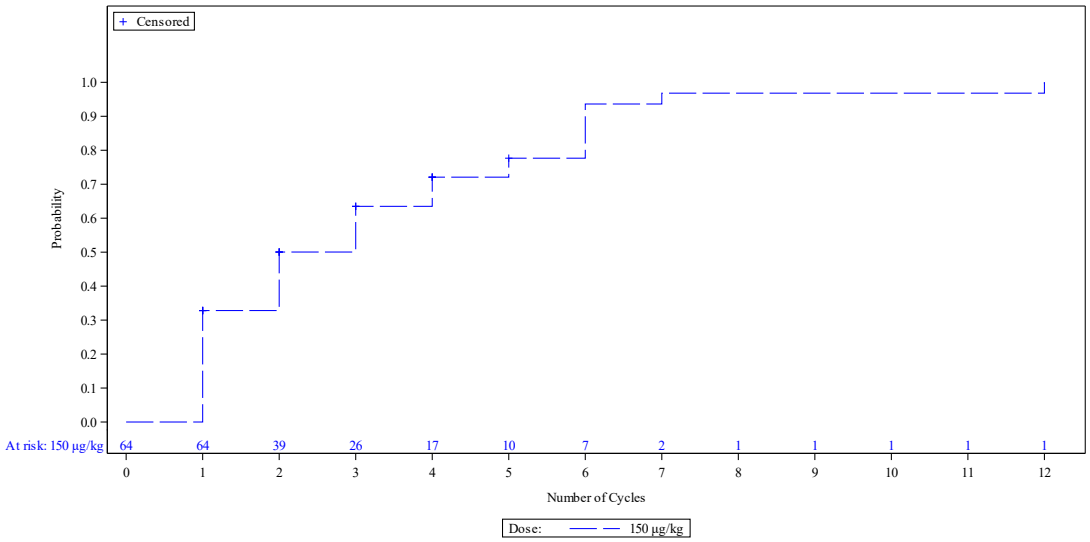
Supplementary Figure S3 Forest Plot of Overall Response Rate by Subgroup, as assessed by independent reviewer (All-Treated Population)



Note: Best overall response (BOR) by independent reviewer. ORR=Overall Response Rate. CI=Confidence Interval.

Note: Relapsed disease was 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 was defined as failure to achieve CR or PR or experienced PD within 6 months after achieving CR or PR, after adequate prior anti-DLBCL therapy.

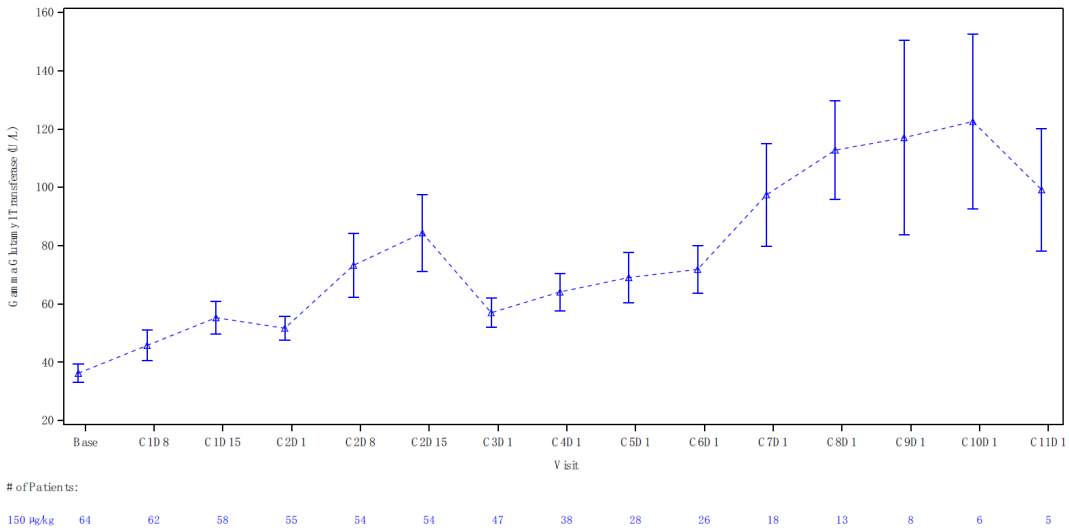
Supplementary Figure S4 Kaplan-Meier Plot of Time to First Adverse Event Leading to Dose Modification Analysis (All-Treated Population)



Dose modification includes drug discontinuation, dose delay, and dose reduction.

