Phase 2 dose-ranging study to evaluate the efficacy and safety of liposomal irinotecan (LY01610) as a second-line treatment for patients with relapsed small cell lung cancer

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eClinicalMedicine
2024;75: 102791
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102791

Summary

Background This was a multicenter, single-arm dose-ranging phase 2 study aimed to assess the efficacy and safety of LY01610, a liposomal irinotecan, at various doses for patients with relapsed small cell lung cancer (SCLC).

Methods This study (NCT04381910) enrolled patients with relapsed SCLC at 10 hospitals across China, who have failed with previous platinum-based treatments. LY01610 was administered at doses of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2. Primary endpoints were investigator-assessed objective response rate (ORR) and investigator-assessed duration of response (DoR). Secondary endpoints included investigator-assessed disease control rate (DCR), investigator-assessed progression-free survival (PFS), overall survival (OS), and safety.

Findings From September 3, 2020 to March 3, 2022, a total of 66 patients were enrolled, with 6, 30, and 30 allocated to the 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose groups, respectively, with 68% (45/66) having a chemotherapy-free interval <90 days. In all 66 patients, the ORR was 32% (21/66, 95% confidence interval [CI], 21–44), with a median DoR of 5.2 months (95% CI, 3.0–8.3). Median PFS and OS were 4.0 (95% CI, 2.9–5.5) and 9.7 (95% CI, 7.2–12.3) months, respectively. The ORR of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 33% (2/6), 33% (10/30), and 30% (9/30), respectively. The median DoR of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 4.2 (95% CI, 2.8–not reached), 6.9 (95% CI, 2.5–9.9), and 4.0 (95% CI, 2.7–6.8) months, respectively. The incidence of ≥ grade 3 treatment-related adverse events (TRAEs) in the 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 33% (2/6), 47% (14/30), and 50% (15/30), respectively. The most common ≥ grade 3 TRAEs of all 66 patients were neutropenia (27%), leukopenia (24%) and anemia (15%).

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Interpretation LY01610 exhibited promising clinical efficacy and manageable safety profiles in patients with relapsed SCLC, the 80 mg/m^2 dose group had the best benefit-risk ratio.

Funding This study was supported by Luye Pharma Group Ltd.

Keywords: Liposomal irinotecan; LY01610; Small cell lung cancer

Research in context

Evidence before this study

The second-line treatment of small cell lung cancer (SCLC) was limited. We searched PubMed for all clinical trial publications up to March 15, 2024 on liposomal irinotecan for the treatment of SCLC, published in any language, with the terms "small cell lung cancer" AND ("irinotecan liposome" OR "liposomal irinotecan"), and found one matched article. Prior to this study, ONIVYDE® reported its main results from RESILIENT Part 1, which showed that the anti-cancer activity of liposomal irinotecan in patients with relapsed SCLC was promising.

Added value of this study

LY01610 is a novel liposomal irinotecan. As a new drug delivery system, it offers enhanced tumor targeting, prolonged drug release, reduced adverse events, and improved cellular affinity. The results of this study suggest that LY01610 exhibited promising clinical efficacy and manageable safety profiles in patients with relapsed SCLC, the 80 mg/m^2 dose group had the best benefit-risk ratio.

Implications of all the available evidence

Results of this study support the further investigation of LY01610, and the phase 3 study (NCT06128837) in patients with relapsed SCLC is ongoing.

Introduction

Small cell lung cancer (SCLC), accounting for 13–17% of all lung cancer patients, is characterized by its highly aggressive nature and poor prognosis. The reported number of SCLC-related deaths has increased annually.[1–3] Despite the initial treatments have high efficacy, options for managing relapsed SCLC are limited. The high mortality rate is mainly due to refractory or relapse of the disease, resulting in a 5-year overall survival (OS) rate <5%. Topotecan monotherapy is considered the standard chemotherapy for patients with relapsed SCLC, but its efficacy is modest. Previous studies have shown that the response rate of topotecan monotherapy as second-line treatment ranges from 17 to 25%, with a median OS of approximately 5.8–8.4 months.[4–12] The efficacy in patients resistant to chemotherapy (chemotherapy-free interval [CTFI] < 90 days) is even lower, with a response rate <10% and shorter OS.[4–13] Moreover, severe myelotoxicity of a 5-day administration cycle treatment limited the tolerability and convenience of topotecan. Therefore, patients with relapsed SCLC need innovative therapies.

Irinotecan, a semi-synthetic derivative of camptothecin, exerts its anti-cancer effect by transforming into the active metabolite SN-38 through the action of liver carboxylate esterase in vivo. Irinotecan demonstrates lower long-term cumulative toxicity, such as neurotoxicity, which enhances its tolerability compared to taxanes and platinum compounds. Irinotecan is recommended as a primary treatment for patients with extensive stage SCLC and as one of the second-line treatment options for patients with relapsed SCLC. A phase III study conducted in Japan[14] showed a survival advantage with irinotecan plus platinum regimen, compared with etoposide plus platinum, as the first-line treatment for extensive stage SCLC. However, a similar study in the United States did not replicate this finding.[15,16]

Liposomal irinotecan offers improved tumor targeting, extended drug release, decreased toxicity, and enhanced cellular affinity. Encapsulated within lipid bilayer nanoparticles, this drug delivery system slows down the release of irinotecan into the bloodstream, preventing rapid conversion into the toxic metabolite SN-38. This encapsulation alters irinotecan's pharmacokinetics by facilitating a gradual and consistent release of SN-38, avoiding the toxicity peaks associated with traditional irinotecan administration.[17–19] Liposomal irinotecan ONIVYDE® has been approved by the United States Food and Drug Administration (FDA) for pancreatic cancer treatment.[20] Exploring the use of such agents for the second-line treatment of patietns with SCLC is a reasonable and promising direction.

LY01610, another nano-preparation liposomal irinotecan, has been developed. It utilizes a unique encapsulation method with a more acidic internal aqueous phase, which enhances the stability of irinotecan's active lactone ring and reduces the loss of efficacy before targeted organ release. In a first-in-human clinical study for advanced solid tumors, pharmacokinetic study has

demonstrated that LY01610 significantly elevates the plasma concentration of free irinotecan and SN-38, prolongs half-life, and displays slow-release characteristic of liposome-encapsulated agents.[21] Under the acceptable toxicity profile presented in the phase 1 study, LY01610 exhibited notable anti-cancer activity at a dose of 90 mg/m^2 achieving an ORR of 50% (3/6) for solid tumors.[21]

This multi-centre, single-arm, dose-ranging phase 2 study (LY01610/CT-CNH-202, ClinicalTrials.gov Identifier: NCT04381910) evaluated the efficacy and safety of different doses of LY01610 in patients with relapsed SCLC.

