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PI3Kδ inhibitor linperlisib combined with gemcitabine and oxaliplatin for relapsed or refractory diffuse large B-cell lymphoma: a multicenter, single-arm phase Ib/II trial

Peng Sun[1], Hong Cen[2], Haiyan Yang[3], Rui Huang[4], Zhen Cai[5], Xuekui Gu[6], Hanying Bao[7], Zusheng Xu[7], Zuhong Xu[7] and Zhi-Ming Li[1*]

Abstract

Background This investigation assessed the therapeutic potential of combining linperlisib, a targeted inhibitor of phosphatidylinositol 3-kinase delta (PI3Kδ), with gemcitabine and oxaliplatin (GEMOX) for patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

Methods This was a multicenter, phase Ib/II clinical study conducted across six sites in China, enrolling 39 individuals with histologically confirmed R/R DLBCL. The treatment protocol included oral linperlisib alongside GEMOX administered intravenously every three weeks for up to six cycles. The primary efficacy endpoint was the objective response rate (ORR).

Results The ORR observed in the full study population was 53.8% (95% confidence interval [CI]: 37.2–69.9). The median duration of response was 5.7 months (95% CI: 4.3–9.1), and the median progression-free survival was 5.4 months (95% CI: 1.8–6.7). The 1-year OS rate was 65.5% (95% CI: 48.1–78.3). Frequently observed adverse events included decreases in neutrophil counts (74.4%), white blood cell counts (64.1%) and platelet counts (64.1%).

Conclusions This study highlights the potential of linperlisib plus GEMOX as a treatment for R/R DLBCL, demonstrating a tolerable safety profile and encouraging efficacy results.

Trial registration NCT04500561.

Keywords Linperlisib, Gemcitabine, Oxaliplatin, PI3Kδ-selective inhibitor, Diffuse large B-cell lymphoma

*Correspondence:
Zhi-Ming Li
lizhm@sysucc.org.cn
[1]Department of Medical Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Yuexiu District, Guangzhou, China
[2]Department of Lymphohematology and Pediatric Oncology, Guangxi Medical University Affiliated Tumor Hospital, Nanning, China
[3]Department of Lymphoma, Zhejiang Cancer Hospital, Hangzhou, China
[4]Department of Hematology, Zhujiang Hospital of Southern Medical University, Guangzhou, China
[5]Bone Marrow Transplantation Center of Hematology Department, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China
[6]Department of Hematology, The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, Guangzhou, China
[7]Clinical Development Department, Shanghai Yingli Pharmaceutical Co., Ltd, Shanghai, China

Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most prevalent subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 30–40% of newly diagnosed NHL cases [1, 2]. The standard first-line therapy for DLBCL involves immunochemotherapy, typically the R-CHOP regimen [3]. For patients who fail to achieve remission or experience relapse following initial treatment, high-dose chemotherapy combined autologous stem cell transplantation (ASCT) is often pursued as a salvage strategy [4, 5]. However, the outcomes associated with such interventions remain suboptimal in refractory DLBCL, with real-world data indicating objective response rates (ORR) below 30% and 2-year overall survival (OS) rates nearing 20% [6–8]. In contrast, the CORAL study demonstrated a 3-year OS rate of 53% overall, although patients with early relapse (≤ 12 months) had a markedly poorer survival outcome [5]. The REAL-TREND study revealed that approximately 20% of patients develop refractory disease within five years of diagnosis [8]. Among this group, the reported ORR and complete remission rates were 30% and 9%, respectively, with a median OS of only 5.9 months [9]. These findings underscore the critical need for novel, effective therapies to address the significant unmet clinical needs of patients with refractory DLBCL, particularly in China, where prognoses are often worse. Furthermore, there is a pressing demand for innovative therapeutic approaches that can be integrated with existing regimens.