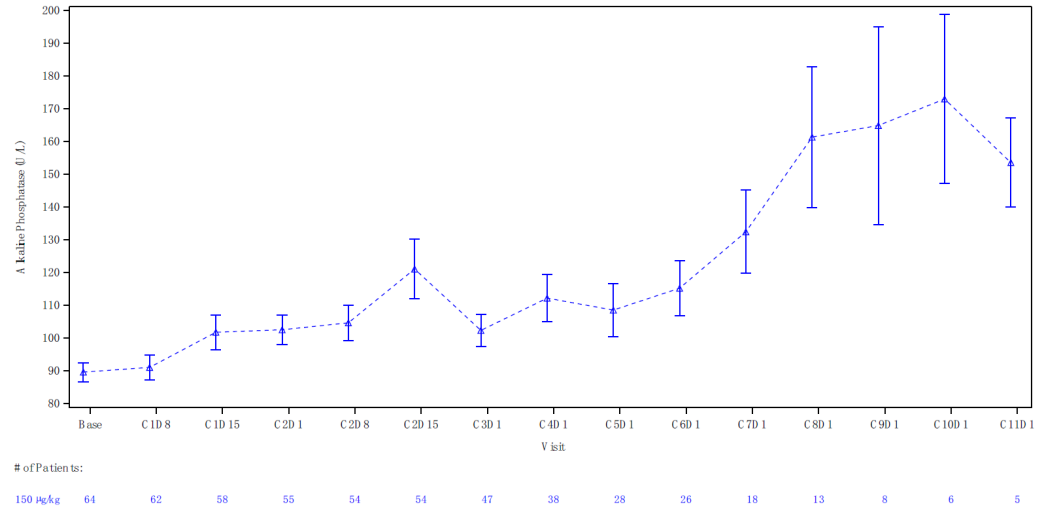
Supplementary Figure S5 Mean (±SE) levels of (A) gamma glutamyltransferase (U/L); (B) alkaline phosphatase (U/L); (C) neutrophils (x10^9/L); and (D) platelets (x10^9/L) levels by visit

(A)



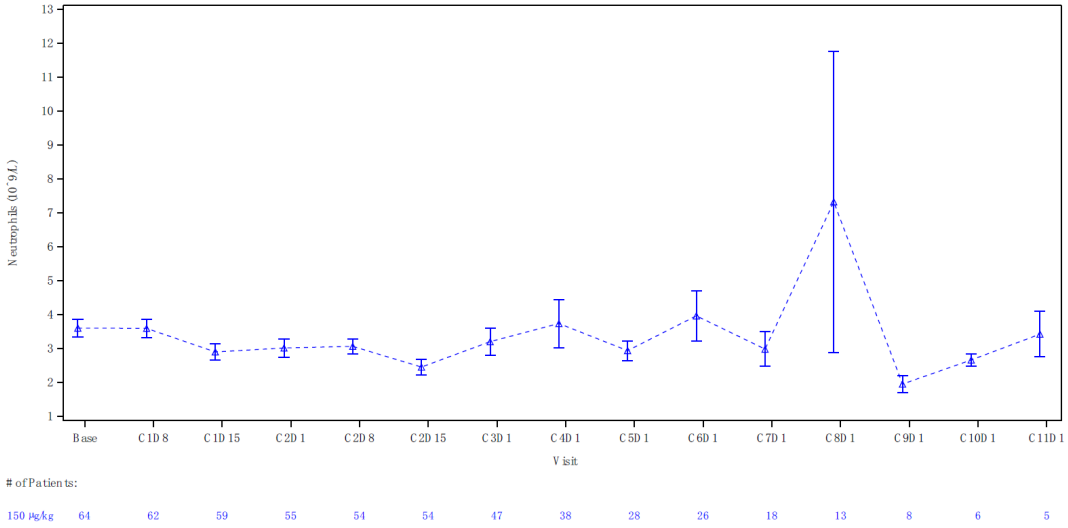
# of Patients:														
150 µg/kg	64	62	58	55	54	54	47	38	28	26	18	13	8	6	5

