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Veliparib in Combination with Carboplatin and Etoposide in Patients with Treatment-Naïve Extensive-Stage Small Cell Lung Cancer: A Phase 2 Randomized Study



Lauren Averett Byers¹, Dmitry Bentsion², Steven Gans³, Konstantin Penkov⁴, ChoonHee Son⁵, Anne Sibille⁶, Taofeek K. Owonikoko⁷, Harry J.M. Groen⁸, Carl M. Gay¹, Junya Fujimoto^{1,9}, Patricia de Groot¹, Martin Dunbar¹⁰, Kingston Kang¹⁰, Lei He¹⁰, Vasudha Sehgal¹⁰, Jaimee Glasgow¹⁰, Bruce Allen Bach¹⁰, and Peter M. Ellis¹¹

ABSTRACT

Purpose: This study investigated the efficacy and safety of oral PARP inhibitor veliparib, plus carboplatin and etoposide in patients with treatment-naïve, extensive-stage small cell lung cancer (ED-SCLC).

Patients and Methods: Patients were randomized 1:1:1 to veliparib [240 mg twice daily (BID) for 14 days] plus chemotherapy followed by veliparib maintenance (400 mg BID; veliparib throughout), veliparib plus chemotherapy followed by placebo (veliparib combination only), or placebo plus chemotherapy followed by placebo (control). Patients received 4–6 cycles of combination therapy, then maintenance until unacceptable toxicity/progression. The primary endpoint was progression-free survival (PFS) with veliparib throughout versus control.

Results: Overall ($N = 181$), PFS was improved with veliparib throughout versus control [hazard ratio (HR), 0.67; 80% confidence

interval (CI), 0.50–0.88; $P = 0.059$]; median PFS was 5.8 and 5.6 months, respectively. There was a trend toward improved PFS with veliparib throughout versus control in SLFN11-positive patients (HR, 0.6; 80% CI, 0.36–0.97). Median overall survival (OS) was 10.1 versus 12.4 months in the veliparib throughout and control arms, respectively (HR, 1.43; 80% CI, 1.09–1.88). Grade 3/4 adverse events were experienced by 82%, 88%, and 68% of patients in the veliparib throughout, veliparib combination-only and control arms, most commonly hematologic.

Conclusions: Veliparib plus platinum chemotherapy followed by veliparib maintenance demonstrated improved PFS as first-line treatment for ED-SCLC with an acceptable safety profile, but there was no corresponding benefit in OS. Further investigation is warranted to define the role of biomarkers in this setting.

Introduction

Small cell lung cancer (SCLC) is a neuroendocrine carcinoma characterized by aggressive behavior, rapid cell division, and early metastases, and constitutes approximately 15% of lung carcinomas (1). Although tumor, node, metastases (TNM) classification has been recently shown to be prognostic in SCLC, only one third of patients have limited-stage disease at presentation and prognostic characterization in more advanced patients has historically focused on extent of

disease, including the development of central nervous system (CNS) or other extrathoracic metastases, which is associated with poor prognosis (2–4). Although first-line treatment is often effective in achieving tumor cytoreduction, the duration of first-line response is typically short, and most patients with extensive-stage disease (ED-SCLC) will relapse within a year, reflecting the need for new therapeutic options (5). Negative prognostic factors include male gender, poor performance status, and high pretreatment lactate dehydrogenase (LDH) level (6, 7). Systemic, platinum-based doublet chemotherapy was the standard of care for first-line treatment of ED-SCLC for several decades (8, 9), with median progression-free survival (PFS) of less than 6 months and typical median overall survival (OS) of approximately 9 to 10 months (10, 11). The recent addition of checkpoint inhibitors to chemotherapy regimens has expanded treatment options (12, 13). However, despite high response rates, median OS remains limited to approximately 1 year (12, 13). Alternative combination strategies are being explored to improve the efficacy of cytotoxic regimens and to exploit the inactivation of TP53 and retinoblastoma tumor-suppressor function, and the resultant dependency on DNA damage response pathways for survival; other recently reported subsets of SCLC may help guide patient selection and further identify a niche for such novel combinations (14–17).

The PARP enzyme family catalyzes the addition of ADP-ribose to cellular molecules, including damaged DNA, thereby facilitating the repair of DNA damage (18, 19). Inhibition of PARP1 has demonstrated synthetic lethality in genetically vulnerable cancer cells and enhances the activity of DNA-targeting anticancer agents (20). Veliparib is a potent, oral PARP1/2 inhibitor that enhances the activity of platinum-based agents and etoposide in preclinical models (21, 22) and in patients with solid tumors (23–27). High

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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Translational Relevance

Despite an evolving treatment landscape for extensive-stage small cell lung cancer (ED-SCLC), overall survival (OS) remains limited to approximately 1 year. PARP inhibitors have been shown to confer synthetic lethality in genetically vulnerable cancer cells, and there is evidence of frequent disruption of DNA damage repair pathways in SCLC. Veliparib is a PARP1/2 inhibitor that has been shown to enhance activity of platinum-based agents, though biomarkers are needed to aid treatment decisions. In this Phase 2 study, we show improved progression-free survival (PFS) with veliparib added to chemotherapy and continued as maintenance, versus chemotherapy with placebo. There was also a trend toward improved PFS with veliparib in patients expressing the candidate biomarker SLFN11, whose expression is associated with PARP inhibitor sensitivity. Although the PFS benefit did not translate to OS benefit (with OS unexpectedly favoring control arm), these data show that veliparib can be safely added to first-line platinum-based chemotherapy and continued as monotherapy in patients with ED-SCLC.

inhibition of PARylation and relatively low PARP-trapping activity of veliparib enable antitumor activity at doses concomitant with full-dose chemotherapies (28).

SCLC is characterized by rapid cell division and overexpression of PARP1 compared with normal lung epithelial cells and other solid tumors, presenting a novel therapeutic target that has demonstrated preclinical activity in SCLC models (29). PARP inhibitors are under investigation for SCLC as monotherapy and in combination with several different drugs in first-line and maintenance settings (30). Studies combining PARP inhibitors with chemotherapy in the first-line setting include the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network (ECOG-ACRIN) Phase 1/2 study of veliparib or placebo in combination with cisplatin and etoposide in patients with ED-SCLC (E2511 study). The regimen was found to be tolerable, and the Phase 2 part of the study met its primary endpoint of improved PFS at a 1-sided alpha level of 0.1 (31, 32). In the maintenance setting following first-line treatment, niraparib is being investigated in combination with temozolomide (NCT03830918; ref. 33). Veliparib in combination with temozolomide has demonstrated significantly improved overall response rate in relapsed or recurrent disease, but not PFS, versus temozolomide alone, and Phase 2 trials of olaparib and talazoparib in combination with temozolomide in this setting are ongoing (34–36).