Linperlisib is a newly developed, orally bioavailable inhibitor selectively targeting PI3Kδ, which plays a critical role in tumor cell growth. Preclinical studies have shown its efficacy in suppressing the proliferation of PI3Kδ-positive tumor cells. Moreover, T-cell detection indicates that linperlisib not only directly inhibits tumor growth through the PI3K pathway but also involves the T-cell immune microenvironment (unpublished data). In a subcutaneous xenograft mouse tumor model of SU-DHL-6 human lymphatic cancer cells, linperlisib exhibited an inhibitory effect on the growth of subcutaneous xenograft tumors [10]. A previous phase I study evaluated linperlisib to assess its tolerability, pharmacokinetics, and preliminary efficacy in patients with R/R B-cell hematological malignancies. In this trial, linperlisib demonstrated an ORR of 64%. Based on these findings, the recommended phase II dosage of linperlisib was established at 80 mg/day, supporting its potential use in patients with R/R DLBCL [11]. Compared to duvelisib, linperlisib was associated with notably lower rates of toxicities. Specifically, grade 3 or higher diarrhea occurred in 1% of patients receiving linperlisib, compared to 15% with duvelisib [12–14]. Similarly, elevated aspartate transaminase (AST) and alanine aminotransferase (ALT) levels of grade 3 or higher were reported in 1% of patients treated with linperlisib, compared to 3% and 3–5%, respectively, for duvelisib [12–14]. In November 2022, linperlisib was approved in China as a PI3K inhibitor for the treatment of R/R follicular lymphoma. However, the efficacy of linperlisib monotherapy in R/R DLBCL patients was insufficient. Therefore, this phase Ib/II study combining linperlisib with gemcitabine and oxaliplatin (GEMOX) is being conducted to further explore its potential in treating patients with R/R DLBCL.

Methods

Study design and patients

This multicenter phase Ib/II trial enrolled patients with histologically verified R/R DLBCL from six clinical sites in China. The trial adhered to ethical guidelines, receiving approval from independent ethics committees at each participating site, and all participants provided written informed consent. The trial is registered on ClinicalTrials.gov under identifier NCT04500561.

Participants were required to be aged 18 to 75 years, have undergone at least one prior treatment involving a CD20 monoclonal antibody, demonstrate an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and present with at least one measurable lesion according to the 2007 International Working Group (IWG) criteria. Adequate organ function was also necessary for eligibility. Exclusion criteria included previous exposure to PI3K-targeting therapies, prolonged corticosteroid use (≥ 20 mg/day prednisone equivalent for over 14 days within four weeks prior), central nervous system involvement, or ASCT within 90 days prior to enrollment. Primary refractory disease was defined as the failure to achieve remission after treatment with a rituximab-containing regimen or as disease progression within six months of completing the initial therapy.

Procedure

The treatment regimen began with oral linperlisib at a dose of 80 mg per day combined with intravenous GEMOX, which included gemcitabine (1000 mg/m² D1) and oxaliplatin (100 mg/m² on D2), administered every three weeks to the initial six patients. Dose adjustments were planned based on toxicity outcomes: if fewer than two patients experienced grade ≥ 4 hematological toxicity or grade ≥ 3 non-hematological toxicity related to linperlisib, the 80 mg/day dose was maintained. However, if two or more patients exhibited such toxicities, the linperlisib dose was reduced to 60 mg/day for subsequent participants. GEMOX was administered for up to six cycles. Patients achieving remission continued linperlisib monotherapy until unacceptable toxicity, consent withdrawal, disease progression, death, or another investigator-determined reason for discontinuation. Oral trimethoprim-sulfamethoxazole (500 mg/tablet, 2 tablets per dose,

administered either once daily or three times per week) was used as prophylaxis to prevent Pneumocystis jirovecii pneumonia.

Tumor response was assessed every two cycles using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) following the IWG 2007 criteria. Adverse events (AEs) were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Endpoints

The primary objective of this study was to assess the ORR, defined as the percentage of patients achieving complete response (CR) or partial response (PR). Secondary outcomes encompassed time to response (TTR), and duration of response (DOR). TTR and DOR were measured as the intervals from treatment initiation to first documented CR or PR, and from first response to disease progression or death, respectively. Additional endpoints included progression-free survival (PFS) and OS, assessing the time from treatment initiation to disease progression or death and to death from any cause, respectively.

Statistical analysis

The sample size was calculated based on an anticipated improvement in the ORR, projected to increase from 26% [7] to 46%. With a two-sided significance level (α) of 0.05, it was estimated that a minimum of 35 participants would provide 80% power to detect this difference. To account for a potential dropout rate of 10%, the target enrollment was set at 39 patients. Statistical analyses were performed using SAS version 9.4 software. ORR was summarized using numbers and percentages, with 95% confidence intervals (CIs) calculated via the Clopper-Pearson method. Kaplan-Meier estimates were applied for analyzing time-to-event outcomes, enabling the computation of median durations and corresponding 95% CIs.