Methods

Study design and participants

This study enrolled patients aged 18–75 years from 10 hospitals across China. Patients had histologically or cytologically confirmed SCLC and had experienced relapse and progression after treatment with one platinum-based systemic anti-cancer regimen. Patients with asymptomatic brain metastases were admitted to this study regardless of prior brain radiotherapy histories. Patients who received second-line systemic therapy with original regimen of first-line were cautiously acceptable, while SCLC transformation were ineligible. Eligible enrollment criteria mainly included: 1) Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1; 2) presence of at least one measurable lesion per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; 3) adequate bone marrow, liver, and kidney function; and 4) an expected survival time of ≥3 months. The main exclusion criteria included: 1) symptomatic brain metastasis, meningeal metastasis, spinal cord tumor invasion, and spinal cord compression; 2) superior vena cava syndrome, obstructive atelectasis, and symptomatic bone metastases requiring radiotherapy/surgery/interventional therapy; 3) uncontrolled pleural fluid, ascites, and pericardial effusion; 4) persistent or active infection; 5) unstable or severe cardiovascular disease, asthma, interstitial lung disease, and active hemoptysis; 6) serious digestive diseases such as gastrointestinal bleeding, infection, obstruction, or enteritis; and 7) history of treatment with irinotecan or liposomal irinotecan.

Ethics statement

The institutional review board or independent ethics committee at each participating hospital approved the protocol and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices guideline. Written informed consent was obtained from all patients before any study-related procedures. The full trial protocol can be accessed in Supplementary materials.

Procedures

This study consists of three dose groups: 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 of LY01610 (provided by Nanjing Luye Pharmaceutical Co., Ltd., Nanjing, P. R. China). Patients were enrolled sequentially in increasing doses, with an initial enrollment of six patients in each dose group. Both therapeutic and secondary prophylactic use of recombinant human granulocyte colony stimulating factor (rhG-CSF) were routinely applied. Within 14 days after the first administration to the first six patients in each dose group, the primary focus was to confirm the safety of LY01610, particularly dose-limiting toxicity as defined in the phase I study[21] including treatment-related adverse events (TRAEs) such as non-hematological adverse events (AEs) of ≥ grade 3 (e.g., diarrhea, nausea, vomiting), grade 4 neutropenia lasting ≥3 days, or ≥grade 3 febrile neutropenia, and grade 3 thrombocytopenia accompanied by bleeding or grade 4 thrombocytopenia. The absence of these TRAEs was considered a qualified indicator to proceed with further dose expansion. After the 14-day observation period, both the investigators and the sponsor jointly decided to escalate the appropriate dose group. Each dose group could enroll a maximum of 30 patients, with the actual number being adjustable as per study requirements. The study aimed to enroll a total of 30–90 patients across all dose groups to explore both efficacy and safety.

Enrolled patients were received the corresponding dosage of LY01610, for which the allowable error in the dose calculation was ±2%. LY01610 was diluted in 250 mL of 5% glucose. It was administered through intravenous infusion for at least 90 min, once on the first day of each 2-week cycle. Patients underwent imaging every 6 weeks (±7 days) after the first administration (either enhanced computed tomography or magnetic resonance imaging). During the 6-week interval, if there were clinical signs of progressive disease, adjustments to the frequency of imaging examination were allowed. The efficacy evaluation was conducted by investigators according to the RECIST version 1.1. The multi-cycle administration continued until disease progression, death, intolerable toxicity, withdrawal of informed consent, or study termination. The study concluded 12 months after the first administration of the last patient.

Endpoints and evaluation

The primary endpoints were investigator-assessed objective response rate (ORR) and investigator-assessed duration of response (DoR). The secondary endpoints included investigator-assessed disease control rate (DCR), investigator-assessed progression-free survival (PFS), OS, and safety. The best response rate was defined as the proportion of patients with unconfirmed response, including unconfirmed complete response (CR) and unconfirmed partial response (PR) across two imaging evaluations. The ORR was defined as the

proportion of patients with confirmed response, including confirmed CR and confirmed PR across two imaging evaluations. DoR was defined as the time from confirmed response to disease progression or death. The DCR was defined as the proportion of patients with confirmed CR, confirmed PR and stable disease (SD). PFS was defined as the time from enrollment to the first documented disease progression, or to death from any cause, whichever occurred first. OS was defined as the time from enrollment to death from any cause.

Safety evaluation included treatment-emergent adverse events (TEAEs), TRAEs, serious adverse events (SAEs), adverse events of special interest (AESIs), and severe adverse reactions (SARs). SAE was defined as any adverse event that results in death, poses a life-threatening risk, requires hospitalization, or extends existing hospital stays, leads to persistent or significant disability, exhibits teratogenicity, or causes birth defects and other significant medical events subsequent to study enrollment. SAR was defined as a treatment-related SAE. AESI included grade 4 neutropenia and ≥ grade 3 diarrhea. All AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Beyond the primary and secondary endpoints, this study assessed the impact of stratification factors on outcomes, including dose group, platinum sensitivity, and the influence of different UDP glucuronosyltransferase family 1 member A1 (*UGT1A1*) mutations. Furthermore, Cox regression analysis for PFS and OS was conducted.

Statistical analysis

All statistical analyses were performed using the SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA). The intent-to-treat (ITT) population included all patients who successfully enrolled in this study and received LY01610 treatment. Efficacy evaluation was conducted in the full analysis set (FAS). Safety evaluation was conducted in the safety set (SS). The FAS and the SS were consistent with the ITT population. The ORR and DCR, along with their 95% confidence interval (CI), were calculated. The Clopper Pearson method was used for calculating 95% CIs of the ORR and DCR. The DoR, PFS, and OS for all patients and each dose group were analyzed using Kaplan-Meier (K-M) method. Univariate Cox regression analysis was used in subgroup analysis of ORR, PFS, and OS. Median estimates and their 95% CI were calculated. The Forest plot for subgroup analysis and K-M curves were plotted. AEs, TEAEs, TRAEs, SAEs, and AESIs were summarized and described by system organ class and preferred term after coding, with corresponding calculation of numbers and percentages of patients. SARs were also compiled.

