Original Article

Tolerability, safety, and preliminary antitumor activity of fuzuloparib in combination with SHR-1316 in patients with relapsed small cell lung cancer: a multicenter, open-label, two-stage, phase Ib trial

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Background: Second-line treatment options for small cell lung cancer (SCLC) are limited. Preclinical research shows that inhibition of poly (ADP-ribose) polymerase (PARP) could upregulate programmed death-ligand 1 (PD-L1), and thus render cancer cells more sensitive to immune checkpoint inhibitors. This study investigated the tolerability, safety, and preliminary antitumor activity of fuzuloparib (a PARP inhibitor) plus SHR-1316 (a PD-L1 inhibitor) for relapsed SCLC.

Methods: Patients with SCLC who failed previous first-line platinum-based therapy were enrolled in this two-stage phase Ib trial. In stage 1, 2 dose levels were designed: fuzuloparib 100 mg or 150 mg twice daily plus SHR-1316 600 mg every 2 weeks, with 6 patients in each dose level. Based on the tolerability during the first 28-day cycle and the preliminary antitumor activity in stage 1, a recommended phase II dose (RP2D) was determined and introduced in the stage 2 expansion phase. The primary endpoints were safety and RP2D in stage 1 and objective response rate (ORR) in stage 2.

Results: A total of 23 patients were enrolled, with 16 receiving fuzuloparib 100 mg plus SHR-1316 and 7 receiving fuzuloparib 150 mg plus SHR-1316. At data cutoff on April 23, 2021, the median follow-up duration was 6.4 months (IQR, 3.0–9.7 months). All patients discontinued study treatment. One patient receiving fuzuloparib 150 mg plus SHR-1316 had clinically significant toxicities, and fuzuloparib 100 mg plus SHR-1316 was considered as the RP2D. In the RP2D cohort, the confirmed ORR was 6.3% (95% CI: 0.2–30.2%), and the disease control rate was 37.5% (95% CI: 15.2–64.6%). The median progression-free survival was 1.4 months (95% CI: 1.3–2.8 months), and the median overall survival was 5.6 months (95% CI: 3.0–16.7 months). Grade ≥3 treatment-related adverse events (TRAE) occurred in 8 patients (34.8%). No treatment-related death occurred, and no patients discontinued treatment due to TRAEs.

Conclusions: Fuzuloparib combined with SHR-1316 failed to improve the outcomes in unselected patients with relapsed SCLC. Future studies with biomarker analysis are warranted to select patients most likely to benefit from this combination treatment. Fuzuloparib 100 and 150 mg plus SHR-1316 were both tolerable with no new signals observed.

Keywords: Poly (ADP-ribose) polymerase inhibitor (PARP inhibitor); anti-PD-L1; small cell lung cancer (SCLC); fuzuloparib; SHR-1316

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Introduction

Small cell lung cancer (SCLC), which accounts for approximately 13% to 15% of all lung cancers, is an aggressive malignancy characterized by rapid tumor growth, early metastasis, and poor prognosis (1-3). The treatment strategies and clinical outcomes of SCLC have remained unchanged for decades (4). First-line treatment in patients with advanced SCLC is a combination of carboplatin or cisplatin with etoposide (4). Despite the initial response in the majority of patients, roughly 80% of patients with limited-stage SCLC and nearly all patients with extensive-stage SCLC develop tumor relapse (5). For patients who relapse within 6 months from previous therapy, the traditionally recommended option is topotecan (4). However, the clinical outcome of topotecan was modest (6). Recently, the introduction of immune checkpoint blockade agents has offered new hope, with a small subset of patients deriving prolonged benefit (7,8). However, although SCLC has a high mutation rate, the low expression of programmed death-ligand 1 (PD-L1), the lack of class I major histocompatibility antigen, and the immunosuppressive tumor microenvironment hinder the antitumor activity of immune checkpoint inhibitors for SCLC, and no remarkable antitumor activity of immunotherapy alone has been observed in second-line treatment and beyond (9-11).