Results

Baseline characteristics of patients

Patient enrollment for this study occurred between September 2020 and June 2021, resulting in 39 participants who began the study treatment. By the data cutoff date of February 9, 2023, three participants were still undergoing treatment (Fig. 1). The median age of the cohort was 58 years, ranging from 27 to 72 years, and 25 patients (64.1%) were male. Based on Ham's classification, nine

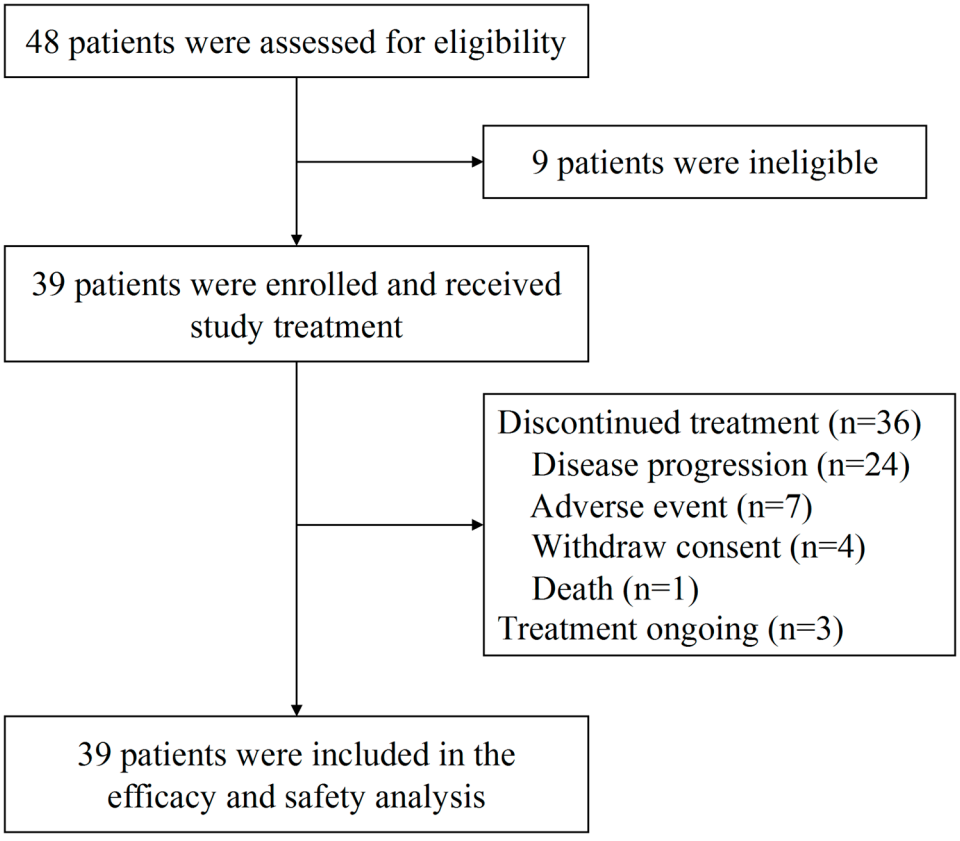

Fig. 1 Patient flowchart

Table 1 Baseline characteristics of patients

Variables	All (*n* = 39)
Age, years, median (range)	58 (27–72)
< 65, n (%)	28 (71.8)
≥ 65, n (%)	11 (28.2)
Male sex, n (%)	25 (64.1)
Disease stage, n (%)	
II	4 (10.3)
III	4 (10.3)
IV	22 (56.4)
Missing	9 (23.1)
ECOG PS score, n (%)	
0	3 (7.7)
1	36 (92.3)
Cell of origin, n (%)	
GCB	9 (23.1)
Non-GCB	25 (64.1)
Unclassified	5 (12.8)
Double-expressor, n (%)	30 (77.0)
Prior treatment lines, median (range)	2 (1–7)
< 3, n (%)	20 (51.3)
≥ 3, n (%)	19 (48.7)
Prior autologous stem cell transplantation, n (%)	1 (2.6)
Prior CAR-T therapy	4 (10.3)
Median time from initial diagnosis, months (range)	12.6 (5.0-125.5)
Refractory to most recent treatment, n (%)	37 (94.9)

