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A Phase I Dose-Escalation Study of Veliparib Combined with Carboplatin and Etoposide in Patients with Extensive-Stage Small Cell Lung Cancer and Other Solid Tumors

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Abstract

Purpose: This study examined safety, pharmacokinetics, and efficacy of veliparib, a PARP inhibitor, combined with carboplatin and etoposide in patients with extensive-stage (ED) small cell lung cancer (SCLC) and other solid tumors.

Patients and Methods: The 3 + 3 design was used for dose escalation of oral veliparib in combination with carboplatin (AUC 5 on day 1) and etoposide (100 mg/m^2 on days 1–3) in 21-day cycles. Veliparib dose was explored from 80 to 240 mg b.i.d. on 7-day, 14-day, or continuous schedules. Patients without disease progression continued on maintenance monotherapy (veliparib 400 mg b.i.d.) until disease progression or unacceptable toxicity.

Results: Thirty-nine patients were enrolled to determine the recommended phase II dose of 240 mg veliparib for 14 days combined with carboplatin and etoposide based on long-term tolerability. Dose-limiting toxicity occurred in 1 patient (grade 2 toxic motor polyneuropathy) at veliparib 240 mg b.i.d. for 7 days. Most common adverse events related to veliparib were nausea (39%), fatigue (39%), and hematologic toxicities. Continuous dosing of veliparib 240 mg b.i.d. with carboplatin and etoposide resulted in excessive chemotherapy dose delays due to hematologic toxicity (grade 3/4 neutropenia/thrombocytopenia). Etoposide pharmacokinetics was not affected by veliparib. Confirmed responses occurred in 17 of 39 (44%) and 16 of 25 (64%) of all enrolled and ED SCLC patients, respectively. At the RP2D, confirmed responses occurred in 6 of 13 (46%) and 5 of 6 (83%) of all enrolled and ED SCLC patients, respectively.

Conclusions: Veliparib (240 mg b.i.d. 14 days) plus carboplatin/etoposide can be safely combined. Phase II of this study is ongoing in first-line patients with ED SCLC.

Introduction

The majority of small cell lung cancer (SCLC) cases are diagnosed as extensive-stage disease (ED), for which there is a poor prognosis and no curative treatment (1). Carboplatin in combination with etoposide has been extensively tested in randomized trials in SCLC and has shown efficacy in treatment of ED SCLC (2, 3). Incorporation of novel targeted agents, such as PARP inhibitors, that potentially enhance the efficacy of standard chemotherapy warrant exploration.

PARP1 is overexpressed in SCLC tumors, and PARP inhibitors have shown activity in SCLC cell lines and animal models (4–6). Upon DNA damage induced by various chemotherapeutic agents, PARPs 1 and 2 bind to the damaged DNA sites and further recruit repair protein complexes. Inhibition of PARP results in less efficient DNA repair following DNA-damaging insults.

Veliparib is an orally bioavailable PARP 1/2 inhibitor shown to enhance the antitumor activity of platinum-based agents and etoposide against SCLC in preclinical models (7, 8). Veliparib is well tolerated as monotherapy (9), and combinations of veliparib with platinum-based and other cytotoxic chemotherapy are feasible (10–15). Single-agent PARP inhibitors are efficacious in tumor types with genetic defects of DNA repair (e.g., in *BRCA* and functionally related loci), or in platinum-sensitive ovarian cancer where such genetic defects are frequent (16–18). The underlying reason for SCLC platinum sensitivity may be different from that of ovarian cancer, given the BRCA loss of function is not frequently observed in SCLC (19). In SCLC tumors where PARP1

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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

This phase I dose-escalation study is the first-in-human report of the safety and tolerability of administering veliparib, a PARP inhibitor, combined with carboplatin and etoposide chemotherapy in patients with extensive-stage small cell lung cancer or other advanced/metastatic solid tumors. Veliparib at a dose of 240 mg b.i.d. as 14-day treatment during combination therapy had an acceptable safety profile and significant antitumor activity. However, continuous dosing of veliparib 240 mg b.i.d. with carboplatin and etoposide resulted in excessive chemotherapy dose delays due to hematologic toxicity.