(B)

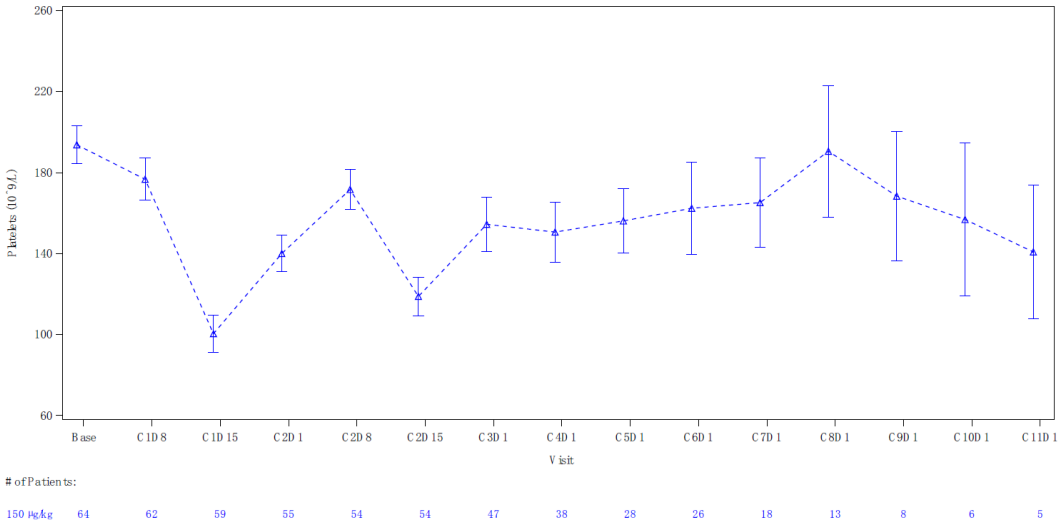


# of Patients:														
150 µg/kg	64	62	58	55	54	54	47	38	28	26	18	13	8	6	5

(C)



(D)