ECOG PS, Eastern Cooperative Oncology Group performance status; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell like; non-GCB, non-germinal center B-cell like

Table 2 Tumor response

Outcomes	All (*n* = 39)
Best overall response, n (%)	
Complete response	6 (15.4)
Partial response	15 (38.5)
Stable disease	4 (10.3)
Progressive disease	10 (25.6)
Not evaluable	4 (10.3)
Objective response, n (%)	21 (53.8)
95% CI	37.2, 69.9
Time to response, months, median (range)	1.3 (1.2, 4.0)

CI, confidence interval

patients (23.1%) were categorized as having germinal center B-cell (GCB) DLBCL, while 25 (64.1%) had non-GCB DLBCL. A substantial proportion (76.9%) of the patients presented with primary refractory disease. The participants had undergone a median of two previous lines of therapy (range: 1–7), with one individual receiving prior ASCT and four undergoing anti-CD19 CAR-T therapy. The majority (94.9%) were refractory to their most recent line of treatment (Table 1).

Efficacy

The ORR in this study was 53.8% (95% CI: 37.2–69.9), with six patients (15.4%) achieving a CR and 15 patients (38.5%) demonstrating a PR (Table 2; Fig. 2). The median TTR was 1.3 months, with a range of 1.2 to 4.0 months. At the data cutoff, the median follow-up duration was 24.1 months (range: 1.4–33.3 months). The median DOR was 5.7 months (95% CI: 4.3–9.1), and the median PFS was 5.4 months (95% CI: 1.8–6.7). The the 1-year OS rate estimated at 65.5% (95% CI: 48.1–78.3) (Fig. 3). For patients with primary refractory DLBCL, the ORR was 43.3% (13/30; 95% CI: 23.3–65.5), with two patients (6.7%) achieving CR. In this subgroup, the median DOR was 5.4 months (95% CI: 1.4–7.6), and the median OS was 17.2 months (95% CI: 6.7-not estimated [NE]). In our study, nine patients (23.1%) had germinal center B-cell-like (GCB) DLBCL, and 25 patients (64.1%) had non-GCB DLBCL, while five patients (12.8%) were unclassified. The ORR was 66.7% (6 out of 9) for patients with GCB DLBCL and 40% (10 out of 25) for patients with non-GCB DLBCL.

Safety

Treatment-related adverse events (TRAEs) were experienced by all participants, with 30 patients (76.9%) experiencing TRAEs of grade 3 or higher severity. The most frequently noted TRAEs included decreases in neutrophil counts (74.4%), white blood cell counts (64.1%), platelet counts (64.1%), and elevations in AST levels (61.5%). Among the grade 3 or higher TRAEs, the most prevalent were reduced neutrophil counts (46.2%), platelet counts (41.0%), and white blood cell counts (28.2%). AEs that required dose reductions occurred in three patients (7.7%), while seven patients (17.9%) discontinued treatment due to AEs. Importantly, no deaths attributable to TRAEs were observed (Table 3).

The incidence of diarrhea/colitis related to linperlisib was 43.6% (17/39) for any grade, resulting in 5.1% (2/39) of patients discontinuing treatment; no grade 3 or higher cases were reported. The median occurrence time of diarrhea/colitis was 4 weeks (range: 0.1–48.0 weeks). Linperlisib-related pneumonia of any grade occurred in 17.9% of patients (7/39), with 12.8% (5/39) experiencing grade 3 or higher. This led to the discontinuation of linperlisib in 10.3% (4/39) of patients. The median occurrence time of pneumonia was 27 weeks (range: 4.7–42.4 weeks). All pneumonia cases were resolved.