is overexpressed, proteomic analysis showed that PARP1 inhibition has activity in preclinical models (4, 6) and in a subset of SCLC patients in which a PARP inhibitor was combined with the DNA alkylator temozolomide (20). In addition, due to frequently loss of retinoblastoma protein in SCLC, E2F is expressed leading to activation of several E2F targets including DNA repair pathways (19). Therefore, inhibition of DNA repair with veliparib in combination with contemporaneous DNA damage by carboplatin was evaluated based on these studies. In a phase I study, Owonikoko and colleagues (12) showed promising preliminary efficacy of veliparib plus cisplatin and etoposide, with partial responses (PR) or complete responses (CR) in 5 of 7 patients with ED SCLC. Thus, we aimed to evaluate the safety, feasibility, and preliminary efficacy of veliparib in combination with carboplatin and etoposide in patients with tumors for which this treatment was considered appropriate with a special focus in ED SCLC.

Biomarkers for SCLC have been proposed to associate with clinical responses to therapy (4). c-Kit is expressed in 37% of SCLC patients and is related to poor prognosis (21). E2F1 has an important role in the induction of apoptosis in response to DNA damage, with increased levels of E2F1 triggering invasion and tumor growth. PARP1 has been identified as an important coactivator of E2F1 (22). SLFN11 was also shown to correlate with PARP inhibitor activity in SCLC (5, 20, 23). Expression of candidate biomarkers was explored in this study.

Patients and Methods

Patients

Patients with histologically or cytologically confirmed advanced or metastatic solid tumors for which carboplatin and etoposide treatment was considered appropriate were included. Eligible patients were $\geq$18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and had adequate hematology, blood chemistry, bone marrow, liver, and renal functions.

Patients were not eligible if they received prior anticancer therapy other than: hormonal, nonmyelosuppressive, biological, targeted, or immune therapy (completed $\geq$ 4 weeks prior to cycle 1 day -2); 1 line of cytotoxic chemotherapy (including carboplatin, cisplatin, etoposide, paclitaxel, doxorubicin, cyclophosphamide, methotrexate; completed $\geq$ 4 weeks prior to cycle 1 day -2); adjuvant/neoadjuvant radiotherapy (completed $\geq$ 12 months prior to cycle 1 day -2, with field not involving >10% of bone marrow reserve). Patients with central nervous system or leptomeningeal metastases were not eligible (brain imaging was performed if brain metastases were suspected), nor were patients with a history of seizures within 12 months of cycle 1 day -2 or at increased risk of seizures.

Study design and treatment

This phase I dose-escalation study was conducted at 12 sites globally and is registered at Clinicaltrials.gov, number NCT02289690. Primary objectives were to establish the MTD, recommended phase II dose (RP2D) for veliparib combined with carboplatin and etoposide, and to evaluate the pharmacokinetic (PK) interaction between veliparib and etoposide. Secondary objectives were to evaluate the safety of maintenance veliparib monotherapy at 400 mg b.i.d. continuously in patients completing 4 cycles of carboplatin, etoposide, and veliparib without evidence of disease progression.

Dose escalation followed a standard 3 + 3 design, with a condition applied for dose level 1, which allowed 3 additional patients to be entered in the dose level 1 if 2 of 6 initial patients experienced dose-limiting toxicities (DLT); the dose-escalation decision depended on review of DLTs and discussion with investigators. A minimum of 3 evaluable patients were enrolled at each dose level. Dose-escalation decisions were made following the completion of the DLT observation period (cycle 1 day -2 to predose cycle 2 day 1) for the evaluable patients in the intended cohort size. The MTD was defined as the maximum dose at which less than 2 of 6 or $\leq$2 of 9 patients experienced a DLT during the DLT observation period.

The veliparib starting dose and schedule was 80 mg b.i.d. orally administered on days -2 to 5 (7-day schedule) during cycles 1, 3, and 4 combined with intravenous infusions of carboplatin (AUC 5 mg/mL•min) on day 1 and etoposide (100 mg/m^2) on days 1 to 3 during 21-day cycles. Prespecified veliparib dose-escalation cohorts consisted of 80, 120, 160, and 200 mg.