We previously reported the Phase 1 results of a Phase 1/2 study, which demonstrated an acceptable safety profile and promising antitumor activity for veliparib in combination with carboplatin and etoposide followed by veliparib monotherapy in patients with treatment-naïve ED-SCLC (37). Here, we report results from the Phase 2 part of the study that evaluated veliparib or placebo in combination with carboplatin and etoposide followed by veliparib or placebo maintenance therapy.

Schlafen-11 (SLFN11), a protein that is actively recruited to sites of DNA damage and inhibits homologous recombination (38), is a biomarker that has been evaluated for PARP inhibitor response based on its role in regulating cellular responses to DNA damage and replication stress. The expression of SLFN11 is associated with sensitivity to both chemotherapy and PARP inhibition in SCLC

models (39–41), and its expression was also associated with improved PFS and OS in exploratory subgroup analyses of patients with SCLC receiving veliparib with temozolomide (34). The current study therefore included an exploratory analysis on the correlation of SLFN11 expression with clinical outcomes.

Patients and Methods

Patients

Patients with histologically or cytologically confirmed, treatment-naïve ED-SCLC measurable per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were included. Eligible patients were ≥ 18 years of age, had an ECOG Performance Status (ECOG-PS) of 0 to 1 and had adequate hematologic, renal, and hepatic function. Patients were required to have available formalin-fixed, paraffin-embedded (FFPE) tissue samples of SCLC lesions for review and biomarker analysis.

Exclusion criteria included prior chemotherapy, investigational anticancer agents, or biologic therapy for SCLC and radiotherapy other than single non-target lesion irradiation for symptom palliation ≥ 2 weeks before Cycle 1 Day –2 (first dose of study drug). Patients with known CNS or leptomeningeal metastases were not eligible (CNS imaging was not required before randomization unless symptomatic), nor were patients with a history of seizures within 12 months of Cycle 1 Day –2 or those at increased risk of seizures. Patients who had undergone major surgery within 6 weeks before Cycle 1 Day –2, who had clinically significant and uncontrolled medical conditions, or who had history of another active cancer within the last 3 years (with the exception of *in situ* tumors following curative-intent excision) were also excluded.

Study design and treatment

This Phase 2, randomized, double-blind study was conducted at 49 sites in 12 countries and is registered at clinicaltrials.gov (NCT02289690). Randomization was stratified by baseline LDH and gender. Patients completed a minimum of four 21-day cycles of combination therapy unless disease progression or unacceptable toxicity warranted earlier discontinuation. An additional two cycles of combination therapy (up to a total of six cycles) could be administered at the investigator's discretion. After completion of combination therapy, patients without evidence of disease progression received veliparib 400 mg twice daily (BID) or matching placebo maintenance monotherapy until unacceptable toxicity or disease progression.

Patients were randomized in a 1:1:1 ratio to one of three treatment arms: veliparib throughout group (veliparib plus chemotherapy followed by veliparib maintenance), veliparib combination-only group (veliparib plus chemotherapy followed by placebo maintenance), or control group (placebo plus chemotherapy followed by placebo maintenance therapy). During the combination phase, patients received veliparib at a dose of 240 mg BID, or matching placebo, on Day –2 through 12 for each cycle. Veliparib dosing was based on the recommended Phase 2 dose (RP2D) of the Phase 1 part of the study (37). Chemotherapy consisted of carboplatin (given at an area under the curve of 5 mg/mL/min) on Day 1 and etoposide (100 mg/m²) on Days 1–3 of each 21-day cycle.

This study was conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki. Independent ethics committee/institutional review board approval was obtained before

study commencement at each site. All patients provided written informed consent before participation in the trial.

Endpoints and assessments

The primary efficacy endpoint was PFS from randomization in the veliparib throughout group as compared with the control group. In PFS analyses, all events of disease progression before the initiation of anticancer post-treatment therapy were included, as were events of death before initiation of anticancer therapy for patients who had not experienced disease progression. Secondary endpoints included PFS (veliparib combination-only group vs. control group), objective response rates (ORR), and OS. Tertiary endpoints included duration of response (DOR), and change from baseline in ECOG-PS. Planned efficacy subgroup analyses included OS and PFS according to SLFN11 expression (positive vs. negative). Tumor responses were evaluated according to RECIST v1.1 criteria. Safety evaluations were performed throughout the study with adverse events (AE) and laboratory evaluations assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Biomarker analysis

SLFN11 immunohistochemical (IHC) analysis was performed by an outcomes-blinded central laboratory as previously described (34) using unstained, FFPE sections from patient tumor biopsies. After rehydration, a steamer (pH = 9) was used for antigen retrieval, 3% hydrogen peroxide for quenching intrinsic peroxidase activity, and 5% goat serum for blocking. Sections were then incubated with SLFN11 primary antibody (HPA023030, Sigma-Aldrich). IHC staining was performed with a Bond Max automated staining system (Leica Microsystems Inc.) using previously optimized IHC parameters. A thoracic pathologist then scored each slide for tumor intensity and extent of expression (i.e., proportion, 0%–100%) of cells staining positively for SLFN11 and the overall intensity of SLFN11 staining (0–3+). An H-score was calculated by multiplying extent and intensity of staining (range, 0–300) wherein an H-score ≥ 1 was considered positive, as previously validated (34).

Statistical analyses

Sample size was calculated assuming a median PFS of 5.5 months for the placebo group and a hazard ratio (HR) of 0.63 for the veliparib throughout group versus the control group. A total of 85 PFS events would provide $\geq 80\%$ power to detect a statistically significant difference between the veliparib throughout group and the control group at a one-sided $\alpha = 0.1$. Assuming an HR of 0.75 for the veliparib combination-only group versus the control group, a total of 126 PFS would be observed across the three arms at the time 85 PFS events were observed for the veliparib throughout and control groups. A sample size of approximately 180 patients was calculated to obtain the 126 PFS events. The primary PFS analysis was triggered on September 14, 2018, by which time 136 events were observed across all 3 arms, out of a total sample size of 181; OS data were, as expected, immature at the time of the primary PFS analysis. The final database lock for the study occurred on July 15, 2019 (triggered by the last patient's last on-site visit), at which time the 136 OS events ($\sim 75\%$) required for the pre-specified primary OS analysis had accrued; therefore, survival data were analyzed formally at the time of the final analysis using all events. PFS and OS endpoints were analyzed using Kaplan–Meier methodology, with a stratified log-rank test. HRs and their corresponding 80% confidence intervals (CI) were estimated using a Cox proportional hazards model. ORR and corresponding 80% CI were estimated and

compared between the veliparib throughout and control groups or veliparib combination-only and control groups using a Cochran–Mantel–Haenszel test. PFS, OS, and ORR analyses were stratified by LDH level. In this proof-of-concept Phase 2 study, statistical significance for superiority compared with the control arm was determined by a 2-sided alpha level of 0.2. Demographic, baseline, and efficacy analyses were performed on the intent-to-treat population, and safety analyses were performed on the as-treated population, which comprised all randomized patients who received at least 1 dose of veliparib or placebo.