Among the 24 participants with elevated AST levels, 23 cases were classified as grade 1 and 1 as grade 2, while among the 20 participants with elevated ALT levels, 18 cases were grade 1 and 2 were grade 2. Hepatoprotective treatments, including polyene phosphatidylcholine, bicyclol, and ursodeoxycholic acid, were administered with regular liver function monitoring. One participant

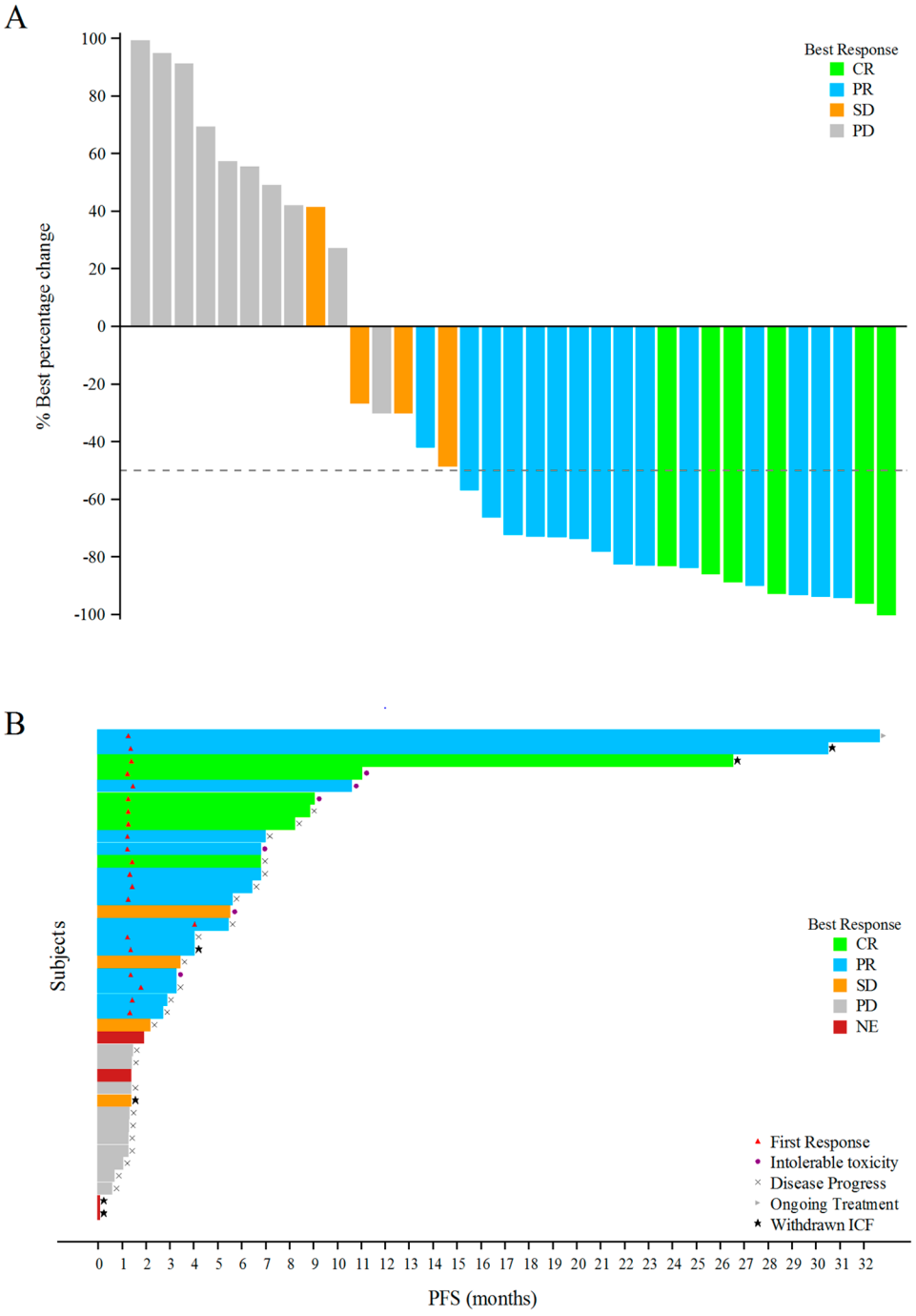

Fig. 2 Antitumor activity. (**A**) The best percentage changes from baseline in target lesions of evaluable patients ($n=35$); (**B**) Treatment exposure and response duration of evaluable patients ($n=35$). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not estimated; ICF, informed consent form; PFS, progression-free survival

discontinued treatment due to elevated ALT levels, and another due to elevated AST levels. For the remaining participants, linperlisib was continued, and spontaneous resolution of ALT and AST elevations occurred with a median recovery time of 21 days and 20.5 days, respectively.