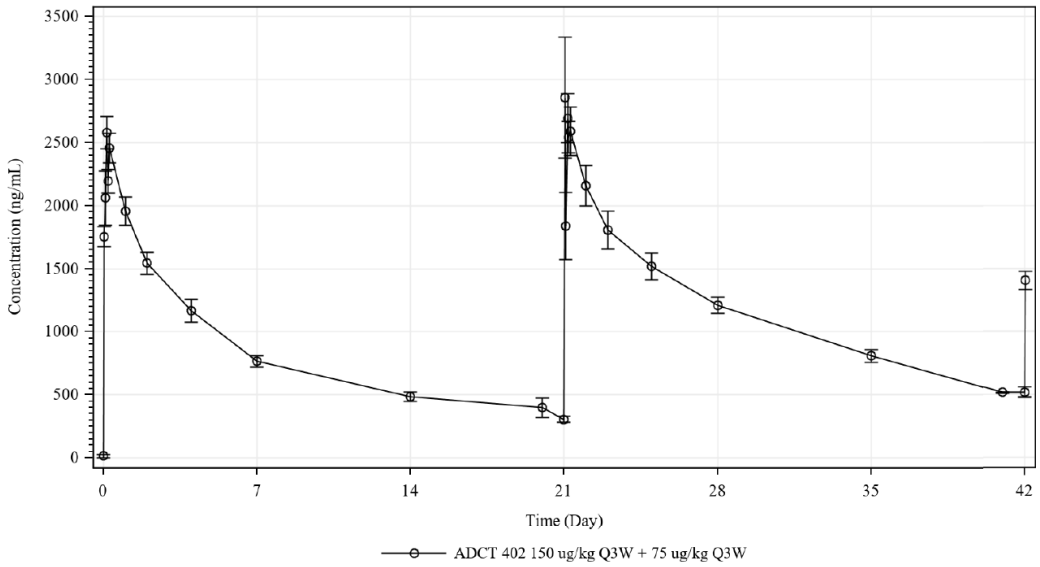


Baseline was defined as the last non-missing value before administration of loncastuximab tesirine.

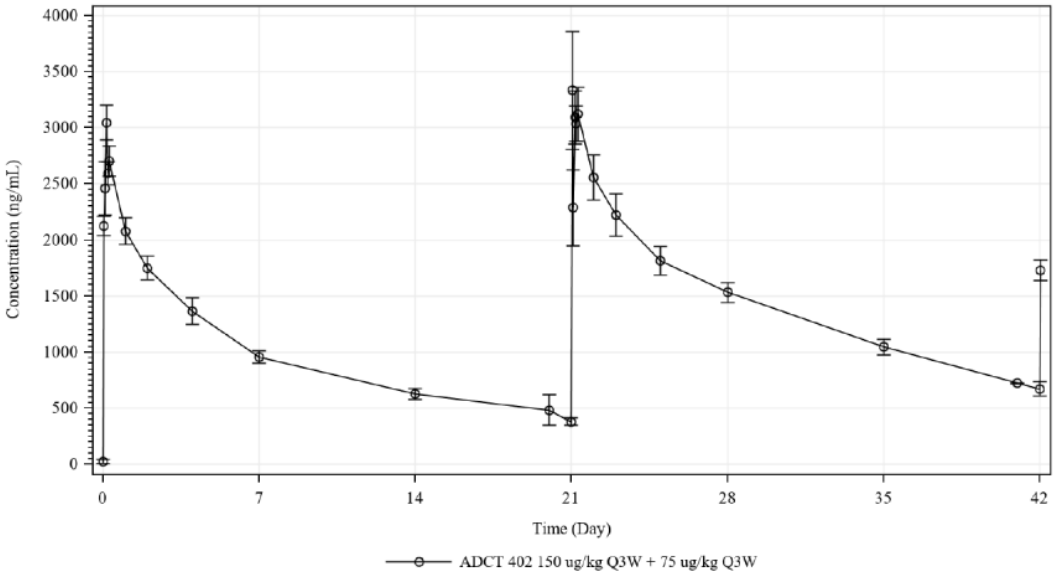
C, cycle; D, day; SE, standard error.

Supplementary Figure S6 Mean (±SE) concentration of PBD-conjugated antibody and total antibody in serum vs. time by for patients during cycles 1, 2 and 3