Results

Patient characteristics

Enrollment began on October 31, 2016, and continued through June 18, 2018. In total, 181 patients with ED-SCLC were randomized to the veliparib throughout group ($n = 61$), veliparib combination-only group ($n = 59$), or placebo group ($n = 61$), and 178 patients received study drug. Patient disposition is outlined in **Fig. 1**. The majority of patients were White, male, and had an ECOG-PS of 1. Baseline characteristics were broadly similar across the treatment arms (**Table 1**), with the exception of the veliparib throughout group, which had a larger proportion of younger patients (Supplementary Fig. S1).

Efficacy

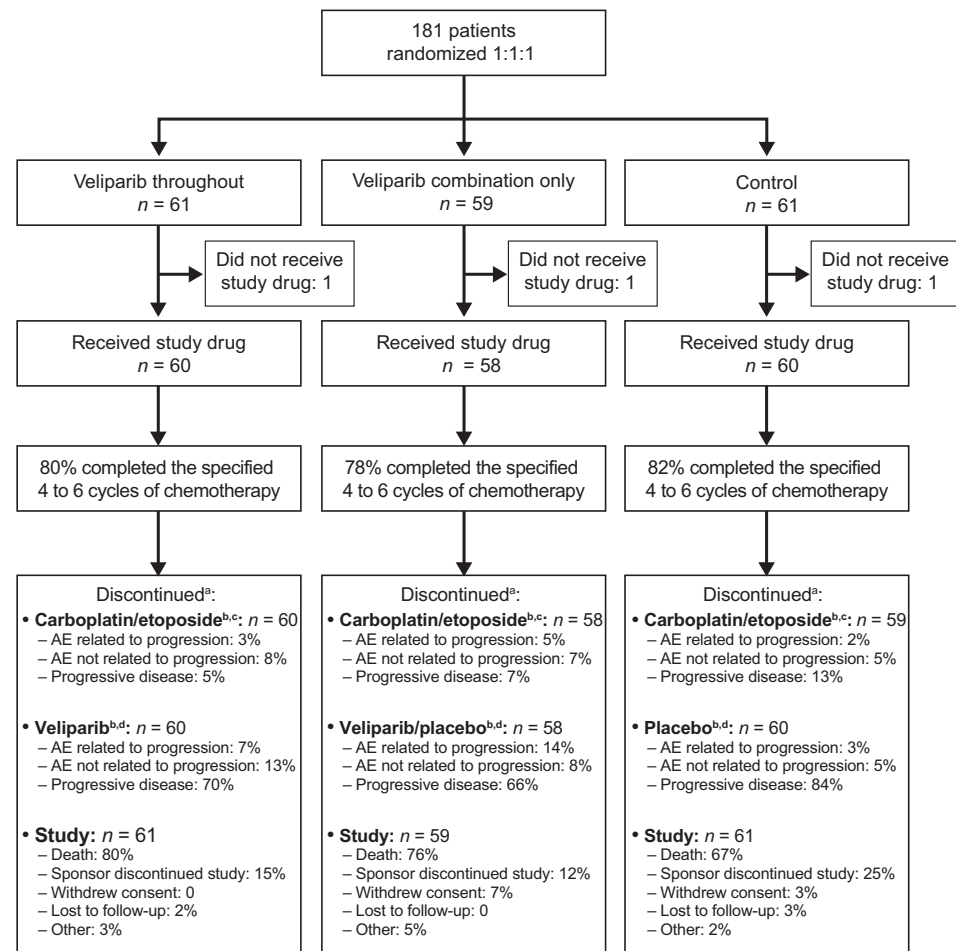
At the primary PFS analysis cutoff date (September 14, 2018), approximately 75% of patients had experienced a PFS event. The primary objective was met: the improvement of PFS in the veliparib throughout group compared with the control group as measured by the stratified log-rank test met the pre-specified significance level of 2-sided $P < 0.2$ (**Fig. 2A**; 2-sided $P = 0.059$; HR, 0.665; 80% CI, 0.503–0.880). There was also a reduction in the hazard of progression or death for the veliparib throughout group compared with the veliparib combination-only group (HR, 0.683; 80% CI, 0.514–0.906), but the statistical difference between veliparib groups was not formally tested (not a protocol-defined objective). No significant difference was observed between the veliparib combination-only and control groups (HR, 0.979; 80% CI, 0.744–1.288; 2-sided $P = 0.924$). Median PFS was similar between the three arms at 5.8, 5.7, and 5.6 months for the veliparib throughout, veliparib combination-only, and control groups, respectively.

There were 136 deaths in the study population at the time of the final database lock (July 15, 2019), which was the required number of events for the pre-specified primary OS analysis. Median OS was 10.1, 10.0, and 12.4 months for the veliparib throughout, veliparib combination-only, and control groups, respectively. There was no statistically significant improvement in the veliparib-containing arms compared with the control group (**Fig. 2B**), and HRs strongly favored the control group at 1.432 (80% CI, 1.092–1.879; 2-sided $P = 0.088$) and 1.460 (80% CI, 1.104–1.931; 2-sided $P = 0.083$) for the veliparib throughout and veliparib combination-only arms, respectively, versus control.

The ORR [complete response (CR) + partial response (PR)] was 77% in the veliparib throughout group, 59% in the veliparib combination-only group, and 64% in the control group. Although numerically higher in the veliparib throughout group, no statistically significant differences in ORR were observed between treatment arms. Objective responses were mostly PRs; CRs were reported in 3.3%, 3.4%, and 3.3% of patients in the veliparib throughout, veliparib combination-only, and control groups, respectively (Supplementary Table S1). Waterfall plots depicting the best percentage of change in each patient's sum of target lesion sizes are presented by treatment arm

Figure 1.

CONSORT diagram. ^a, Reasons for discontinuation reflect the primary reason (one per patient); multiple reasons for discontinuation were reported for some patients. ^b, Only discontinuation due to AEs and progressive disease are shown; does not include discontinuation because of study treatment completion, withdrawal of consent, or other reasons. ^c, Combination phase only. ^d, Combination and maintenance phases.



in Fig. 3; these show a higher proportion of patients with $\geq 50\%$ reduction in target lesion size in the veliparib throughout arm (82%) relative to the veliparib combination-only (60%) and control arms (62%). Median DOR was 4.7, 4.3, and 5.3 months in the veliparib throughout, veliparib combination-only, and control groups, respectively (Supplementary Fig. S2). At 6 months, the percentage of patients with an ongoing response was 38% in the veliparib throughout arm and was 23% in the veliparib combination-only and control arms.

HRs for PFS generally favored veliparib throughout across subgroups defined by key clinical characteristics (Supplementary Fig. S3A), consistent with the overall population. In particular, a trend toward a PFS benefit in the veliparib throughout group was noted for the US and EU subgroups versus the rest of the world, females versus males, ≥ 65 versus < 65 years of age, and former smokers versus current smokers. OS across subgroups was consistent with overall OS, and HRs tended to favor the control group over the veliparib throughout group, particularly for males versus females, high versus low baseline levels of LDH, and < 65 versus ≥ 65 years of age (Supplementary Fig. S3B). Overall, there were fewer patients with progression due to CNS metastases in the control arm ($n = 7$) compared with either of the veliparib arms ($n = 13$ each), and more patients in the veliparib-containing arms had a short interval (< 2 months) between detection of CNS metastases and death; outcomes for these patients are shown in Supplementary Fig. S4.