Role of the funding source

This study was funded and supported by Luye Pharma Group Ltd., Nanjing, P. R. China (LY01610/CT-CNH-202). Tianyi Gan PH.D and the principle investigator of this study professor Yuankai Shi had roles in data collection, data analysis, data interpretation, and writing of the manuscript. Tianyi Gan PH.D and the principle investigator of this study professor Yuankai Shi had full access to all the dataset of this study and the decision to submit for publication.

Results

Patient baseline characteristics

From September 3, 2020, to March 3, 2022, a total of 66 patients were enrolled in the ITT population, with the distribution of 6, 30, and 30 patients into the 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group, respectively (Fig. 1). The study protocol is designed to allow for the expansion of each dose group up to 30 patients, contingent upon a joint decision by the leading principal investigator and the sponsor of this study based on a benefit/risk assessment, but it is not mandatory to include 30 patients for each dose group. Regarding the 60 mg/m^2 dose group, the leading principal investigator and sponsor of this study jointly concluded that this initial exploratory dose might not provide optimal therapeutic efficacy. Besides, dose limited toxicity and maximum tolerated dose did not occur in the 60 mg/m^2 dose group. Therefore, it was decided not to expand the 60 mg/m^2 dose group to the full number of 30 patients. The data cut-off date was March 4, 2023, the end of the 12-month follow-up period following the initial administration to the last patient. All 66 patients in the ITT population were included in the FAS and SS. The baseline characteristics of patients in the ITT population were shown in Table 1. With regard to ethnic distribution, 65 (98%) patients were the Han people, only one from ethnic minority. Among all 66 patients, 45 (68%) were resistant patients (chemotherapy-free interval [CTFI] < 90 days), while 21 (32%) were sensitive patients (CTFI ≥90 days); 25 (38%) and 14 (21%) had baseline brain and liver metastasis, respectively. Only 10 (40%) of the 25 patients with brain metastasis previously received brain radiotherapy. Twelve (18%) patients previously received thoracic radiotherapy for primary lung lesions. At the data cut-off date, all patients were end of treatment.

Drug exposure

Exposure of LY01610 in the ITT population was showed in the Supplementary Table S1. The average exposure durations of all dose groups was 8.6 cycles (standard deviation was 7.7). The average exposure durations (standard deviation) of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 9.2 (4.3), 10.3 (9.3), and 6.8 (6.1) cycles, respectively. The median exposure durations of all dose groups was 6.0 cycles (first, third quartile, 3.0 and 12.0). The median exposure durations (first, third quartile) of 60 mg/m^2, 80 mg/m^2, and

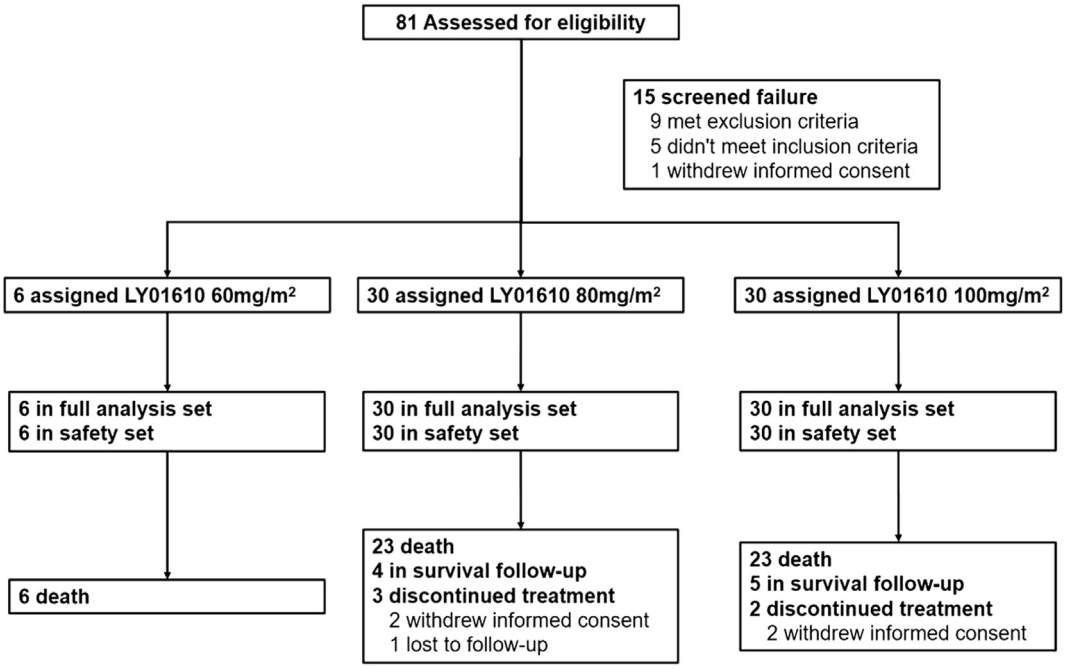

Fig. 1: **The study flowchart**.

100 mg/m^2 dose group were 9.5 (6.0, 12.0), 6.5 (3.0, 14.0), and 5.0 (3.0, 8.0) cycles, respectively. The total average exposure of all dose groups was 1178.3 mg (standard deviation was 1036.0 mg). The total average exposure (standard deviation) of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 974.6 (487.1), 1387.0 (1301.6), and 1010.3 (766.8) mg, respectively. The maximum duration of exposure of all dose groups was 41 cycles. The maximum duration of exposure of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 15, 41, and 26 cycles, respectively. The highest total exposure of all dose groups was 5576.0 mg. The highest total exposure of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 1593.0, 5576.0 and 3066.2 mg, respectively.

Efficacy

The efficacy data were detailed in Table 2. In all 66 patients of the FAS, the median follow-up period was 20.3 months (95% CI 18.8–23.4), and the best response rate was 44% (29/66). Among these responders (unconfirmed PR), 21 were confirmed, resulting in a ORR of 32% (21/66, 95% CI: 21–44). The waterfall plot (Fig. 2A) and swimming plot (Fig. 2B) illustrating the best percentage change from baseline target lesions and tumor response and survival effect over time by treatment. The median DoR was 5.2 months (95% CI, 3.0–8.3) (Fig. 3A). DCR was 68% (45/66, 95% CI, 56–79) with 21 confirmed PR and 24 SD. Meanwhile, disease progression was observed in 41 patients, and total 52 patients died. The median PFS for all 66 patients was 4.0 months (95% CI, 2.9–5.5) (Fig. 3B). The median OS for all 66 patients was 9.7 months (95% CI, 7.2–12.3), 1-year OS rate was 40% (95% CI, 29–54) (Fig. 3C).