The poly (ADP-ribose) polymerase (PARP) is an essential protein involved in the base excision repair pathway, which plays a critical role in the repair of DNA single-strand breaks (12-14). Inhibition of PARP compromises the repair of DNA single-strand breaks, which might lead to the accumulation of double-strand breaks, resulting in genomic instability and ultimately cell death in tumor cells with homologous recombination repair deficiency (15,16). Preclinical research shows that PARP inhibitors upregulate programmed death-ligand 1 (PD-L1) expression and further enhance cancer-related immunosuppression (17). PARP enzymes are also overexpressed in SCLC (18). Based on the above mechanisms, blockade of PARP activity and immune checkpoint pathways might demonstrate synergistic antitumor activity.

Fuzuloparib, a newly developed, selective, orally administered PARP inhibitor, exhibited comparable or better performance to olaparib in both *in vitro* and *in vivo* assays with favorable drug-like properties. Fuzuloparib showed potent antitumor activity in preclinical models (19-21). SHR-1316 is a recombinant, fully humanized immunoglobulin G (IgG4) monoclonal antibody that specifically binds to PD-L1. We therefore conducted this phase Ib study to investigate the tolerability, safety, and preliminary antitumor activity of fuzuloparib in combination with SHR-1316 for SCLC relapsed after previous platinum-based chemotherapy. We present the following article in accordance with the TREND reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-356/rc).

Methods

Study design and patients

This open-label, two-stage, phase Ib study was conducted at 3 sites in China (ClinicalTrials.gov identifier: NCT04041011). Eligible patients were 18–70 years old, had histologically or cytologically confirmed SCLC, and had progressed radiologically after previous first-line platinum-based therapy. Patients were included in the trial if they had at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy of at least 12 weeks, and adequate baseline organ and hematologic

function. The key exclusion criteria included carcinomatous meningitis, active central nervous system (CNS) metastases, a history of autoimmune disease or immunodeficiency, or pneumonitis and/or interstitial lung disease. Patients had to provide archived formalin-fixed, paraffin-embedded tumor tissue within 12 months before the first dose of treatment or a freshly obtained pathologic biopsy for biomarker analyses.

The study protocol and all amendments were approved by the Ethics Committee of Zhejiang Cancer Hospital (No. IRB-[2019]311), the Ethics Committee of Peking University Cancer Hospital (No. 2020YW13), and the Ethics Committee of The Second Affiliated Hospital of Nanchang University (No. 2019-40). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the International Council for Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

Treatment procedure

Stage 1 was designed to determine the recommended phase II dose (RP2D) of fuzuloparib plus SHR-1316. Two dose levels were initially planned with 6 patients in each dose level: fuzuloparib 100 mg twice daily plus SHR-1316 600 mg every 2 weeks (dose level 1) and fuzuloparib 150 mg twice daily plus SHR-1316 600 mg every 2 weeks (dose level 2). Fuzuloparib was administered in capsule formulation, and SHR-1316 was administered intravenously. If clinically significant toxicity was reported in more than 1 patient during the first 28-day treatment cycle at dose level 1, this dose level was deemed intolerable by the safety monitoring committee (SMC), and an additional dose level was introduced at the recommendation of the SMC. According to the safety and preliminary antitumor activity data in stage 1, an RP2D was determined by the SMC. Stage 2 dose expansion was designed to further evaluate the antitumor activity and safety of the RP2D established in stage 1. Treatment continued until disease progression, unacceptable toxicity, patient withdrawal, or the investigators' decision. Continuation of study treatment beyond the first assessment of disease progression was permitted until disease progression was confirmed 4 weeks later if the patient was still benefiting from the treatment and willing to sign informed consent.

Fuzuloparib dose modification was permitted for the 150 mg dose level (reduced to 100 mg twice daily), and dose re-escalation was not allowed. Dose reduction for the fuzuloparib 100 mg dose level and SHR-1316 was not permitted. Administration of fuzuloparib or SHR-1316 could be delayed to manage toxicity.