Shifts in baseline ECOG-PS of 0–1 to ECOG 3 were observed in 7% of patients in the veliparib throughout group and in 5% of those in the veliparib combination-only group. No patients in the control group changed to ECOG 3 or 4.

Biomarker analysis

Sufficient tissue with adequate tumor cellularity was available from 127 patients for SLFN11 IHC analysis. Among tested patients, 69 (54%) were SLFN11 positive. These were evenly distributed across treatment arms with 25 in the veliparib throughout group and 22 each in the veliparib combination-only and control groups (Supplementary Fig. S5).

Within the SLFN11-positive population, median PFS was 7.5 months in the veliparib throughout group ($n = 25$), 5.7 months in the veliparib combination-only group ($n = 22$), and 5.8 months in the control group ($n = 22$); HR for PFS with veliparib throughout versus control was 0.6 (80% CI, 0.36–0.97; 2-sided $P = 0.2$; Fig. 4A). No differences were observed for PFS in patients positive for SLFN11 between the veliparib combination-only and control groups (HR, 1.21; 80% CI, 0.76–1.92; 2-sided $P = 0.7$). Among patients negative for SLFN11, median PFS was 5.7, 5.6, and 5.5 months in the veliparib throughout, veliparib combination-only, and control groups, respectively. No differences in PFS were noted between the veliparib throughout group and the control group (HR, 0.95; 80% CI, 0.54–1.66; 2-sided $P = 0.8$) or the veliparib combination-only and control

Table 1. Baseline characteristics and demographics.

Parameter	Veliparib throughout (n = 61)	Veliparib combination only (n = 59)	Control (n = 61)
Gender, n (%)			
Male	40 (65.6)	38 (64.4)	38 (62.3)
Female	21 (34.4)	21 (35.6)	23 (37.7)
Ethnicity, n (%)			
White	55 (90.2)	51 (86.4)	52 (86.7)
Black or African American	2 (3.3)	1 (1.7)	1 (1.7)
Asian	4 (6.6)	7 (11.9)	7 (11.7)
Missing	0	0	1
Age			
Median (range; years)	62.0 (39.0–77.0)	64.0 (46.0–86.0)	63.0 (37.0–87.0)
<50 years, n (%)	7 (11)	2 (3)	3 (5)
≥50 years, n (%)	54 (89)	57 (97)	58 (95)
<65 years, n (%)	33 (54)	34 (58)	39 (64)
≥65 years, n (%)	28 (46)	25 (42)	22 (36)
Baseline LDH value, n (%)			
≤ULN	24 (39.3)	22 (37.3)	24 (39.3)
>ULN	37 (60.7)	37 (62.7)	37 (60.7)
Baseline ECOG performance, n (%)			
0	21 (35.0)	16 (27.6)	23 (38.3)
1	39 (65.0)	42 (72.4)	37 (61.7)
Missing	1	1	1
Number of metastatic sites, n (%)			
0/1	22 (36.1)	26 (44.8)	20 (32.8)
≥2	39 (63.9)	32 (55.2)	41 (67.2)
Missing	0	1	0
TNM staging at diagnosis, n (%)			
M0	2 (3.3)	3 (5.1)	3 (4.9)
M1	54 (88.5)	51 (86.4)	52 (85.2)
Unknown	5 (8.2)	5 (8.5)	6 (9.8)
SLFN11-positive, n (%)	25 (53)	22 (59)	22 (51)
Tobacco use, n (%)			
Former	31 (50.8)	32 (55.2)	31 (50.8)
Current	29 (47.5)	23 (39.7)	27 (44.3)
Never	1 (1.6)	3 (5.2)	3 (4.9)
Missing	0	1	0

Note: Percentages calculated on non-missing values.

Abbreviation: ULN, upper limit of normal.

groups (**Fig. 4B**; HR, 0.94; 80% CI, 0.55–1.62; 2-sided $P = 0.8$), suggesting that SLFN11-negative patients have similar outcomes independent of veliparib exposure.

Median OS among patients positive for SLFN11 was 10.8 months in the veliparib throughout group, 9.9 months in the veliparib combination-only group, and 15.1 months in the control group. Within the SLFN11-negative population, median OS was 10.3, 12.9, and 12.1 months in the veliparib throughout, veliparib combination-only, and control groups, respectively. Consistent with the overall analysis, there was a trend toward longer OS in the control group compared with the veliparib throughout and the veliparib combination-only groups for both SLFN11-positive and -negative populations (**Fig. 4C and D**).

It should also be noted that no differences were observed for within-group analyses of PFS and OS for SLFN11-positive versus SLFN11-negative populations (veliparib throughout vs. control HR, 0.71; 80% CI, 0.34–1.49; $P_{\text{interaction}} = 0.56$; Supplementary Fig. S6).

Subsequent anticancer therapy

Post-progression survival is known to be highly influenced by post-treatment anticancer therapies, which were received by 61% of patients