The best response rate of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 33% (2/6), 50% (15/30), and 40% (12/30), respectively. The ORR of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 33% (2/6, 95% CI: 4–78), 33% (10/30, 95% CI: 17–53), and 30% (9/30, 95% CI: 15–49), respectively. The median DoR of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 4.2 (95% CI, 2.8-not reached [NR]), 6.9 (95% CI, 2.5–9.9), and 4.0 (95% CI, 2.7–6.8) months, respectively (Fig. 3A). The median PFS of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 4.9 (95% CI, 1.4–NR), 4.8 (95% CI, 2.7–6.8), and 3.8 (95% CI, 2.4–5.4) months, respectively (Fig. 3B). The median OS of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 8.8 (95% CI, 3.2–NR), 9.6 (95% CI, 4.2–15.7), and 10.5 (95% CI, 7.2–12.3) months, respectively (Fig. 3C). The 1-year OS rate of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were 17% (95% CI, 3–100), 48% (95% CI, 33–70), and 32% (95% CI, 19–55), respectively (Fig. 3C).

Stratified efficacy evaluation by CTFI and *UGT1A1* gene mutation

Among all 66 patients, 45 (68%) patients were identified as platinum-resistant (CTFI <90 days). The patients were identified as platinum-resistant (CTFI <90 days) of 60 mg/m^2, 80 mg/m^2, and 100 mg/m^2 dose group were

Characteristic	60 mg/m²	80 mg/m²	100 mg/m²	Total
No. of patients	6	30	30	66
Gender, *n* (%)				
Male	6 (100)	25 (83)	29 (97)	60 (91)
Female	0 (0)	5 (17)	1 (3)	6 (9)
Age, years				
Range	50–68	42–72	31–71	31–72
Median	58.5	61.0	60.0	60.5
Body surface area, m²				
Range	1.6–2.0	1.4–2.1	1.4–1.9	1.4–2.1
Median	1.74	1.77	1.69	1.75
ECOG PS, *n* (%)				
0	0 (0)	4 (13)	2 (7)	6 (9)
1	6 (100)	26 (87)	28 (93)	60 (91)
*UGT1A1**6*28 polymorphism, *n* (%)				
*UGT1A1**6 mutation	0 (0)	10 (33)	14 (47)	24 (36)
*UGT1A1**28 mutation	3 (50)	10 (33)	6 (20)	19 (29)
Both of two mutations	0 (0)	5 (17)	1 (3)	6 (9)
Any of two mutations	3 (50)	15 (50)	19 (63)	37 (56)
Stage, *n* (%)				
III	1 (17)	4 (13)	3 (10)	8 (12)
IV	5 (83)	26 (87)	27 (90)	58 (88)
ES-SCLC	6 (100)	30 (100)	30 (100)	66 (100)
CTFI, *n* (%)				
CTFI ≥ 90 days	0 (0)	14 (47)	7 (23)	21 (32)
CTFI < 90 days	6 (100)	16 (53)	23 (77)	45 (68)
CTFI < 30 days	2 (33)	4 (13)	9 (30)	15 (23)
Baseline history of brain/liver metastasis				
Brain	3 (50)	13 (43)	9 (30)	25 (38)
Liver	0 (0)	6 (20)	8 (27)	14 (21)
Baseline metastatic sites, *n* (%)				
<3	4 (67)	14 (47)	16 (53)	34 (52)
≥3	2 (33)	16 (53)	14 (47)	32 (48)
Number of previous treatment lines, *n* (%)				
1	5 (83)	29 (97)	29 (97)	63 (95)
>1	1 (17)	1 (3)	1 (3)	3 (5)
Previous radiation therapy history, *n* (%)	3 (50)	14 (47)	12 (40)	29 (44)
Previous PD-1/PD-L1 therapy history, *n* (%)	0 (0)	6 (20)	11 (37)	17 (26)
Months since diagnosis of ES-SCLC				
Median	8.0	9.3	7.0	8.1
Range	3.7–28.7	1.4–18.7	2.1–30.1	1.4–30.1

ITT: intent-to-treat; *UGT1A1*: UDP glucuronosyltransferase family 1 member A1; ES-SCLC: extensive-stage small cell lung cancer; ECOG: Eastern Cooperative Oncology Group; PS: performance status; CTFI: chemotherapy-free interval; PD-1: programmed cell death protein 1; PD-L1: programmed death-ligand 1.

Table 1: **Baseline characteristics of patients in the ITT population (N = 66).**

100% (6/6), 53% (16/30), and 77% (23/30), respectively. The stratified efficacy according to CTFI is displayed in Supplementary Table S2.

Within the 66 patients, 24 were found to carry the *UGT1A1**6 mutation, 19 had the *UGT1A1**28 mutation; six were identified as carrying both *UGT1A1**6 and *UGT1A1**28 mutations, and 37 patients were carriers of mutations at either of these two gene sites. The stratified efficacy based on *UGT1A1* mutation status is presented in Supplementary Table S2.

Subgroup analysis and univariate cox regression analysis

For the subgroup analysis of ORR and univariate Cox regression analysis of PFS, the result showed that patients with CTFI ≥30 days had a longer PFS compared to those with CTFI <30 days (hazard ratio [HR] 0.51, 95% CI, 0.27–0.97, p = 0.040) (Supplementary Figure S1).

Univariate Cox regression analysis of the influence of stratification factors on OS was shown in Supplementary Table S3. Univariate Cox regression analysis showed that liver metastasis and the number of tumor metastatic sites were two statistically significant factors affecting OS. Patients with liver metastasis had a shorter OS than those without liver metastasis (HR 2.70, 95% CI, 1.41–5.18, p = 0.0028). Additionally, patients with <3 metastatic sites had a longer OS than those with ≥3 metastatic sites (HR 0.46, 95% CI, 0.25–0.83, p = 0.010).

Safety

The incidence of AEs were detailed in Table 3. In all 66 patients of the SS, the incidences of TEAEs, TRAEs, SAEs, AESIs, SARs, ≥ grade 3 TEAEs, and ≥ grade 3 TRAEs were 98% (65/66), 98% (65/66), 39% (26/66), 14% (9/66), 33% (22/66), 58% (38/66), and 47% (31/66), respectively. The incidences of TRAE leading to dose reduction, transient discontinuation, permanent discontinuation, withdrawal from study, and death were 32% (21/66), 29% (19/66), 6% (4/66), 2% (1/66), and 3% (2/66), respectively.