(A) Analyte=PBD-conjugated antibody



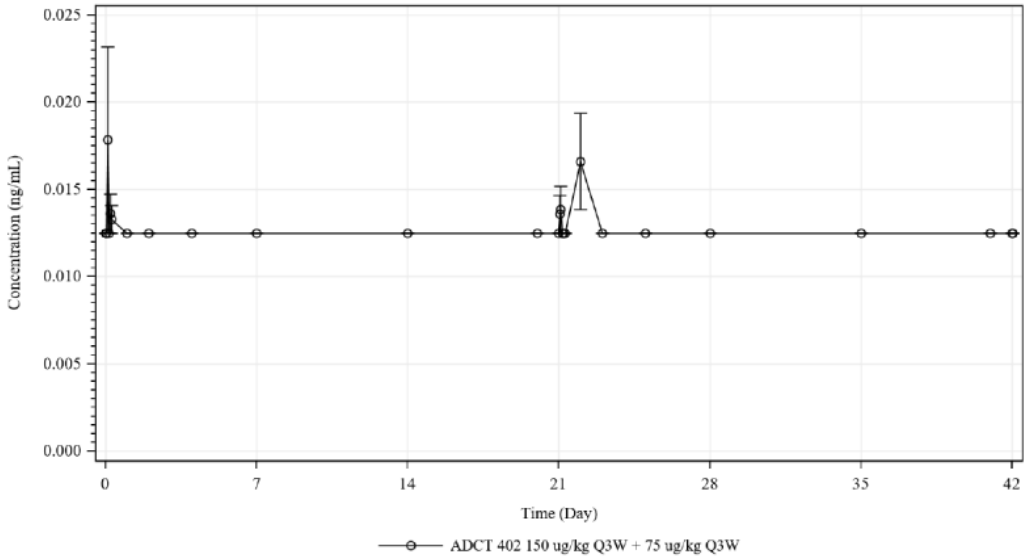
(B) Analyte=total antibody



SE=standard error; kg=kilogram; LOQ=limit of quantification; mL=milliliter; ng=nanogram; Q3W=every three weeks; ug=microgram

Concentrations below the lower limit of quantification are imputed as LLOQ/2

Supplementary Figure S7 Mean (±SE) concentration of SG3199 in serum vs. time by for patients during cycles 1, 2 and 3



SE=standard error; kg=kilogram; LOQ=limit of quantification; mL=milliliter; ng=nanogram; Q3W=every three weeks; ug=microgram

Concentrations below the lower limit of quantification are imputed as LLOQ/2

Supplementary Tables

Supplementary Table 1. Overall Response Rate by Investigator Assessment (All-Treated Population)

	All-Treated Population (N=64)
Best Overall Response	
Complete response	14 (21.9)
Partial response	24 (37.5)
Stable disease	11 (17.2)
Not evaluable	5 (7.8)
Progressive disease	10 (15.6)
ORR (CR + PR)	38 (59.4)
95% CI for ORR	(46.4 to 71.5)
95% CI for CR	(12.5 to 34.0)

Data are n (%). Response was assessed by investigator.

ORR=overall response rate, CR=complete response, PR=partial response, CI=confidence interval.

Supplementary Table 2. Overall Response Rate by Independent Reviewer (Per-Protocol Population)

	Per-Protocol Population (N=60)
Best Overall Response	
Complete response	15 (25.0)
Partial response	16 (26.7)
Stable disease	17 (28.3)
Not evaluable	5 (8.3)
Progressive disease	7 (11.7)
ORR (CR + PR)	31 (51.7)
95% CI for ORR	(38.4 to 64.8)

Data are n (%). Response was assessed by central independent review.

CI=confidence interval, CR=complete response, ORR=overall response rate, PR=partial response

Best overall response by independent reviewer. Not evaluable included patients without any scan to the independent reviewer (even clinical progressive disease) or patients whose scan was determined to be not evaluable by the independent reviewer.

Per-Protocol Population included all patients in the All-Treated Population who met the inclusion/exclusion criteria, did not take prohibited concomitant treatments, nor had other protocol deviations which had major impact on efficacy results.

Supplementary Table 3. Maintenance of Response by Independent Review (All-Treated Population)

	All-Treated Population (N=64)
Total number of responders	33
Patients maintaining response at 3 months	24 (72.7)
Patients maintaining response at 6 months	12 (36.4)
Patients maintaining response at 9 months	6 (18.2)
Patients maintaining response at 12 months	Not Reached

Data are n (%). Percentage is calculated using total number of responders as denominator, number of patients at risk at 3, 6, 9 and 12 months as numerator.