Discussion

The results of our study indicated that the linperlisib-GEMOX combination led to an ORR of 53.8% in patients with heavily pretreated DLBCL. The overall safety profile was deemed manageable, with particular attention to the occurrence of diarrhea and pneumonia, both of which were effectively managed. These findings highlight the

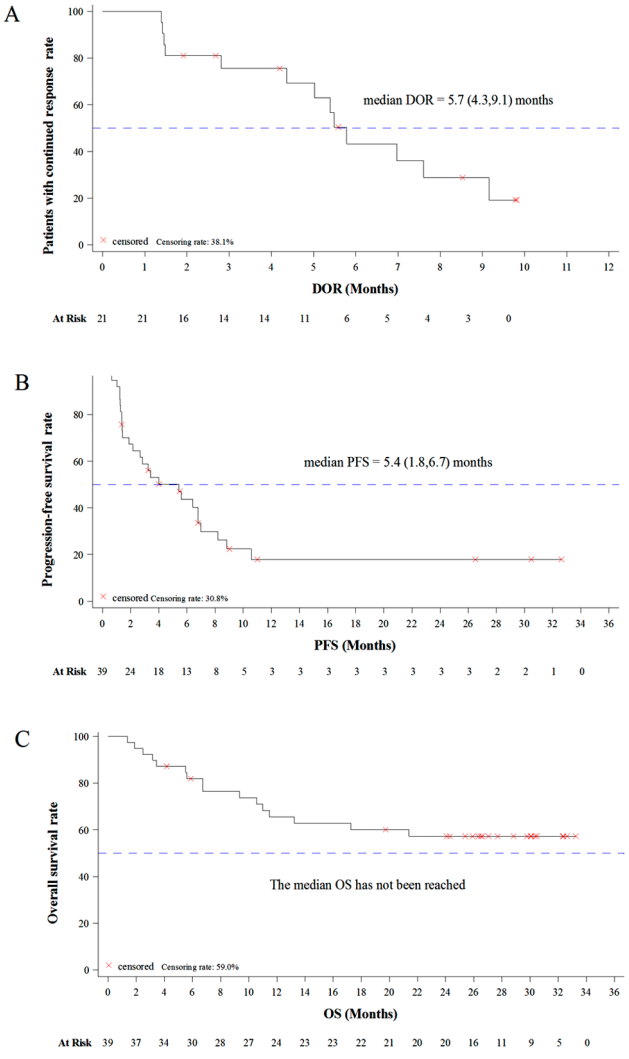

Fig. 3 Kaplan-Meier curve of (**A**) duration of response (DOR), (**B**) progression-free survival (PFS) and (**C**) overall survival (OS)

potential of this combination therapy as a promising new treatment strategy for R/R DLBCL.

PI3K is integral to the regulation of B-cell proliferation and survival. The PI3Kδ isoform, in particular, serves as a pivotal node in the signaling pathways governing B-cell growth and maintenance. Its dysregulated activation is a critical factor in the malignant transformation of B cells [15, 16]. Additionally, the interlinkage between B-cell receptor signaling and PI3Kδ-mediated pathways, as well as other survival networks such as the JAK-STAT pathway, underscores the potential for combined therapeutic effects in B-cell malignancies [17, 18]. Wright et al. [19] proposed the seven subtypes of DLBCL, among which multiple genetic subtypes, including MCD, BN2, ST2, and EZB, exhibit activation of the PI3K signaling pathway. This suggests that these subtypes may benefit from PI3K-targeted therapies.

Table 3 Treatment-related adverse event (TRAE) occurring in at least 10% of patients

Events, *n* (%)	Any grade	Grade 3 or higher
At least one TRAE	39 (100.0)	30 (76.9)
Neutrophil count decreased	29 (74.4)	18 (46.2)
White blood cell decreased	25 (64.1)	11 (28.2)
Platelet count decreased	25 (64.1)	16 (41.0)
Aspartate aminotransferase increased	24 (61.5)	0
Anemia	22 (56.4)	0
Alanine aminotransferase increased	20 (51.3)	0
Diarrhea	17 (43.6)	0
Anorexia	13 (33.3)	0
Nausea	12 (30.8)	0
Vomiting	10 (25.6)	0
Serum amylase increased	10 (25.6)	0
Lipase increased	8 (20.5)	0
Hypokalemia	7 (17.9)	0
Pneumonia	7 (17.9)	5 (12.8)
Abdominal pain	6 (15.4)	0
Abdominal distension	6 (15.4)	0
Hyperuricemia	5 (12.8)	0
Lymphocyte count decreased	4 (10.3)	4 (10.3)
Weight loss	4 (10.3)	0
Hypesthesia	4 (10.3)	0