In all 66 patients of the SS, ≥ grade 3 TRAEs with incidence ≥10% included neutropenia (18/66, 27%), leukopenia (16/66, 24%), and anemia (10/66, 15%). The incidence of ≥ grade 3 neutropenia in the 60 mg/m², 80 mg/m², and 100 mg/m² dose group, were 33% (2/6), 33% (10/30), and 20% (6/30), respectively. The incidence of ≥ grade 3 leukopenia in the 60 mg/m², 80 mg/m², and 100 mg/m² dose group, were 33% (2/6), 27% (8/30), and 20% (6/30), respectively. The incidence of ≥ grade 3 anemia in the 60 mg/m², 80 mg/m², and 100 mg/m² dose group, were 0 (0/6), 17% (5/30), and 17% (5/30), respectively. In all 66 patients of the SS, SARs with incidence ≥10% was leukopenia (10/66, 15%). The incidence of leukopenia of SAR in the 60 mg/m², 80 mg/m², and 100 mg/m² dose group were 0 (0/6), 17% (5/30), and 17% (5/30), respectively. The incidence of SAR for diarrhea was 5% (3/60) in all 66 patients of the SS. The incidence of diarrhea of SAR in the 60 mg/m², 80 mg/m², and 100 mg/m² dose group were 0 (0/6), 7% (2/30), and 3% (1/30), respectively.

Regarding the use of rhG-CSF for treatment and prevention, 52% (34/66) of patients received 155 times of therapeutic rhG-CSF while 24% (16/66) of patients

received 55 times of secondary prophylactic rhG-CSF (Supplementary Table S4). Regarding the impact of *UGT1A1* genetic phenotype on safety, there was no significant difference in the incidence of ≥ grade 3 TRAE and SAR among patients with different *UGT1A1**6 or *28 gene phenotypes (Supplementary Table S5). The incidence of ≥ grade 3 TRAEs was similar between patients treated with LY01610 for 4 cycles or less and those treated for more than 4 cycles, indicating that extended treatment duration did not significantly increase TRAE (Supplementary Table S6).

Discussion

Relapsed SCLC is prone to rapid progression and development of resistance to treatment, leaving limited therapeutic options and leading to a dismal prognosis. This gap underscores a persistent unmet clinical need. Previous studies have demonstrated limited efficacy of agents used in second-line treatment for SCLC patients. Topotecan is recognized as the evidence-based second-line therapy for patients with relapsed SCLC within six months of completing platinum-based therapy, and it remains the sole standard treatment.[4,5] Despite not being surpassed in efficacy by other agents in numerous controlled trials, its efficacy remains constrained, particularly for refractory patients. Historical studies on second-line treatments indicate that both topotecan monotherapy and combination regimens including topotecan, yield a similar ORR of about 16%, with median PFS and median OS of approximately 3.5 months and 8.0 months,[6,9,12] respectively. In the CheckMate-331 study, the ORR among 43 resistant patients (51%) in the Chinese control subgroup receiving second-line topotecan treatment was merely 5%, with median PFS and median OS of 2.2 months and 7 months, respectively. Regarding safety, topotecan is associated with significant hematologic toxicity, including grade 4 neutropenia in up to 70% of patients, which markedly impacts its long-term tolerability.[9] Another second-line treatment option recommended by guidelines is irinotecan, which some studies suggest may have comparable efficacy to topotecan but with lower hematologic toxicity. Nonetheless, the occurrence of gastrointestinal AEs, particularly severe diarrhea, exceeds 20%.[4,22,23] Lurbinectedin has emerged as a novel second-line treatment for SCLC in recent years, with an ORR of 33% as evaluated by an independent review committee (IRC) in a single-arm trial of SCLC patients, and median PFS and median OS of 3.5 months and 9.3 months, respectively.[24] However, its hematologic toxicity cannot be overlooked, with 46% experiencing ≥ grade 3 neutropenia and 7% ≥ grade 3 thrombocytopenia in the Caucasian patient population,[24] while the incidence of these two AEs were even higher in Chinese patient population, with 77% and 41%, respectively.[25] More effective treatment approaches that offer improved safety and tolerability are widely required.

Efficacy	60 mg/m^2 (N = 6)	80 mg/m^2 (N = 30)	100 mg/m^2 (N = 30)	Total (N = 66)
Best response rate, *n* (%)	2 (33)	15 (50)	12 (40)	29 (44)
Confirmed CR, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Confirmed PR, *n* (%)	2 (33)	10 (33)	9 (30)	21 (32)
SD, *n* (%)	3 (50)	12 (40)	9 (30)	24 (36)
PD, *n* (%)	1 (17)	4 (13)	6 (20)	11 (17)
NE, *n* (%)	0 (0)	4 (13)	6 (20)	10 (15)
ORR, *n* (%, 95% CI)	2 (33, 4–78)	10 (33, 17–53)	9 (30, 15–49)	21 (32, 21–44)
DCR, *n* (%, 95% CI)	5 (83, 36–100)	22 (73, 54–88)	18 (60, 41–77)	45 (68, 56–79)
Median DoR (months, 95% CI)	4.2 (2.8–NR)	6.9 (2.5–9.9)	4.0 (2.7–6.8)	5.2 (3.0–8.3)
Median PFS (months, 95% CI)	4.9 (1.4–NR)	4.8 (2.7–6.8)	3.8 (2.4–5.4)	4.0 (2.9–5.5)
Median OS (months, 95% CI)	8.8 (3.2–NR)	9.6 (4.2–15.7)	10.5 (7.2–12.3)	9.7 (7.2–12.3)
1-year OS rate (%, 95% CI)	17 (3–100)	48 (33–70)	32 (19–55)	40 (29–54)

*Abbreviation: FAS: full analysis set; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable; ORR: objective response rate; DoR: duration of response; DCR: disease control rate; NR: not reached; PFS: progression-free survival; OS: overall survival; CI: confidence interval.