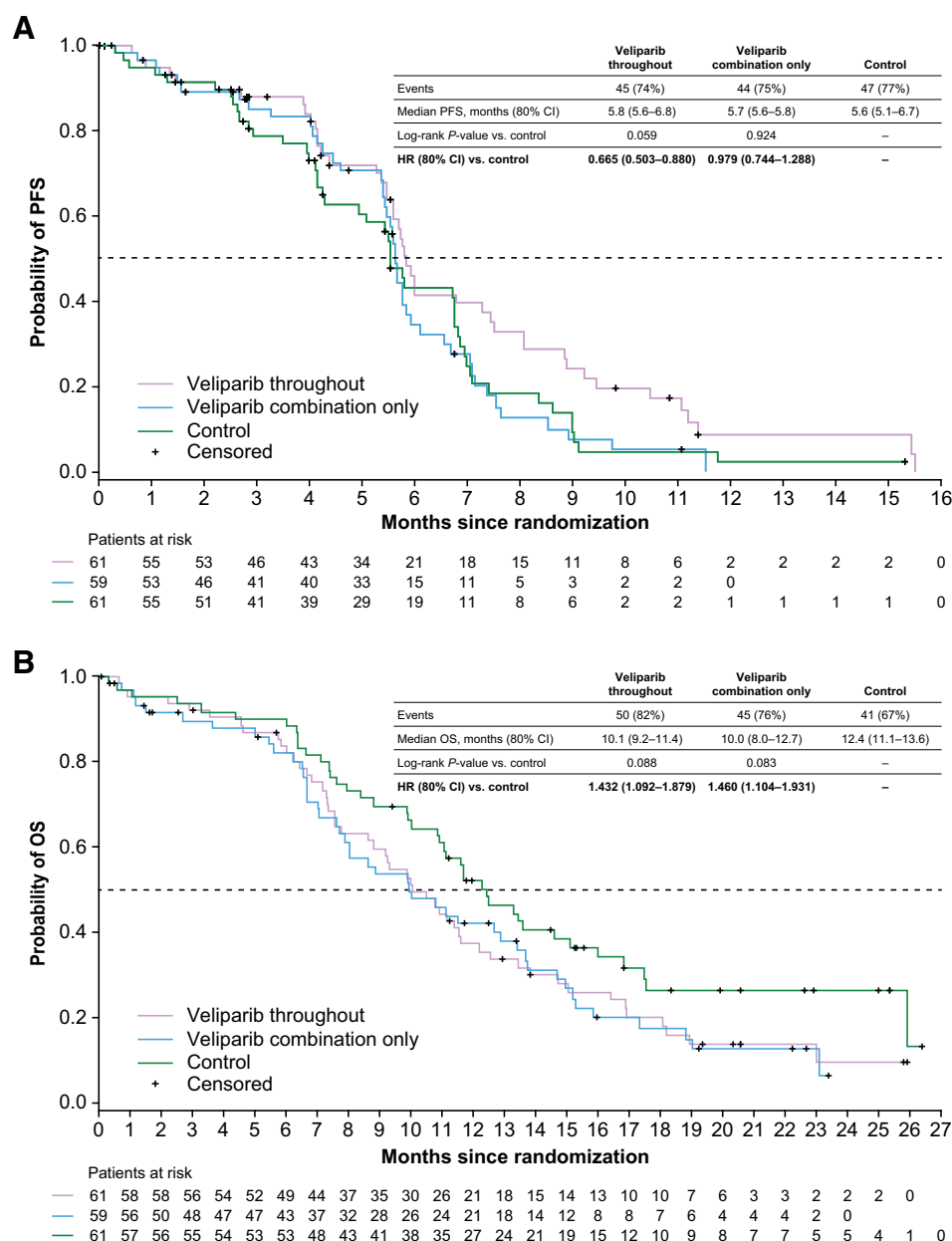
in the control group, 51% in the veliparib throughout group, and 44% in the veliparib combination-only group. The number of patients by treatment arm receiving each systemic post-treatment medication, grouped by therapy type, is shown in Supplementary Table S2. Although infrequent, subsequent immunotherapy was more common in the control group than in the veliparib-containing arms. Post-treatment therapy was initiated earlier relative to randomization in the control group than in the veliparib throughout group, with a median time-to-treatment initiation of 191 (range, 68–679) and 240 days (range, 45–620), respectively.

Treatment exposure

The majority of patients completed the specified 4 to 6 cycles of chemotherapy (80% in the veliparib throughout arm, 78% in the veliparib combination-only arm, and 82% in the control arm; Supplementary Table S2). In the veliparib throughout arm, the median exposure to veliparib in the combination phase was 6.0 cycles; 54% received the maximum of 6 cycles of chemotherapy. In the veliparib combination-only arm, the median exposure to veliparib was 5.5 cycles, with 49% receiving 6 cycles of chemotherapy. In the control arm, median exposure to placebo was 4.5 cycles, and

Figure 2.

Kaplan-Meier curves of PFS (A) and OS (B) for all randomized patients. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.



46% received 6 cycles. The median average daily dose of study drug during the combination phase was 480 mg in all treatment arms (the expected maximum daily dose with 240 mg BID dosing). A total of 127 patients received maintenance therapy (44, 41, and 42 in the veliparib throughout, veliparib combination-only, and control groups, respectively). During the maintenance phase, the median daily dose of study drug was 800 mg (the expected maximum daily dose with 400 mg BID dosing) and the median duration of maintenance therapy was 62 days in the veliparib throughout group, 52 days in the veliparib combination-only group, and 74 days in the control group.

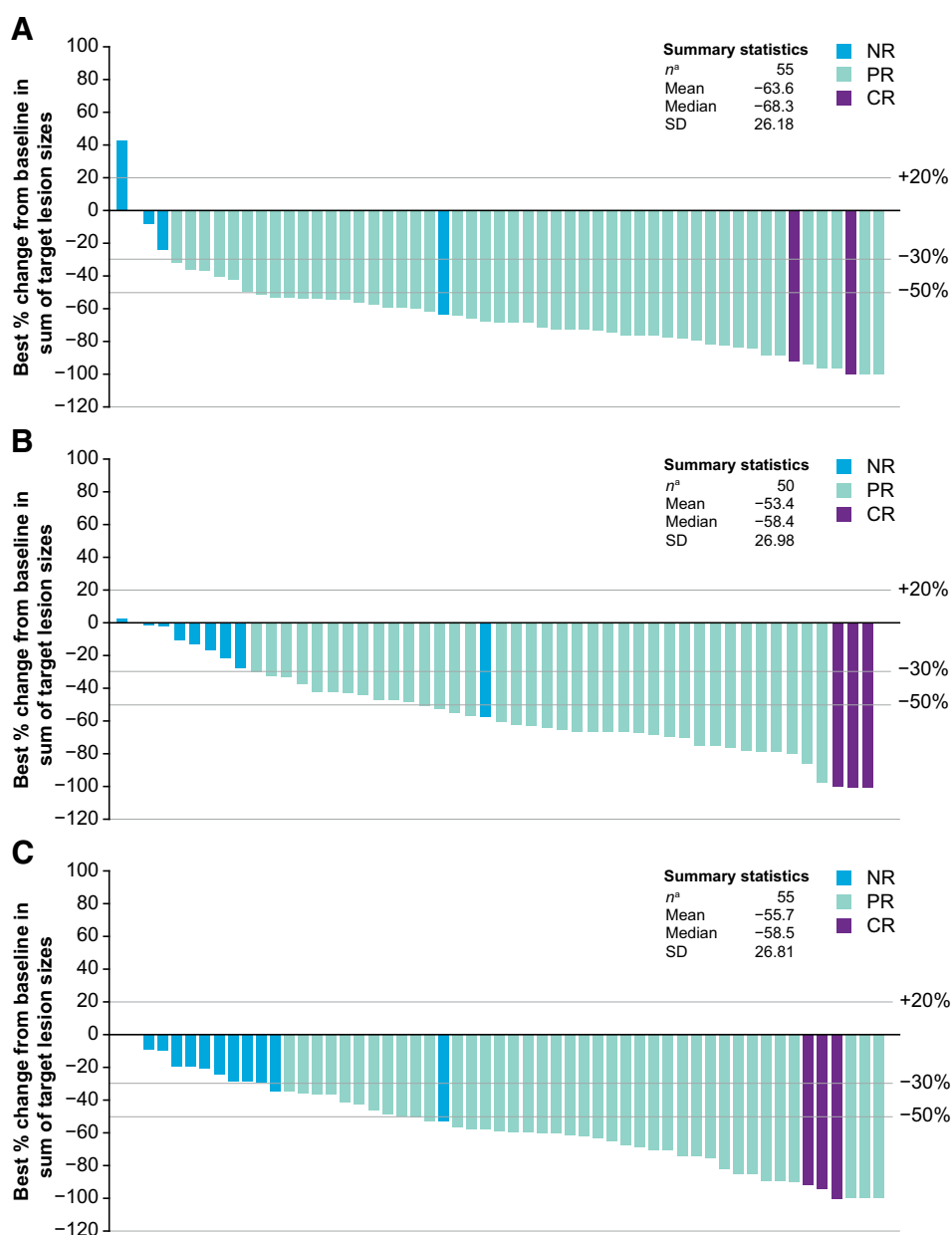
The most common reason for discontinuation of veliparib or placebo was disease progression. Throughout the whole study, 20%, 22%, and 8% of patients in the veliparib throughout, veliparib com-