Despite the potential of PI3K inhibitors, their use as monotherapy in treating DLBCL has shown limited success. For example, the PI3K inhibitor copanlisib resulted in an ORR of 25% in patients with R/R DLBCL, with five out of 40 patients achieving CR [20]. A phase II trial evaluating the efficacy of parsaclisib in DLBCL also reported a modest ORR of 25.5%, leading to early termination due to the lack of sufficient efficacy in interim analyses [21]. In a phase Ib trial of linperlisib, including 24 DLBCL patients, the ORR was 29.2% [22]. In light of these findings, we conducted a phase Ib/II clinical trial to assess the combination of linperlisib and GEMOX in patients with R/R DLBCL. The results demonstrated an ORR of 53.8% in this cohort, with a median PFS of 5.4 months. By the data cutoff date, three patients were still undergoing treatment. This trial included a significant proportion of heavily pretreated patients, many of whom had primary refractory disease, a group typically associated with poor prognosis. In the SCHOLAR-1 study, primary refractory patients had a median OS of only 6.1 months [7]. In contrast, in our study, the ORR for primary refractory DLBCL patients was 43.3%, with a median DOR of 5.4 months, and a median OS of 17.2 months. Notably, the combination of linperlisib and GEMOX improved outcomes in R/R DLBCL without a substantial increase in treatment-related toxicities. These results suggest that linperlisib combined with chemotherapy may provide meaningful therapeutic benefits for patients with R/R DLBCL, warranting further exploration.

Several studies have evaluated the efficacy of GEMOX-based regimens in patients with R/R DLBCL. A phase II trial investigated GEMOX combined with rituximab (GEMOX-R) in 49 patients and reported an ORR of 61%, with a CR rate of 44%, a median PFS of 5 months, and a median OS of 11 months [23]. In another study involving 32 patients treated with GEMOX-R, the ORR was 43%, with a CR rate of 34%, a 1-year PFS rate of 29%, and a 1-year OS rate of 41%, with a median OS of 9.1 months [24]. These data suggest that while GEMOX-R shows efficacy, outcomes remain suboptimal for patients with poor prognostic factors, particularly those who are primary refractory or non-candidates for ASCT. In comparison, the current study demonstrated an ORR of 53.8% and a median PFS of 5.4 months in heavily pretreated patients receiving linperlisib plus GEMOX, with a 1-year OS rate of 65.5%. Notably, this cohort included a significant proportion of patients with primary refractory disease, a population associated with worse outcomes. These findings indicate that the addition of the PI3Kδ inhibitor linperlisib to GEMOX may enhance treatment efficacy. However, a future clinical trial combining linperlisib with GEMOX-R could provide additional insights and potentially establish a more effective salvage regimen for R/R DLBCL.