Table 2: **Efficacy of LY01610 in the FAS (N = 66).**

In this study, LY01610, administered across three dose groups, demonstrated an ORR and DCR of 32% (21/66) and 68% (45/66), respectively, and a median DoR, median PFS, and median OS was 5.2 months, 4.0 months, and 9.7 months, respectively. The 1-year OS rate was 40%. Specifically, in the 80 mg/m^2 does group, the best response rate was 50% (15/30), with an ORR of 33% (10/30). The median DoR, median PFS, and median OS were 6.9 months, 4.8 months, and 9.6 months, respectively, with the 1-year OS rate was 48%. Compared to the 100 mg/m^2 dose group, the 80 mg/m^2 dose group has the higher mean drug exposure, the better anti-cancer activity, and superior safety characteristics. Thus, the 80 mg/m^2 dose group offer a more favorable benefit-risk ratio. Compared with historical study results of second-line treatment, LY01610 is more effective than topotecan and has a comparable response to lurbinectedin. It is noteworthy that the lurbinectedin trial excluded patients with brain metastases,[24] whereas LY01610 also showed a notably promising response and OS even 38% (25/66) patients with baseline brain metastases. The TRAEs were generally reversible and manageable with appropriate supportive care. The ≥ grade 3 myelosuppression including neutropenia (27%, 18/66) and thrombocytopenia (5%, 3/66), which was numerically lower than that reported for topotecan or lurbinectedin. The ≥ grade 3 TRAE of diarrhea was only 5% (3/66). The promising efficacy and manageable safety profile of LY01610 provided a solid foundation for advancing to a subsequent phase 3 study.

A significant advantage of this study is that it reports for the first time the better efficacy and lower chemotherapeutic toxicity of liposomal irinotecan as a novel drug delivery system for the treatment of Chinese

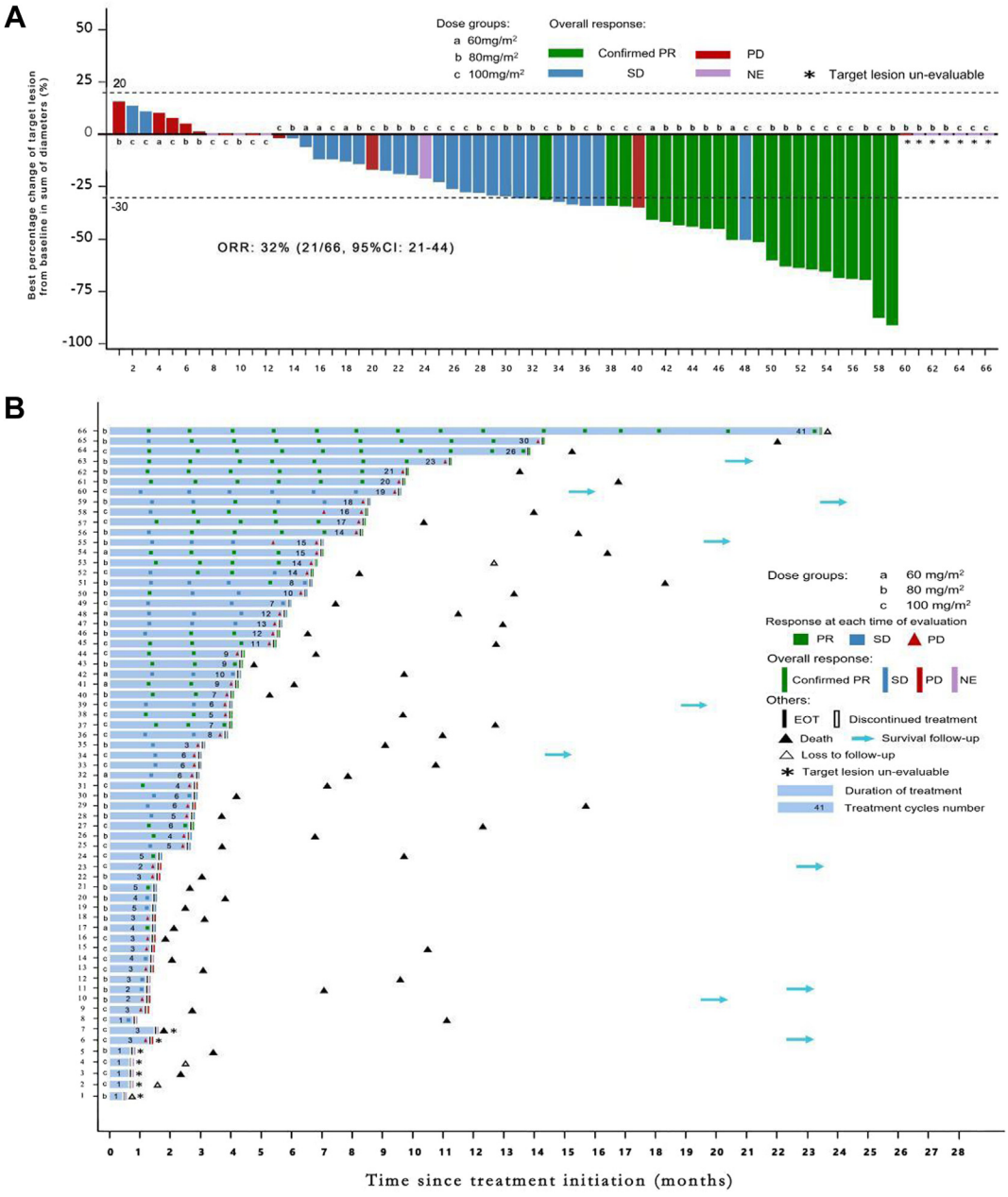

***Fig. 2:* Efficacy of LY01610 in the FAS (N = 66)**. A: the waterfall plot. The dashed lines at 20% and −30% indicate the thresholds for PD and PR. There were seven of 66 patients un-evaluable in target lesion for efficacy, including three withdrew consent before the first efficacy evaluation, three discontinued treatment and dead before the first efficacy evaluation due to disease or AE, and one PD discontinued treatment before the first efficacy evaluation due to brain metastasis. B: the swimming plot. The No. 1 to the No. 7 patients were the seven patients in Figure 2A with un-evaluable in target lesion for efficacy evaluation. The No. 8 patient underwent additional imaging assessments after first cycle of treatment due to signs of PD. FAS: full analysis set; AE: adverse event; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable for confirmed response; ORR: objective response rate; EOT: end of treatment.

patients with relapsed SCLC. Another key strength is the inclusion of patients with refractory diseases (CTFI <90 days), who constitute 68% (45/66) of the enrolled patients. Compared to historical second-line efficacy results for patients with refractory SCLC, where the ORR is typically less than 10%, the ORR for the refractory patients in this study was 36% (16/45) and 31% (5/16) among all dose groups and in 80 mg/m^2 dose group, respectively. Additionally, this study included a significant proportion of patients with baseline brain