bination-only, and control groups, respectively, discontinued either veliparib or placebo owing to an AE (Fig. 1). The most common AE leading to veliparib/placebo discontinuation was metastasis to the CNS (3% in the veliparib throughout group, 7% in the veliparib combination-only group, and 0% in the control group; Supplementary Table S3).

Adverse events

Most patients experienced at least 1 AE of any grade (>95% in all three treatment arms; Table 2 and Supplementary Table S4). AEs potentially related to study drug are listed in Supplementary Table S5. Grade 3/4 AEs were experienced by 82%, 88%, and 68% of patients in the veliparib throughout, veliparib combination-only, and control groups, respectively. Furthermore, Grade 3/4 AEs occurred more

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**Figure 3.**

Waterfall plots depicting best percentage of change in each patient's sum of target lesion sizes for the veliparib throughout (A), veliparib combination-only (B), and control groups (C). ^a, Excluding patients without any evaluable postbaseline tumor assessment. The best tumor response is defined as the maximum reduction/minimum increase from baseline in sum of target lesion size. Responses are best overall responses, including unconfirmed. NR, nonresponder (stable disease or progressive disease); SD, standard deviation.

frequently during the combination phase than the maintenance monotherapy phase. Differences of $\geq 10\%$ between the veliparib throughout and veliparib combination-only groups compared with the control group were seen for Grade 3/4 AEs of neutropenia, anemia, thrombocytopenia, and pneumonia (Table 2).

Serious AEs (SAEs) were reported for 55% of patients in the veliparib throughout group, 67% in the veliparib combination-only group, and 45% in the control group. Those reported in $\geq 10\%$ of patients in at least 1 treatment arm were febrile neutropenia (8%, 12%, and 5% of patients in the veliparib throughout, veliparib combination-only, and control groups, respectively), thrombocytopenia (5%, 10%, and 3%), and pneumonia (10%, 2%, and 0%). SAEs occurred more frequently during the combination phase than the maintenance monotherapy phase (43% vs. 30%, 52% vs. 42%, and 37% vs. 19% in the veliparib throughout, veliparib combination-only, and control

groups, respectively; Supplementary Table S4). There were a total of 22 patients who died due to an AE, including 7 in the veliparib throughout group, 10 in the veliparib combination-only group, and 5 in the control group; the most frequent AE leading to death was malignant neoplasm progression, and no fatal AEs were considered treatment related (as assessed by the sponsor).

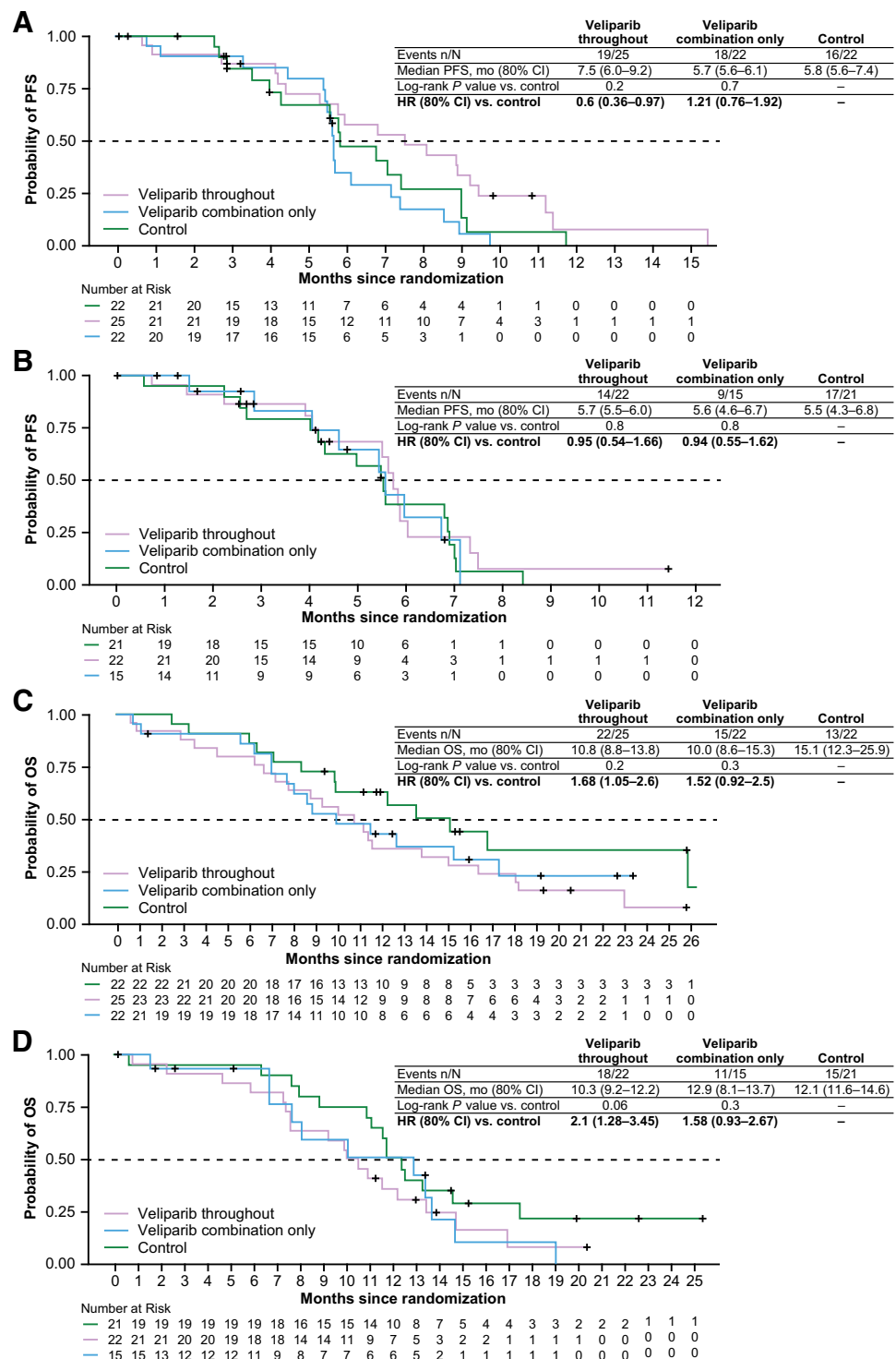
Discussion

This Phase 2 study met its primary endpoint at a 2-sided alpha level of 0.2, demonstrating improved PFS with the addition of veliparib to chemotherapy followed by veliparib maintenance as first-line treatment for ED-SCLC versus chemotherapy alone followed by placebo. The PR rate accounted for the numerically higher ORR in the veliparib throughout group (77% vs. 64% in the control group) and a greater

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Figure 4.