Definition of clinically significant toxicity

Clinically significant toxicity was defined as any of the following adverse events occurring during the first treatment cycle in stage 1 and assessed by the investigator as related to the study drugs: hematologic toxicities including grade 4 neutropenia, grade 3 febrile neutropenia, grade 4 anemia, grade 4 thrombocytopenia, and grade 3 thrombocytopenia complicated with bleeding; nonhematologic toxicities including grade 3 adverse events (with the exception of grade 3 nausea, vomiting, diarrhea, and rash that resolved within 48 h with symptomatic treatment; grade 3 fatigue relieved within 7 days; alopecia; grade 3 endocrine adverse events controllable with hormone replacement therapy; and grade 3 infusion reaction relieved within 6 hours after supportive care), grade 3 clinically significant laboratory abnormalities (with the exception of abnormal liver function resolved to grade ≤2 within 7 days of treatment), and any grade 4 adverse events; any grade 5 adverse events; or other grade ≥2 adverse events leading to treatment discontinuation at the discretion of the investigator.

Assessments

Adverse events and laboratory measures were classified per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Safety was monitored continuously during study treatment until 90 days after treatment discontinuation. During the safety follow-up period, safety assessments were performed at outpatient visits on day 30 and by telephone on days 60 and 90. Tumor response was assessed by investigators every 6 weeks according to RECIST version 1.1. An assessment of complete or partial response needed to be confirmed at least 4 weeks later. Survival was assessed every 30 days by telephone after treatment discontinuation. For the pharmacokinetic analysis of fuzuloparib in stage 2, blood samples (3 mL) were collected at the following time points: within 0.5 h predose and 3 h postdose on days 1 and 15 of cycle 1 and day 1 of cycle 2, 3, and 4. Blood samples obtained were placed in a heparin anticoagulant tube, inverted several times, and centrifuged at 4 ℃ at 1,500 ×g for 10 min within 30 min after blood collection. The supernatant was collected for plasma fuzuloparib concentration assay using a validated high-

performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with Turbo-V electrospray ionization. SHR168770 was used as the internal standard. Chromatography was achieved on an analytical reversed phase ultra-high performance liquid chromatography (UPLC) column with gradient elution. PD-L1 expression was assessed in tumor samples using immunohistochemistry assay with E1L3N antibody (AmoyDx, Xiamen, China). PD-L1 positivity was defined as PD-L1 expression in ≥1% of tumor cells.

Endpoints

In stage 1, the primary endpoints were adverse events, serious adverse events, and RP2D. The second endpoint was the objective response rate (ORR), which was defined as the proportion of patients with a confirmed complete or partial response. In stage 2, the primary endpoint was ORR, and the second endpoints were safety, pharmacokinetics of fuzuloparib, and clinical activity, measured as duration of response (DOR, the time duration from the first evidence of objective response to disease progression or death), disease control rate (DCR, the percentage of patients who had confirmed complete response, partial response, or stable disease), progression-free survival (PFS, the time duration from treatment commencement to disease progression or death), overall survival (OS, the time duration from treatment commencement to death), and 6- and 12-month OS rates.

Statistical analyses

In stage 1, 6 patients in each dose level were required to evaluate the RP2D. In stage 2, assuming an ORR of 40%, with a one-sided α of 0.025, a sample size of 29 patients would provide 80% power to declare that the lower bound of the 95% CI for ORR was not less than 18%. Considering a dropout rate of 10%, 32 patients were required, including the 6 patients who received RP2D in stage 1. Therefore, a total of 38 patients were required in this study, with 12 patients in stage 1 and 26 patients in stage 2.

Efficacy and safety analyses were performed in the full analysis set, which included all enrolled patients who had received at least 1 dose of study treatment. The 95% CIs of ORR and DCR were calculated using the Clopper-Pearson method. The Kaplan–Meier method was employed to plot the survival curves and estimate the median survival time and the 95% CIs (Brookmeyer and Crowley method). The OS rates and the corresponding 95% CIs (normal approximation based on the log-log transformation) were also provided. Other efficacy analyses, adverse events and pharmacokinetic parameters were summarized descriptively. The pharmacokinetic parameters were analyzed using the non-compartmental methods. All statistical analyses were performed with SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and distribution