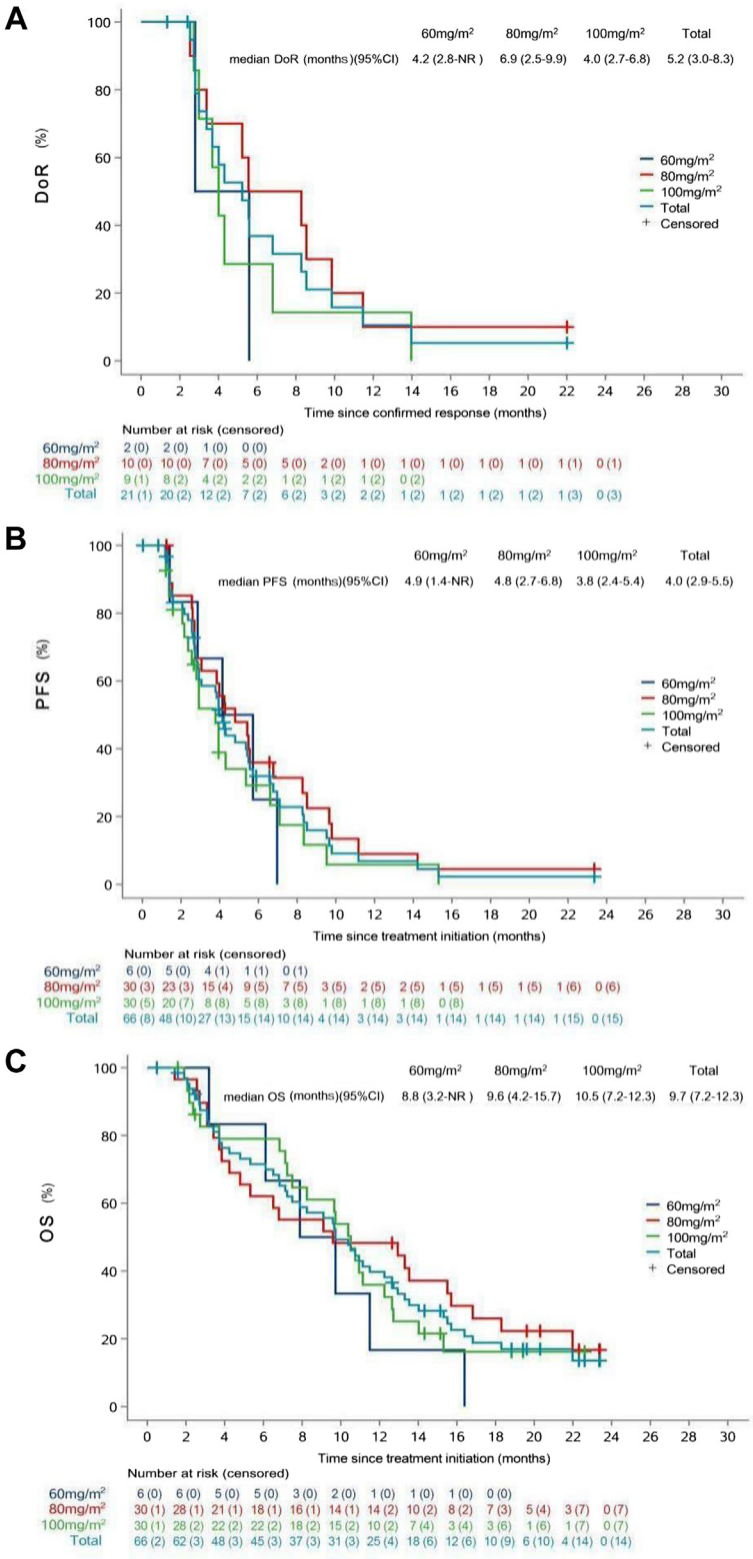

Fig. 3: **The Kaplan-Meier curves for patients in the FAS (N = 66)**. A: DoR; B: PFS; C: OS. FAS: full analysis set; DoR: duration of response; NR: not reached; PFS: progression-free survival; OS: overall survival.

	60 mg/m^2 (N = 6)	80 mg/m^2 (N = 30)	100 mg/m^2 (N = 30)	Total (N = 66)
AEs, *n* (%)				
TEAE	6 (100)	30 (100)	29 (97)	65 (98)
TRAE	6 (100)	30 (100)	29 (97)	65 (98)
SAEs	0 (0)	12 (40)	14 (47)	26 (39)
AESIs	1 (17)	5 (17)	3 (10)	9 (14)
SARs	0 (0)	9 (30)	13 (43)	22 (33)
≥ Grade 3 TEAEs	2 (33)	18 (60)	18 (60)	38 (58)
≥ Grade 3 TRAEs	2 (33)	14 (47)	15 (50)	31 (47)
TRAE leading to dose reduction	1 (17)	8 (27)	12 (40)	21 (32)
TRAE leading to transient discontinuation	0 (0)	11 (37)	8 (27)	19 (29)
TRAE leading to permanent discontinuation	0 (0)	1 (3)	3 (10)	4 (6)
TRAE leading to withdrawal from study	0 (0)	0 (0)	1 (3)	1 (2)
TRAE leading to death	0 (0)	0 (0)	2 (7)	2 (3)
≥ Grade 3 TRAEs, ≥ 3% (total)				
Neutropenia	2 (33)	10 (33)	6 (20)	18 (27)
Leukopenia	2 (33)	8 (27)	6 (20)	16 (24)
Febrile neutropenia	0 (0)	3 (10)	0 (0)	3 (5)
lymphocytopenia	0 (0)	2 (7)	0 (0)	2 (3)
Anemia	0 (0)	5 (17)	5 (17)	10 (15)
Thrombocytopenia	0 (0)	3 (10)	0 (0)	3 (5)
Vomiting	0 (0)	2 (7)	4 (13)	6 (9)
Diarrhea	0 (0)	2 (7)	1 (3)	3 (5)
Nausea	0 (0)	0 (0)	4 (13)	4 (6)
Infectious pneumonia	0 (0)	2 (7)	2 (7)	4 (6)
SARs, ≥ 3% (total)				
Leukopenia	0 (0)	5 (17)	5 (17)	10 (15)
Neutropenia	0 (0)	2 (7)	4 (13)	6 (9)
Febrile neutropenia	0 (0)	3 (10)	0 (0)	3 (5)
Anemia	0 (0)	1 (3)	3 (10)	4 (6)
Thrombocytopenia	0 (0)	1 (3)	1 (3)	2 (3)
Elevated ALT	0 (0)	0 (0)	2 (7)	2 (3)
Elevated AST	0 (0)	0 (0)	2 (7)	2 (3)
Elevated blood creatinine	0 (0)	1 (3)	1 (3)	2 (3)
Vomiting	0 (0)	2 (7)	4 (13)	6 (9)
Nausea	0 (0)	0 (0)	4 (13)	4 (6)
Diarrhea	0 (0)	2 (7)	1 (3)	3 (5)
Infectious pneumonia	0 (0)	2 (7)	2 (7)	4 (6)
AESI				
Neutropenia	1 (17)	1 (3)	2 (7)	4 (6)
Diarrhea	0 (0)	2 (7)	1 (3)	3 (5)
Febrile neutropenia	0 (0)	3 (10)	0 (0)	3 (5)

Abbreviation: AEs: adverse events; SS: safety set; TEAEs: treatment-emergent adverse events; TRAEs: treatment-related adverse events; SAEs: serious adverse events; AESI: adverse events of special interest; SARs: serious adverse reactions; ALT: alanine transaminase; AST: aspartate aminotransferase.