Supplementary Table 4. Overall Summary of Treatment-emergent Adverse Events (All-Treated Population)

	All-Treated Population (N=64)
Patients with any TEAE	64 (100)
Patients with any grade 3 or higher TEAE	61 (95.3)
Patients with any TEAE related to loncastuximab tesirine	63 (98.4)
Patients with any grade 3 or higher TEAE related to loncastuximab tesirine	58 (90.6)
Patients with any TEAE leading to loncastuximab tesirine dose delay	47 (73.4)
Patients with any TEAE leading to loncastuximab tesirine dose reduction	10 (15.6)
Patients with any TEAE leading to loncastuximab tesirine withdrawal	11 (17.2)
Patients with any serious TEAE	35 (54.7)
Patients with any serious TEAE related to loncastuximab tesirine	31 (48.4)
Patients with any TEAE with fatal outcome	4 (6.3)
Patients with any fatal TEAE related to loncastuximab tesirine	3 (4.7)
Patients with infusion related reaction	2 (3.1)

Data are n (%). TEAE=treatment-emergent adverse event.

“Related” was classified based on binary causality assessment by the investigator.

Supplementary Table 5. Treatment emergent Adverse Events by Preferred Term (All-Treated Population) in >=10% of patients

Preferred Term	All-Treated Population (N=64)
Patients with any TEAE	64 (100)
Gamma-glutamyltransferase increased	46 (71.9)
Anaemia	45 (70.3)
Platelet count decreased	42 (65.6)
Aspartate aminotransferase increased	41 (64.1)
White blood cell count decreased	41 (64.1)
Neutrophil count decreased	39 (60.9)
Alanine aminotransferase increased	33 (51.6)
Hypokalaemia	24 (37.5)
Blood alkaline phosphatase increased	21 (32.8)
Lymphocyte count decreased	19 (29.7)
Hypoalbuminaemia	18 (28.1)
Hyperuricaemia	17 (26.6)
Neutropenia	16 (25.0)
Blood bilirubin increased	15 (23.4)
Hyperglycaemia	15 (23.4)
Oedema peripheral	15 (23.4)
Blood lactate dehydrogenase increased	13 (20.3)
Leukopenia	13 (20.3)
Pleural effusion	13 (20.3)
Pneumonia	13 (20.3)
Rash	13 (20.3)
Total bile acids increased	12 (18.8)
Upper respiratory tract infection	11 (17.2)
Sinus tachycardia	10 (15.6)
Thrombocytopenia	10 (15.6)
Blood creatinine increased	9 (14.1)
Face oedema	9 (14.1)
Hyperlipidaemia	9 (14.1)
Hyponatraemia	9 (14.1)
Alpha hydroxybutyrate dehydrogenase increased	8 (12.5)
Constipation	8 (12.5)
Hypocalcaemia	8 (12.5)
Malaise	8 (12.5)
Abdominal pain	7 (10.9)
Decreased appetite	7 (10.9)
Nausea	7 (10.9)

Preferred Term	All-Treated Population (N=64)
Pruritus	7 (10.9)
Pyrexia	7 (10.9)

Data are n (%). TEAE=treatment-emergent adverse event.

Supplementary Table 6. Overall Summary of Treatment-emergent Adverse Events by age Group

Treatment-emergent adverse event	< 65 years (N=40)	≥ 65 - < 75 years(N=19)	≥ 75 years (N=5)	Total (N=64)
Patients with any TEAE	40 (100)	19 (100)	5 (100)	64 (100)
Patients with any grade 3 or higher TEAE	39 (97.5)	19 (100)	3 (60.0)	61 (95.3)
Patients with any TEAE related to loncastuximab tesirine	39 (97.5)	19 (100)	5 (100)	63 (98.4)
Patients with any TEAE leading to loncastuximab tesirine dose delay or reduction	31 (77.5)	15 (78.9)	3 (60.0)	49 (76.6)
Patients with any TEAE leading to loncastuximab tesirine withdrawal	6 (15.0)	5 (26.3)	0	11 (17.2)
Patients with any serious TEAE	20 (50.0)	12 (63.2)	3 (60.0)	35 (54.7)
Patients with any TEAE with fatal outcome	3 (7.5)	1 (5.3)	0	4 (6.3)
Patients with infusion related reaction	2 (5.0)	0	0	2 (3.1)

Data are n (%). TEAE=treatment-emergent adverse event.