Between September 24, 2019 and September 25, 2020, 23 Chinese patients with SCLC who had failed frontline treatment were enrolled at 3 sites in China and received study treatment. Among these patients, 16 received fuzuloparib 100 mg plus SHR-1316 (7 patients in stage 1 and 9 patients in stage 2), and 7 received fuzuloparib 150 mg plus SHR-1316. All patients were evaluated for safety and efficacy. At data cutoff on April 23, 2021, the median duration of follow-up was 6.4 months [interquartile range (IQR), 3.0–9.7 months]. All patients discontinued study treatment, with the majority discontinuing due to disease progression (20 patients, 87.0%). Baseline characteristics are shown in *Table 1*. Most patients (78.3%) had a baseline ECOG performance status of 1. All patients had metastasis. A total of 43.5% of patients received at least 2 lines of therapies, and 78.3% of patients had stage IV disease at diagnosis.

Safety

Fuzuloparib 100 mg plus SHR-1316 was well tolerated without protocol-specified clinically significant toxicities. One patient in the fuzuloparib 150 mg plus SHR-1316 group had clinically significant toxicities (decreased platelet count). Given that the fuzuloparib 100 and 150 mg plus SHR-1316 doses were both tolerated with comparable efficacy, fuzuloparib 100 mg plus SHR-1316 was selected as the RP2D.

The median treatment duration was 42 days (range, 21–546 days) for fuzuloparib and 42 days (range, 14–546 days) for SHR-1316. A total of 21 patients (91.3%) had adverse events of any grade related to any study drugs. A summary of treatment-related adverse events (TRAEs) occurring in at least 10% of patients is listed in *Table 2*. Grade ≥3 TRAEs occurred in 8 patients (34.8%), including decreased platelet count (17.4%), hyponatremia (17.4%),

Table 1 Baseline demographics and disease characteristics

Characteristics	Fuzuloparib 100 mg plus SHR-1316 (n=16)	Fuzuloparib 150 mg plus SHR-1316 (n=7)
Median age [IQR], years	63 [59–64]	60 [57–64]
Sex, n (%)		
Male	13 (81.3)	6 (85.7)
Female	3 (18.8)	1 (14.3)
ECOG performance status, n (%)		
0	5 (31.3)	0
1	11 (68.8)	7 (100.0)
Smoking status, n (%)		
Never	4 (25.0)	1 (14.3)
Former	11 (68.8)	5 (71.4)
Current	1 (6.3)	1 (14.3)
Metastases[a], n (%)	16 (100.0)	7 (100.0)
Brain metastases, n (%)		
Yes	5 (31.3)	2 (28.6)
No	11 (68.8)	5 (71.4)
Liver metastases, n (%)		
Yes	7 (43.8)	3 (42.9)
No	9 (56.3)	4 (57.1)
Disease stage, n (%)		
III	3 (18.8)	2 (28.6)
IV	13 (81.3)	5 (71.4)
Lines of prior systemic therapy, n (%)		
1	11 (68.8)	2 (28.6)
2	5 (31.3)	3 (42.9)
3	0	2 (28.6)
Prior systemic therapy, n (%)		
Platinum-based chemotherapy[b]	16 (100.0)	7 (100.0)
Temozolomide	0	1 (14.3)
Irinotecan	0	1 (14.3)
Anlotinib	0	1 (14.3)
Docetaxel	0	1 (14.3)
Others[c]	2 (12.5)	1 (14.3)
Sensitivity to first-line therapy, n (%)		
Platinum-sensitive[d]	9 (56.3)	4 (57.1)
Platinum-resistant[e]	6 (37.5)	3 (42.9)
Unknown	1 (6.3)	0
PD-L1 expression level, n (%)		
≥1%	1 (6.3)	0
<1%	15 (93.8)	6 (85.7)

[a], including both regional lymph nodes metastases and distant metastases; [b], including etoposide plus cisplatin, etoposide plus carboplatin, etoposide plus lobaplatin, and irinotecan plus carboplatin. Patients who received re-challenge of platinum-based chemotherapy for relapsed SCLC were counted only once; [c], including traditional Chinese medicine and clinical trials; [d], platinum-sensitive was defined as disease relapse/progression ≥90 days from the last platinum-based dose; [e], platinum-resistance was defined as disease relapse/progression <90 days from the last platinum-based dose. IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.

anemia (8.7%), decreased neutrophil count (8.7%), decreased white blood cell count (4.3%), increased lipase (4.3%), and hypochloremia (4.3%). Treatment-related serious adverse events were observed in 5 patients (21.7%). Fuzuloparib administration was delayed in 5 patients (21.7%) due to TRAEs, but no patients experienced dose reduction. TRAEs led to dose delay of SHR-1316 in 3 patients (13.0%). No patients permanently discontinued study treatment because of TRAEs. Immune-mediated adverse events were observed in 11 patients (47.8%), with the most common being asthenia (17.4%).