Table 3: **The summary of AEs for LY01610 in the SS (N = 66).**

metastases (38%, 25/66) and baseline liver metastases (21% 14/66). There were 44% (29/66) and 26% (17/66) of patients received radiation therapy and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) monoclonal antibodies, indicating patients in this study received adequate previous standard treatment. A subgroup analysis according to *UGT1A1* polymorphism was also conducted in this study. This study has limitations include a single-arm design without a control group and efficacy assessments not based on an IRC, potentially introducing bias. Beyond these, the study's applicability was constrained by its exclusive inclusion of Chinese patients.

Another aspect warranting discussion is the potential of an improved ORR to predict an extended OS when comparing LY01610 to topotecan in randomized controlled trials among patients with relapsed SCLC. This query arises from the outcomes of a phase III study involving ONIVYDE®, which aimed for superiority in OS against topotecan in patients with relapsed SCLC from international multi-center study.[26] Despite nearly doubling the ORR, ONIVYDE® did not achieve the OS endpoint in that study. This disconnect between response rate improvement and survival benefit has also been noted in a pivotal study involving amrubicin for patients with relapsed SCLC.[6] Translating improvements in ORR into OS benefits is a challenge in the treatment of patients with relapsed SCLC. The most likely reason is that the high recurrence rate and generally poor prognosis of SCLC weaken the survival effects of active anti-cancer agents. A considerable proportion of relapsed SCLC patients with heavy tumor burden and rapid progression of liver/brain metastasis have significantly shorter OS. In this study, liver metastasis and the number of metastatic sites are two factors related to poor prognosis. In addition, the post-second-line treatment model also strongly affected the OS of patients in the second-line study. Patients who actively use local treatment, medication for various mechanisms, and new anti-cancer strategies provided from other clinical studies after second-line treatment may often contribute to prolonged OS, which is not limited by second-line treatment options. Therefore, caution is warranted in interpreting the results of this study. How to improve the OS of patients treated with LY01610 is a future challenge. More studies are needed to provide further evidence.

The influence of *UGT1A1* polymorphisms on the efficacy and safety of irinotecan or its modified dosage form is still a topic of debate. The *UGT1A1* *6 or *28 mutant phenotype theoretically leads to slowed metabolic detoxification of irinotecan via pharmacokinetics in vivo, which may lead to increased cytotoxicity, decreased tolerance, and increased potential anti-cancer activity. Some previous studies have shown that *UGT1A1* *6 and *28 polymorphisms are linked to increased gastrointestinal AEs, and in certain studies, may be associated with improved OS in patients with SCLC treated with irinotecan-platinum doublets.[27,28] The results of this study showed that patients benefited from LY01610 treatment regardless of their *UGT1A1*6 or *28 mutation status, and these

genotypes did not significantly affect safety, indicating that LY01610 is effective and safe across a range of patient populations previously thought to be potentially more susceptible to TRAE. Future studies is required for more evidence.

In this study, LY01610 demonstrated promising efficacy and a manageable safety profile, particularly in the 80 mg/m^2 dose group, for patients with relapsed SCLC. The phase 3 randomized controlled study (NCT06128837) is ongoing to confirm the efficacy and safety of this treatment for patients with relapsed SCLC.

Contributors

Yuankai Shi and Clinical Research Center of Luye Pharma Group Ltd. contributed to the conception and design of the study. Puyuan Xing, Shanbin Wang, Minghong Bi, Yong Liu, Jia Zeng, Xicheng Wang, Ke Xiao, Weidong Li, Jun Guo, Pu Wang, Yueyin Pan, Biyong Ren, and Yuankai Shi contributed to the recruitment and clinical care of patients. National Key Laboratory of Advanced Drug Delivery and Release Systems, Nanjing Luye Pharmaceutical Co., Ltd. (Nanjing, Jiangsu 210061, P.R. China), Clinical Research Center of Luye Pharma Group (Beijing 100025, P. R. China), Luye Life Sciences Group contributed to pharmaceutical research, production, preclinical and clinical drug development, as well as providing study materials and funding. Emei Gao, Lei Zhang, Yingchun Wang, Tianyi Gan, Guang Cheng and Yuankai Shi contributed to data collection and assembly, data review, data analysis, interpretation, manuscript writing, and revision. All authors contributed to the administrative, technical, and final approval of manuscript and accountable for all aspects of the work.

Data sharing statement

To request access to the de-identified study data, please contact the corresponding author. Requests will be reviewed and written applications from investigators with the academic capability and credibility to undertake the work proposed will be considered. The scientific merit of the proposal, including the appropriate methods, analysis, and publication plan will be assessed. Consideration will be taken of any overlap with analyses already undertaken or planned to be undertaken by the study team. If a proposal is approved, a signed data transfer agreement will be required before data sharing.

Declaration of interests

All the authors declare no conflicting of interest.

Acknowledgements

This research was mainly supported by National Key Laboratory of Advanced Drug Delivery and Release Systems, Nanjing Luye Pharma Group Ltd., Clinical Research Center of Luye Pharma Group Ltd., and the Chinese Academy of Medical Sciences. We thank all the patients, their families, site investigators, clinical research coordinators, study's sponsor and other persons who made the study possible. Special thanks for Prof. Yuankai Shi's scientific guidance and other hard work, Emei Gao's manuscript writing and other hard work. We also give thanks to Dr. Zucheng Xie and Dr. Tongji Xie (National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College) for revising and editing the manuscript; to Dr. Ke Tang (Luye Life Sciences Group) for the provision of revision comments; to Longhua Luo, Yang Wang and Beijing Trust Medical Consulting Co. Ltd. for the statistical analysis; and to Yucheng Liang for language support.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102791.

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