Supplementary Table 7. Treatment-emergent- Adverse Events Leading to Loncastuximab Tesirine Dose Delay for ≥5% of Patients (All-Treated Population)

Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grade
Gamma-glutamyltransferase increased	0	15 (23.4)	6 (9.4)	0	0	21 (32.8)
Platelet count decreased	0	1 (1.6)	5 (7.8)	6 (9.4)	0	12 (18.8)
Neutrophil count decreased	0	1 (1.6)	7 (10.9)	3 (4.7)	0	11 (17.2)
Neutropenia	0	1 (1.6)	4 (6.3)	4 (6.3)	0	9 (14.1)
Anaemia	0	0	7 (10.9)	0	0	7 (10.9)
Leukopenia	0	1 (1.6)	4 (6.3)	2 (3.1)	0	7 (10.9)
White blood cell count decreased	0	1 (1.6)	5 (7.8)	1 (1.6)	0	7 (10.9)
Pneumonia	0	0	6 (9.4)	0	0	6 (9.4)
Hypokalaemia	0	0	4 (6.3)	1 (1.6)	0	5 (7.8)
Thrombocytopenia	0	1 (1.6)	2 (3.1)	1 (1.6)	0	4 (6.3)

Data are n (%).

Supplementary Table 8. Summary of pharmacokinetic parameters during cycles 1, and 2 for patients treated with loncastuximab tesirine 150 µg/kg Q3Wx 2

Cycle 1

Analyte	Cohort (µg/kg)	C_{max} (ng/mL)	AUC_{last} (day*ng/mL)	AUC_{inf} (day*ng/mL)	T_{half} (day)	CL (L/day)	V_{ss} (L)
Conjugated Antibody	150	2268 (27.2) [64]	15916 (82.9) [63]	16788 (42.0) [25]	8.25 (37.4) [25]	0.464 (46.6) [25]	3.83 (59.7) [25]
Total Antibody	150	2702 (25.5) [64]	18326 (116) [63]	22050 (43.7) [22]	7.72 (42.9) [22]	0.412 (47.1) [22]	3.61 (53.6) [22]
SG3199	150	0.0550 (78.9) [3]	0.00200 (74.8) [3]	-	-	-	-

Cycle 2

Analyte	Cohort (µg/kg)	C_{max} (ng/mL)	AUC_{last} (day*ng/mL)	AUC_{tau} (day*ng/mL)	T_{half} (day)	CL_{ss} (L/day)	V_{ss} （L）	AI
Conjugated Antibody	150	2746 (57.3) [55]	24268 (49.2) [55]	23780 (42.8) [51]	13.0 (35.5) [48]	0.321 (31.9) [51]	5.46 (33.8) [48]	1.51 (17.3) [48]
Total Antibody	150	3262 (56.2) [55]	29283 (52.1) [55]	29479 (43.9) [49]	12.6 (33.1) [43]	0.303 (32.3) [49]	5.05 (37.0) [43]	1.49 (16.0) [43]
SG3199	150	0.0460 (39.0) [3]	0.00600 (293) [3]	-	-	-	-	-

AI=accumulation index; AUC_{inf}=area under the concentration-time curve from time zero to infinity; AUC_{last}=area under the concentration-time curve from time zero to last quantifiable concentration; AUC_{tau}=area under the concentration-time curve from zero to end of dosing interval tau; CL=apparent systemic clearance; C_{max}=maximum concentration; L=liter; mL=milliliter; ng=nanogram; T_{half}=apparent terminal half-life; V_{ss}=apparent volume of distribution at steady-state.

EOI denotes end of infusion; Data were presented in Geometric Mean (CV% GeoMean)[n]; - = Not Calculated; Reliable parameters are based on Rsquare_adj>=0.85 and AUC_%Extrap<=20.

Reference

1. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.

2. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790-800.