The combination of linperlisib and GEMOX was found to be safe and well-tolerated in patients with R/R DLBCL. Compared to linperlisib monotherapy in a previous phase I study, there was no increase in the incidence of grade ≥ 3 neutropenia (46.2% vs. 44.0%) or pneumonia (12.8% vs. 16.0%). However, there was an increase in the incidence of thrombocytopenia (41.0% vs. 4.0%) and leukopenia (28.2% vs. 8.0%) [11]. The incidence of elevated ALT and AST levels related to linperlisib was observed in 51.3% and 61.5% of patients, respectively, in this study. However, grade ≥ 3 elevated ALT and AST levels were not reported in the 39 patients who received linperlisib. In comparison, 50.0% of patients (62/125) treated with idelalisib experienced elevated ALT/AST levels (grade ≥ 3 in 13%) [25]. The incidence of diarrhea/colitis was 43.6% (17/39) for any grade, with no grade ≥ 3 cases reported. The median occurrence time of diarrhea/colitis was 4 weeks, and it was mild and responded well to antidiarrheal agents. In a study involving 64 patients treated with copanlisib monotherapy, 16.4% of patients experienced diarrhea of any grade, with 1.5% reporting grade ≥ 3 diarrhea [26]. Similarly, among 146 patients with indolent non-Hodgkin lymphoma receiving idelalisib monotherapy at a dose of 150 mg, 47% had any grade of diarrhea, including terms such as colitis, enterocolitis, and gastrointestinal inflammation. Grade ≥ 3 diarrhea occurred in 14%, with 11% experiencing severe diarrhea. The median time to onset for diarrhea was 1.9 months [27]. In this study, linperlisib-related pneumonia of any grade was observed in 17.9% of patients (7/39), with 12.8% (5/39) experiencing grade ≥ 3 pneumonia. The median occurrence time of pneumonia was 27 weeks. Treatment with oxygen supplementation, anti-infective therapy, systemic corticosteroids, and drug withdrawal resulted in a favorable outcome. Grade ≥ 3 pneumonia was observed in 10.0% (45/465) of patients who received duvelisib and 13.3% (24/181) of patients who received copanlisib in the global study [27]. No interstitial lung disease was observed in our study. The incidence of grade ≥ 3 interstitial lung disease was 15.4% (2/13) in a study of 13 Chinese patients treated with copanlisib monotherapy [27]. Pneumonia was a concern with linperlisib, mainly related to its PI3Kδ target and chemotherapy. However, with cotrimoxazole prophylaxis and anti-infective therapy in this study, pneumonia improved or stabilized in most patients, and lung injury was generally reversible. The absence of grade 3 or higher events, such as AST/ALT elevations and colitis, in this study may be attributed to several factors. Structurally, linperlisib is designed to have increased selectivity for PI3Kδ while minimizing activity against PI3Kγ, potentially reducing off-target immune-related toxicities commonly associated with less selective PI3K inhibitors [12–14]. Additionally, linperlisib is primarily eliminated via renal excretion, with fecal excretion serving as a secondary pathway, which may further contribute to its favorable safety profile by reducing gastrointestinal and hepatic accumulation [11]. Population pharmacokinetic and exposure-response analyses of linperlisib have not demonstrated a significant correlation between systemic exposure and the incidence of grade 3 or higher diarrhea [11]. However, the relatively small sample size in this study may have limited the ability to detect rare, severe toxicities. Future studies with larger patient cohorts are essential to comprehensively evaluate the safety profile.

This study has several limitations that must be considered. First, the follow-up period was limited, and the median OS has not yet been reached, which restricts the ability to make definitive conclusions about the long-term effectiveness of the treatment Second, the single-arm design and relatively small sample size may impact the external validity of the findings. Third, tumor response was evaluated using contrast-enhanced CT or MRI based on the IWG 2007 criteria, without the incorporation of positron emission tomography-computed tomography (PET-CT) for metabolic assessment. This approach may have underestimated the ORR, as metabolic imaging provides additional sensitivity in detecting residual disease. The adoption of the Lugano 2014 criteria in future studies, which integrates metabolic evaluations, may yield more accurate response assessments.

Conclusion

In summary, linperlisib plus GEMOX was found to have an acceptable safety profile and showed promising efficacy in patients with R/R DLBCL in our study, most of whom had previously received a median of two lines of treatment. These results suggest that this regimen may represent a feasible and effective therapeutic option for this challenging patient population. Furthermore, the study lays the groundwork for future investigations into the use of linperlisib in conjunction with other treatment modalities.

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Author contributions
ZL was responsible for the conception and design of the study. All authors were responsible for the collection, acquisition and analysis of data. PS and ZX drafted the manuscript. All authors read and approved the final version of the manuscript and had full access to all of the trial data and accept responsibility for publication.

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Data availability
The data supporting the results of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The trial adhered to ethical guidelines, receiving approval from independent ethics committees or institutional review boards at each participating site. Written informed consent was obtained from all participants prior to their inclusion in the study.

Consent for publication
Not applicable.

Competing interests
Hanying Bao, Zusheng Xu, and Zuhong Xu are employees of Shanghai Yingli Pharmaceutical Co., Ltd. The remaining authors have declared no conflicts of interest.

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