Kaplan-Meier curves of PFS in SLFN11-positive (A) and -negative (B) groups and of OS in SLFN11-positive (C) and -negative (D) groups. CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.



fraction of patients achieving a 50% reduction in measurable tumor burden; however, the ORR difference was not statistically significant. This increase over carboplatin and etoposide response rates were similar to those observed in the Phase 1 part of this study, in which responses occurred in 83% of patients with ED-SCLC who were treated at the RP2D (37).

Curiously, the benefit in PFS and trend for improved radiographic response in the veliparib throughout arm did not translate to OS, which favored the control arm. This group performed outside the observed historical comparator duration by approximately 20%–30% at the median (12.5 months in our study vs. 9 to 10 months historically; refs. 10, 11). The longer duration of OS in the control arm relative to

Table 2. Treatment-emergent AEs occurring at any grade in $\geq 10\%$ of patients in any treatment arm during the entire study period.

	Veliparib throughout (n = 60)		Veliparib combination only (n = 58)		Control (n = 60)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	58 (96.7)	49 (81.7)	57 (98.3)	51 (87.9)	58 (96.7)	41 (68.3)
Neutropenia	38 (63.3)	34 (56.7)	37 (63.8)	32 (55.2)	30 (50.0)	24 (40.0)
Anemia	38 (63.3)	19 (31.7)	38 (65.5)	20 (34.5)	28 (46.7)	10 (16.7)
Nausea	30 (50.0)	5 (8.3)	25 (43.1)	3 (5.2)	21 (35.0)	2 (3.3)
Thrombocytopenia	25 (41.7)	19 (31.7)	29 (50.0)	16 (27.6)	14 (23.3)	3 (5.0)
Alopecia	22 (36.7)	0	17 (29.3)	0	18 (30.0)	0
Decreased appetite	18 (30.0)	1 (1.7)	13 (22.4)	2 (3.4)	14 (23.3)	0
Fatigue	16 (26.7)	4 (6.7)	16 (27.6)	0	10 (16.7)	0
Constipation	14 (23.3)	2 (3.3)	13 (22.4)	0	11 (18.3)	0
Vomiting	14 (23.3)	2 (3.3)	10 (17.2)	1 (1.7)	9 (15.0)	1 (1.7)
Diarrhea	8 (13.3)	0	12 (20.7)	3 (5.2)	12 (20.0)	1 (1.7)
Dyspnea	14 (23.3)	1 (1.7)	10 (17.2)	4 (6.9)	8 (13.3)	1 (1.7)
Headache	10 (16.7)	0	10 (17.2)	0	7 (11.7)	0
Hypomagnesemia	11 (18.3)	3 (5.0)	7 (12.1)	2 (3.4)	9 (15.0)	1 (1.7)
Back pain	9 (15.0)	0	7 (12.1)	0	9 (15.0)	1 (1.7)
Asthenia	9 (15.0)	2 (3.3)	12 (20.7)	4 (6.9)	3 (5.0)	1 (1.7)
Leukopenia	8 (13.3)	5 (8.3)	12 (20.7)	7 (12.1)	3 (5.0)	3 (5.0)
Hypokalemia	5 (8.3)	1 (1.7)	10 (17.2)	5 (8.6)	7 (11.7)	1 (1.7)
Hyponatremia	6 (10.0)	5 (8.3)	10 (17.2)	10 (17.2)	4 (6.7)	1 (1.7)
Cough	6 (10.0)	0	5 (8.6)	0	7 (11.7)	0
Dizziness	5 (8.3)	0	10 (17.2)	1 (1.7)	3 (5.0)	0
Pyrexia	6 (10.0)	0	4 (6.9)	0	8 (13.3)	0
Febrile neutropenia	6 (10.0)	6 (10.0)	7 (12.1)	7 (12.1)	3 (5.0)	3 (5.0)
Malignant neoplasm progression	5 (8.3)	3 (5.0)	6 (10.3)	4 (6.9)	5 (8.3)	4 (6.7)
Edema peripheral	2 (3.3)	0	8 (13.8)	0	5 (8.3)	0
Dyspepsia	7 (11.7)	1 (1.7)	2 (3.4)	0	4 (6.7)	0
Hyperglycemia	1 (1.7)	0	6 (10.3)	1 (1.7)	6 (10.0)	2 (3.3)
Pneumonia	10 (16.7)	6 (10.0)	1 (1.7)	1 (1.7)	1 (1.7)	0
Weight decreased	3 (5.0)	0	2 (3.4)	0	7 (11.7)	1 (1.7)
Atrial fibrillation	3 (5.0)	2 (3.3)	6 (10.3)	1 (1.7)	2 (3.3)	2 (3.3)
Arthralgia	7 (11.7)	0	2 (3.4)	1 (1.7)	0	0
Metastases to CNS	3 (5.0)	3 (5.0)	5 (8.6)	5 (8.6)	0	0

Note: Values in table are n (%).

the investigational arms is unexpected, particularly given the PFS results, and could be attributed to longer post-progression survival time, a measure that has a stronger correlation with OS than PFS in first-line treatment of SCLC and other cancer types (42–44). Despite a lack of effective post-progression therapies for SCLC, the use of such treatments are a confounding factor that can influence post-progression OS outcomes in first-line treatment trials in SCLC (42–44), and may limit data interpretation, particularly if imbalanced between treatment arms. In our study, use of post-treatment therapy was more common in the control arm compared with the veliparib arms. Toxicity, including hematologic toxicities leading to veliparib/placebo discontinuation, was balanced between the treatment arms suggesting that this did not preclude starting subsequent treatments. Although no single factor in our study fully explains the observed OS treatment effect, imbalances in certain prognostic patient characteristics may also have contributed. A slight age imbalance was noted between treatment arms, with the veliparib throughout group having a higher proportion of younger patients. This may have relevance to the OS duration in the control group given the prognostic implications associated with age; although data on this topic are not uniform, some studies have reported better outcomes in older patients compared with their younger counterparts (12, 45). An additional negative OS prognostic

factor is the development of CNS metastases. More patients in the veliparib-containing arms had progression due to CNS metastasis compared with the control arm, which may have contributed to shorter survival duration after disease progression in some of these patients, as CNS metastasis is a known poor prognostic factor for survival in SCLC (3). Notably, patients with known brain metastases were excluded from enrollment in our study, but baseline brain imaging was not required before randomization unless CNS involvement was suspected, which could have led to enrollment of patients with occult brain metastases; in contrast, many recent clinical trials in this patient population require brain scans at study entry and allow enrollment of patients with stable, treated CNS metastases. Limited patient numbers in this proof-of-concept Phase 2 study (~60 patients per treatment arm) also limit interpretation of the data, particularly in subgroup and biomarker analyses. Therefore, the observed OS outcomes are likely attributable to a combination of confounding factors.