Efficacy

Of the 16 patients who received the RP2D, 1 patient achieved confirmed partial response, 5 patients had stable disease, and 10 patients had progressive disease. The best percentage change from the baseline tumor size is shown in *Figure 1*. The confirmed ORR was 6.3% (95% CI: 0.2–30.2%). The patient with partial response had a response lasting for

Table 2 Summary of TRAEs occurring in at least 10% of all patients

Events	Grade 1–2	Grade 3	Grade 4	Total
Anemia	7 (30.4)	2 (8.7)	0	9 (39.1)
White blood cell count decrease	7 (30.4)	1 (4.3)	0	8 (34.8)
Blood creatinine increase	7 (30.4)	0	0	7 (30.4)
Platelet count decrease	3 (13.0)	4 (17.4)	0	7 (30.4)
Hyponatremia	3 (13.0)	2 (8.7)	2 (8.7)	7 (30.4)
Asthenia	6 (26.1)	0	0	6 (26.1)
Proteinuria	5 (21.7)	0	0	5 (21.7)
Neutrophil count decrease	3 (13.0)	2 (8.7)	0	5 (21.7)
Decreased appetite	4 (17.4)	0	0	4 (17.4)
Aspartate aminotransferase increase	3 (13.0)	0	0	3 (13.0)
Hypoalbuminemia	3 (13.0)	0	0	3 (13.0)
Nausea	3 (13.0)	0	0	3 (13.0)
Vomiting	3 (13.0)	0	0	3 (13.0)

Data are shown as n (%). TRAEs, treatment-related adverse events.

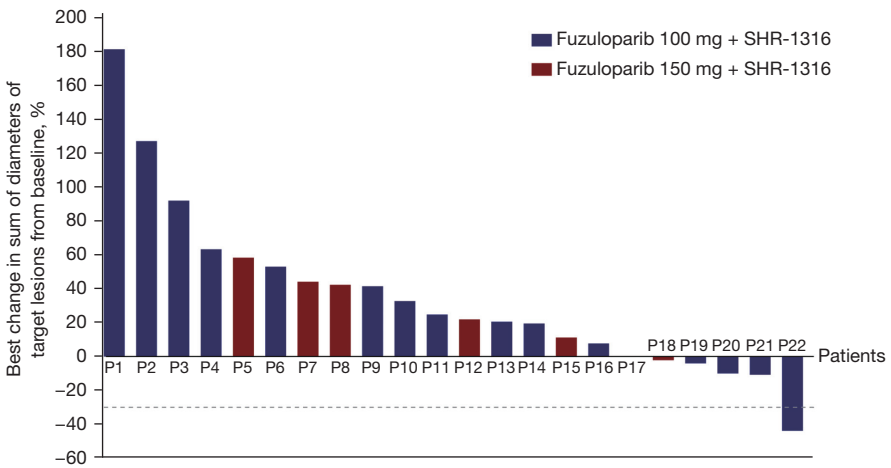

Figure 1 Best percentage change in target lesions from baseline tumor size (n=22). One patient did not have a post-baseline tumor assessment and was not included in the plot.

4.3 months. The DCR was 37.5% (95% CI: 15.2–64.6%). One patient had stable disease lasting for ≥12 months. At data cutoff, the median PFS was 1.4 months (95% CI: 1.3–2.8 months), and the median OS was 5.6 months (95% CI: 3.0–16.7 months). The OS rates at 6- and 12- months were 43.8% (95% CI: 19.8–65.6%) and 27.3% (95% CI: 7.9–51.5%), respectively. PD-L1 expression was evaluable in 22 of the 23 patients, and only 1 patient (4.5%) was PD-L1 positive. This patient experienced disease progression at week 6.