If the MTD of the 7-day schedule was not reached at $\leq$200 mg b.i.d. veliparib dose level, veliparib administration in a 14-day schedule (days -2 to 12) and/or a continuous schedule (days -2 to 19) in combination with carboplatin and etoposide could be explored. Additional cohorts could be enrolled at higher veliparib doses based on the number of DLTs (described below) observed during the first 21 days in the current cohort, the cumulative toxicity rate at that dose combination, upon investigators agreement and considering not exceeding >50% (or corresponding by protocol) of the dose from previous cohort level. For phase I patients receiving noncontinuous dosing, veliparib in cycle 2 was administered on days 2 to 5 or days 2 to 12 depending on the dosing schedule to allow for evaluation of potential impact of veliparib on etoposide kinetics. Upon completion of 4 cycles of combination therapy, patients without evidence of disease progression continued on maintenance monotherapy of veliparib 400 mg b.i.d. until disease progression or unacceptable toxicity. This dose has been previously established for veliparib monotherapy (8, 24).

This study was conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki. The human investigations were performed after approval by an Institutional Review Board and in accordance with an assurance filed with and approved by the U.S.

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Department of Health and Human Services. All patients provided written-informed consent before participation in the trial.

Safety and tolerability

Safety analysis was conducted for all patients who received at least 1 dose of veliparib. Treatment-emergent adverse events (TEAEs) were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 and evaluated throughout the course of the study for evidence of acute, delayed, or cumulative toxicities.

DLTs were defined as any of the following TEAEs considered to be related to veliparib that occurred during the first 21-day cycle: grade 4 thrombocytopenia, grade 4 neutropenia, grade 3 febrile neutropenia with fever lasting more than 7 days, or grade 4 febrile neutropenia of any duration, occurring during cycle 1 and associated with treatment delay of more than 14 days in initiating cycle 2 chemotherapy; grade $\geq$3 nonhematologic toxicity that increased at least 2 grade levels from baseline (excluding nausea and vomiting lasting $\leq$48 hours or inadequately treated, electrolyte abnormalities resolving within $\leq$24 hours, hypersensitivity reactions, or alopecia); grade 2 nonhematologic toxicity that increased at least 2 grade levels from baseline and required a treatment delay of more than 14 days in initiation of cycle 2; and any toxicity that increased at least 2 grade levels from baseline and required at least 1 of: dose modification within cycle 1 or omission of carboplatin, more than 1 daily etoposide dose, or >30% veliparib doses in cycle 1.

All patients were monitored for DLTs from cycle 1 day -2 to predose on cycle 2 day 1. The RP2D was determined by the rate of DLTs and overall tolerability of veliparib plus carboplatin and etoposide.

Serious AEs were those TEAEs that, in the opinion of investigator, were life-threatening, required hospitalization or prolongation of hospitalization, caused persistent or significant disability/incapacity or congenital anomaly, were an important medical event requiring medical or surgical intervention to prevent serious outcome, or resulted in death not related to ED SCLC.

Pharmacokinetics

Blood samples for PK analysis were collected at the following time points for veliparib on cycle 1 day 1: 0 hour (predose), and at 1, 2, 3, 5, 8, and 24 hour(s) postdose. Blood samples for etoposide PK analysis were collected on cycle 1 day 1 when coadministered with veliparib and carboplatin, and on cycle 2 day 1 coadministered with carboplatin but in the absence of veliparib at 55 minutes (5 minutes before the end of infusion) and 3, 5, 8, and 24 hours after dose. Veliparib and etoposide plasma concentrations were determined using liquid chromatography with tandem mass spectrometric detection with a lower limit of quantitation 1.05 ng/mL and 160 ng/mL, respectively. Veliparib and etoposide PK parameters were estimated using noncompartmental methods.

Efficacy

Objective response rate (ORR: confirmed CR or PR) was assessed by the investigator using RECIST version 1.1 and was evaluated in patients with at least 1 measurable lesion at baseline.