No new safety signals were observed for veliparib in combination with carboplatin and etoposide, or as monotherapy. Toxicities were consistent with the known profiles of each drug and were also generally consistent with those typically observed in a patient population with ED-SCLC.

The treatment effect of veliparib added to platinum–etoposide on PFS reached statistical significance both in this study and in the E2511 study in first-line ED-SCLC (32). In the E2511 Phase 2 trial of veliparib (or placebo) combined with cisplatin and etoposide (C/E), veliparib was dosed at 100 mg BID on Days 1–7, which is a lower dose and a less intensive schedule of combination therapy than the current study and did not include veliparib maintenance. Estimated median PFS in the E2511 study was 6.1 and 5.5 months, in favor of the veliparib arm (unstratified HR, 0.75; 1-sided $P = 0.06$; stratified HR, 0.63; 1-sided $P = 0.01$). In contrast with the current study, there was a trend toward improved OS with veliparib plus C/E relative to placebo plus C/E (median 10.3 vs. 8.9 months, respectively), though the difference was not statistically significant (stratified HR, 0.83; 1-sided $P = 0.17$; ref. 32). Notably, the median OS of the veliparib arm of the E2511 study (10.3 months) was comparable with the veliparib-containing arms of the current study (10.1 and 10.0 months in the veliparib throughout and veliparib combination-only groups, respectively).

The ED-SCLC treatment paradigm has evolved with recent data from Phase 3 studies evaluating the addition of checkpoint inhibitors to standard chemotherapy regimens. The IMpower133, CASPIAN, and Keynote-604 studies evaluated the addition of atezolizumab, durvalumab, and pembrolizumab, respectively, to platinum–etoposide regimens. These studies are of clinical importance, not only for evaluating novel therapeutic regimens in SCLC, but also for providing additional benchmarks for expected outcomes in patients receiving standard chemotherapy. In the control arms of these three studies, the median PFS ranged from approximately 4 to 5 months, and the median OS was approximately 10 months (12, 13, 46). Although the median PFS are generally comparable with that in our study, the OS of the chemotherapy control arms in these 3 studies are markedly shorter than that of our study (12.4 months). These results suggest that our control group may have performed better than expected in this patient population with respect to OS, whereas survival in the investigational arms of our study (10 months) was consistent with the observed historical comparator duration. In the IMpower133, CASPIAN, and Italian GOIRC-AIFA FARM6PMFJM studies, the addition of atezolizumab, durvalumab, or bevacizumab, respectively, to platinum–etoposide regimens resulted in improved survival outcomes (11–13). Notably, the median OS of our control group was comparable with that of the investigational arms of IMpower133 and CASPIAN. The reasons for this discrepancy cannot be fully explained but may be influenced by differences in baseline and prognostic factors, which inevitably confound any cross-trial comparisons. It is also pertinent that subsequent immunotherapy, although infrequent, was used more in the control group compared with the veliparib treatment groups in this study.

Biomarkers are of emerging clinical significance in guiding treatment selection in SCLC, and previous preclinical and clinical studies have associated SLFN11 expression with sensitivity to PARP inhibitors in SCLC (34, 39, 41). We found that in patients treated with veliparib plus chemotherapy followed by veliparib maintenance, there was a trend toward improved PFS in patients positive for SLFN11 (H-score ≥ 1) compared with patients negative for SLFN11 (H-score < 1), although it should be noted that small sample sizes and wide CIs limit interpretation of this result. However, there was no significant difference in OS between treatment arms for patients positive for SLFN11. This contrasts with a previous exploratory analysis of veliparib plus temozolomide for relapsed or refractory SCLC (although this included just 23 SLFN11-positive patients). However, it is worth noting that, unlike platinum chemotherapy, SLFN11 is not predictive of temozolomide benefit, and

therefore any predictive biomarker effect may have clearer in this study without the additional effect of chemotherapy benefit (34, 41). The current data support SLFN11 as a potential treatment effect predictive biomarker for PFS with veliparib; however, they fail to explain the uncoupling of the PFS treatment effects with observed OS results in the current study. Although we observed a balanced distribution of SLFN11 signal between treatment arms, this subanalysis was exploratory in nature and the study was not powered or stratified according to SLFN11 status, further limiting the interpretation of these data. In addition to their association with response to PARP inhibitors, *in vitro* data demonstrated an association between SLFN11 expression and sensitivity to DNA-damaging agents, including platinum, across a range of tumor types (47). As all treatment arms in the current study received platinum-based chemotherapy, the observed trend for an association of SLFN11 with veliparib PFS benefit is notable. As expected from prior studies with SLFN11, there was a trend for veliparib benefit in SLFN11-positive patients. Beyond first-line treatment, the predictive value of SLFN11 status remains an area of active investigation in SCLC.

PARP inhibitors are being investigated in a variety of settings in SCLC following promising preclinical studies that demonstrated the sensitivity of SCLC cell lines to PARP inhibition (22, 29, 48). However, this has not been reflected in the clinical setting where inconsistent results mean that the potential for survival benefit has not, to date, borne out (31–36, 49, 50), despite the genomic instability and high tumor mutational burden that characterize SCLC tumors (15, 51). Possible reasons for this include inability to achieve suitably high doses of drugs and lack of patient selection. Studies of PARP inhibitors in SCLC to date have not investigated patient selection for PARP inhibitors or have been underpowered to explore candidate biomarkers due to small patient numbers and/or limited tissue samples. However, increasing understanding of the heterogeneity of SCLC suggests that SCLC subtypes, defined by achaete-scute homologue 1 (ASCL1), neurogenic differentiation factor 1 (NEUROD1), POU class 2 homeobox 3 (POU2F3), and an inflamed gene signature, may have a role in guiding patient selection for specific therapies, including PARP inhibitors (16, 17). Further studies on these emerging biomarkers in combination with SLFN11 are needed to understand patient stratification and identify the appropriate patient subtypes for PARP inhibition.

In summary, we show that veliparib added to first-line platinum-based chemotherapy and continued as monotherapy in patients with ED-SCLC resulted in improved PFS relative to chemotherapy plus placebo; there was no sustained benefit of veliparib observed in combination with chemotherapy without maintenance monotherapy. This PFS treatment effect of veliparib did not translate to an OS benefit, and OS favored the control arm. In the future, correlative biomarker analyses may help to identify patient subtypes appropriate for PARP inhibitor therapy in SCLC and may guide combination partner selection and treatment sequencing. Further study will be required to fully elucidate the role of biomarkers in patient selection and treatment decisions.

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