Pharmacokinetic

Nine patients were evaluable for pharmacokinetic analysis. Mean plasma concentrations of fuzuloparib before or after administration are presented in *Figure 2*. Plasma

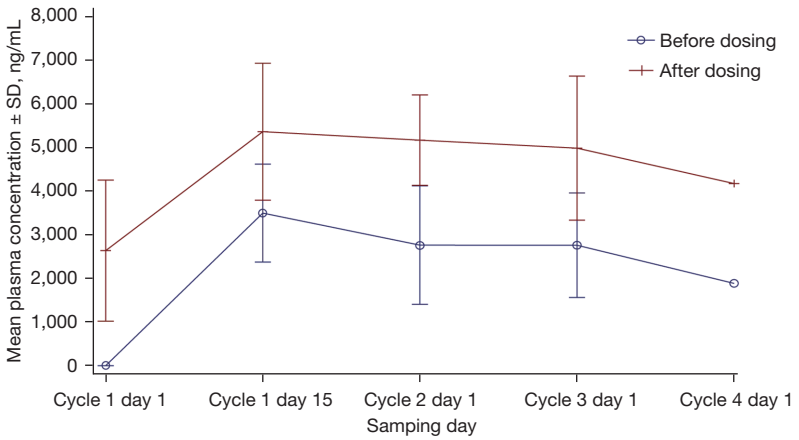

Figure 2 Mean (SD) concentration–time profiles of fuzuloparib (n=9). SD, standard deviation.

Table 3 Mean plasma concentration of fuzuloparib in stage 2

Time points	No. of patients	Mean (SD), ng/mL	CV%
Before fuzuloparib administration			
Cycle 1 day 15	8	3,489 (1,120)	32.09
Cycle 2 day 1	6	3,216 (656)	20.39
Cycle 3 day 1	2	2,754 (1,195)	43.39
Cycle 4 day 1	1	1,881 (NA)	–
After fuzuloparib administration			
Cycle 1 day 1	9	2,631 (1,612)	61.29
Cycle 1 day 15	8	5,350 (1,566)	29.27
Cycle 2 day 1	8	5,156 (1,034)	20.05
Cycle 3 day 1	2	4,974 (1,647)	33.12
Cycle 4 day 1	1	4,164 (NA)	–

SD, standard deviation; CV%, coefficient of variation; NA, not applicable.

concentration of fuzuloparib seemed to reach a steady state by cycle 1 day 15 (*Table 3*).

Discussion

Currently, the recommended treatment strategies for patients with SCLC who progress after frontline therapy include topotecan, lurbinectedin, amrubicin, and re-challenge of platinum-based chemotherapy (recommended for patients who relapse after an interval of >6 months), with a median OS of 6–9 months (6,22-25). No major treatment advances have been made in the past few years. Disappointingly, immune checkpoint blockade alone also failed to improve OS in relapsed SCLC despite the high mutational burden (26). Therefore, a combination treatment of an immune checkpoint inhibitor with another agent, such as chemotherapy, radiotherapy, or targeted therapy, is an attractive strategy. Addition of immunotherapy (atezolizumab or durvalumab) to the traditional standard first-line chemotherapy (platinum and etoposide) significantly improved the OS in patients with extensive-stage SCLC (7,8). In the KEYNOTE-604 study, although the OS improvement was not significant, patients with extensive-stage SCLC showed significantly prolonged PFS with pembrolizumab compared with placebo in combination with platinum and etoposide (27). A phase II study with frontline rucaparib plus nivolumab showed a clinical benefit of 56% in patients with platinum sensitive extensive stage SCLC (28). However, when it comes to second-line setting, there is currently no strong evidence to support the use of combination immunotherapy in patients with SCLC.