Progression-free survival (PFS) was defined as the number of days from the date of patient randomization to the date of earliest disease progression or death of all causes. Radiographic tumor assessments for response were conducted by CT scanning at baseline, every 6 weeks from cycle 1 day–2 for the first 24 weeks, and then every 9 weeks until disease progression (radiographic progression per RECIST version 1.1 or clinical disease progression).

Time to response (for all patients with objective response) was defined as the number of days from the date of the first dose to the date of the first CR or PR. Duration of response (for all patients with response CR or PR) was defined as the number of days from the date of the first CR or PR to the earliest documentation of radiographic PD or death of all causes. If a patient is still responding, then the patient's data were censored at the date of the patient's last available disease assessment (radiographic or clinical).

Biomarker analysis

Tumor macrodissection and nucleic acid isolation. Formalin-fixed, paraffin-embedded archival tumor samples (pretreatment) were analyzed. Tumor RNA was obtained from macrodissected tumors to ensure >50% tumor content. The AllPrep Kit (Qiagen) was used for nucleic acid isolation.

Library preparation and sequencing. Integrity of isolated RNA was performed using an Agilent bioanalyzer and quantitated using picogreen. Library preparation was performed with 1 to 50 ng of total RNA. ds-cDNA was prepared using the SeqPlex RNA Amplification Kit (Sigma). cDNA was blunt ended, had an adenosine base added to the 3′ ends, and then had Illumina sequencing adapters ligated to the ends. Ligated fragments were then amplified for 12 cycles using primers incorporating unique index tags. Fragments were sequenced on Illumina HiSeq-2500 or HiSeq-3000 using single reads extending 50 bases; 25 to 30 M reads per library were targeted.

Data acquisition and processing. RNA-seq reads were aligned to the Ensembl release 76 assembly with STAR v2.0.4b. Gene counts were derived from the number of uniquely aligned unambiguous reads by Subread:featureCount v1.4.5. Transcript counts were produced by Sailfish v0.6.3. Sequencing performance was assessed for total number of aligned reads, total number of uniquely aligned reads, genes and transcripts detected, ribosomal fraction known junction saturation, and read distribution over known gene models with RSeQC v2.3. Individual gene expression levels were examined for their association with clinical outcome; these genes of interest (n = 34) included *BRCA1*, *BRCA2*, *SLFN11*, *PARP1*, *E2F1*, *CKIT*, and Byers DNA-damaging signature genes (4).

Statistical analyses

Toxicity data were tabulated to assess DLTs and the MTD. All patients who received at least 1 dose of study medication were included in the safety assessment. Descriptive statistics were used for demographics and safety. For biomarkers data, a 2-sided group t test was used to compare RNA gene expression with clinical outcome measures. For all statistical analyses, significance was determined using a 2-sided P value $\leq$0.05, unless otherwise stated. The data cutoff for analysis of safety and efficacy results was December 8, 2017. The sample size of patients required for dose escalation was determined by the toxicities observed as the trial progressed. The Kaplan–Meier method was used to estimate PFS.

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Results

Patient characteristics

As of December 8, 2017, 39 patients were included in this trial. These patients had either ED SCLC ($n = 25$) or other solid tumors [$n = 14$; gastrointestinal neuroendocrine ($n = 4$), large cell neuroendocrine carcinoma of the lung ($n = 3$), pancreatic ($n = 1$), neuroendocrine unspecified ($n = 1$), adenoid cystic carcinoma of the parotid gland ($n = 1$), esthesioneuroblastoma of the nose ($n = 1$), squamous cell carcinoma of the penis ($n = 1$), metastasis in sinus cavernosum ($n = 1$), and mediastinum of high-grade neuroendocrine origin ($n = 1$)]. All patients were evaluable for safety, DLT, and efficacy.

Patient demographics and clinical characteristics are shown in Table 1. Eight patients had received prior oncology therapies (3 patients with ED SCLC and 5 patients with other solid tumors). Of 25 ED SCLC patients, only 1 patient (at 80 mg b.i.d. veliparib) had received prior cisplatin and etoposide. Three patients with other solid tumors had received prior cisplatin, and 2 of these also received prior etoposide.