Preclinical study demonstrated that PARP inhibitor might augment the antitumor activity of immune checkpoint inhibitor and result in synergistic clinical activity (17). Disappointingly, in a phase II trial conducted in patients with relapsed SCLC, durvalumab in combination with olaparib did not meet its primary endpoint, with two of 19 evaluable patients achieved confirmed response (29). In the present multicenter, open-label, two-stage, phase Ib study, we aimed to evaluate the tolerability, safety, and antitumor activity of fuzuloparib, a PARP inhibitor, in combination with SHR-1316, an anti-PD-L1 monoclonal antibody, in patients with relapsed SCLC. In the 16 patients who were administered the recommended dose (fuzuloparib 100 mg

twice daily plus SHR-1316 600 mg every 2 weeks), 1 patient achieved partial response, and the confirmed ORR was 6.3%. Clinically meaningful benefit was observed in 1 patient with prolonged stable disease of ≥12 months. The median PFS was 1.4 months, and the median OS was 5.6 months. Our findings were consistent with the phase II trial with durvalumab in combination with olaparib in patients with relapsed SCLC (29). This novel combination did not improve clinical outcomes compared to standard chemotherapy or immunotherapy alone in patients with relapsed SCLC (30).

PD-L1 is the most extensively studied biomarker for immunotherapy. However, the predictive value of PD-L1 expression in patients with relapsed SCLC remains inconclusive. Findings from the CheckMate 032 study, in which 17% of patients were PD-L1 positive, showed that tumor responses occurred in patients irrespective of PD-L1 expression (30). In the IFCT-1603 study, in which patients received atezolizumab or chemotherapy as a second-line treatment, only 1 of the 54 evaluable patients had tumor PD-L1 expression >1%, thus precluding evaluations of predictive value (31). In our study, tumor PD-L1 expression was assessed in 22 evaluable patients, and the only patient (4.5%) with positive PD-L1 expression was assessed as having progressive disease at week 6. Therefore, whether PD-L1 expression affects treatment efficacy requires analysis in a larger population. Notably, in the phase II study with durvalumab plus olaparib in patients with relapsed SCLC, the patient with a complete response had a deleterious somatic *BRCA1* mutation. However, the association between DNA alteration and this combined strategy in SCLC remains inconclusive.

Overall, the most common TRAEs in this trial were hematologic abnormalities, including anemia, decreased white blood cell count, and decreased platelet count. Notably, most hematologic abnormalities were mild or moderate, with no grade ≥4 hematologic toxicities observed. No patients discontinued study treatment, and no death occurred due to study treatment. This combination agent demonstrated a favorable safety profile compared with standard second-line chemotherapy, with a lower proportion of patients reporting grade 3 or 4 adverse events (6,22). The safety profile in the present study was similar to that observed in a previous study of an immune checkpoint inhibitor and a PARP inhibitor in patients with relapsed SCLC, with no unexpected safety signals observed (29).

This study was early terminated due to adjustment of development strategy. Thus, the sample size was small, and only one patient was PD-L1 positive, which restricted the interpretation of the results. Currently, there are few studies on the combined use of PARP inhibitors and immune checkpoint inhibitors in SCLC, our study provided further insights toward the safety and activity of this combination. Future studies with biomarker analyses are warranted to identify patients who would benefit most from this combination treatment.

Conclusions

In conclusion, the combination of fuzuloparib and SHR-1316 failed to improve treatment outcomes in unselected relapsed patients with SCLC, and future studies should be conducted to identify those who are most likely to respond to this novel combination. Fuzuloparib 100 and 150 mg plus SHR-1316 were both tolerable, with no new safety signals reported.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-356/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-356/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-356/coif). XM, WS, YS, and SL are employees of Jiangsu Hengrui Pharmaceuticals and Jiangsu Hengrui Pharmaceuticals provided all support for the present manuscript. YHK reports payment or

honoraria from AstraZeneca, Chugai Pharmaceutical, and Eli Lilly Japan. TH has received personal fees from Chugai Pharmaceutical outside the submitted work. AA has received consulting fees from Amgen, Astrazeneca, Roche, Astellas, Takeda, BMS, MSD, Pfize, Merck and Novartis. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol and all amendments were approved by the Ethics Committee of Zhejiang Cancer Hospital (No. IRB-[2019]311), the Ethics Committee of Peking University Cancer Hospital (No. 2020YW13), and the Ethics Committee of The Second Affiliated Hospital of Nanchang University (No. 2019-40). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the International Council for Harmonization Good Clinical Practice guidelines. All patients provided written informed consent.

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