Treatment exposure and safety

Veliparib dose could be escalated up to 240 mg b.i.d. in a 7-day schedule. The MTD for the 7-day schedule was not reached. Consequently, veliparib was further explored in a 14-day and continuous schedules. DLT occurred in 1 patient, a grade 2 toxic motor polyneuropathy (loss of sphincter function) associated with grade 3 fatigue, grade 3 febrile neutropenia, grade 2 generalized pain, and grade 1 hypomagnesemia, at veliparib dose of 240 mg b.i.d. for 7days (Table 2). All events resolved within 10 days of onset.

During continuous dosing of veliparib 240 mg b.i.d. with carboplatin and etoposide, all patients ($n = 4/4$) reported grade 3/4 neutropenia, and 75% of patients ($n = 3/4$) reported grade 3/4 thrombocytopenia (Table 3A); this level of toxicity at the highest dose was not acceptable. Continuous dosing of veliparib 240 mg b.i.d. with carboplatin and etoposide resulted in excessive carboplatin and etoposide dose delays (Table 2) due to hematologic toxicity (the highest-grade AEs in patients with dose delays were grade 3 or grade 4 neutropenia and grade 3 thrombocytopenia) and did not support administration of full-dose chemotherapy. The RP2D for veliparib was determined to be 240 mg b.i.d. for 14 days with carboplatin (AUC 5 mg/mL•min) on day 1 and etoposide (100 mg/m^2) on days 1 to 3 during 21-day cycles for 4 cycles.

Table 1. Patient demographic and baseline clinical characteristics

Characteristic, *n* (%)		All patients ($n = 39$)	RP2D cohort[a] ($n = 13$)
Age, y	Median (range)	62 (43–79)	66 (52–72)
Gender	Female	13 (33%)	4 (31%)
	Male	26 (67%)	9 (69%)
Tumor type	ED SCLC	25 (64%)	6 (46%)
	Other solid tumors	14 (36%)	7 (54%)
ECOG PS	Grade 0	15 (39%)	3 (23%)
	Grade 1	24 (62%)	10 (77%)
Prior therapies	Any prior oncology medication	8 (21%)	2 (15%)
	Carboplatin	1 (3%)	0
	Cisplatin	4 (10%)	1 (8%)
	Etoposide	3 (8%)	0

[a]RP2D of 240 mg veliparib b.i.d. as 14-day treatment.

Table 2. Overview of TEAEs during combination cycles

N (%)	80 mg-7 d b.i.d. ($n = 4$)	120 mg-7 d b.i.d. ($n = 3$)	160 mg-7 d b.i.d. ($n = 4$)	200 mg-7 d b.i.d. ($n = 3$)	240 mg-7 d b.i.d. ($n = 8$)	240 mg-14 d b.i.d. ($n = 13$)	240 mg-cont b.i.d. ($n = 4$)	Total ($n = 39$)
Grade 3 or 4 AE	4 (100%)	3 (100%)	4 (100%)	3 (100%)	7 (88%)	13 (100%)	4 (100%)	38 (97%)
Serious AE	3 (75%)	1 (33%)	3 (75%)	2 (67%)	3 (38%)	5 (39%)	3 (75%)	20 (51%)
AE leading to veliparib reduction or interruption	2 (50%)	1 (33%)	3 (75%)	2 (67%)	4 (50%)	7 (54%)	3 (75%)	22 (56%)
AE leading to carboplatin reduction or interruption	1 (25%)	1 (33%)	0	1 (33%)	0	5 (39%)	2 (50%)	10 (26%)
AE leading to etoposide reduction or interruption	2 (50%)	1 (33%)	0	1 (33%)	2 (25%)	5 (39%)	2 (50%)	13 (33%)
DLT	0	0	0	0	1 (13%)[a]	0	0	1 (3%)
Dose delays[b]	1 (25%)	2 (67%)	1 (25%)	0	1 (13%)	4 (31%)	1 (25%)	10 (26%)

[a]Toxic motor polyneuropathy (grade 2).

[b]The highest-grade AEs in patients with dose delays (by cohort): 80 mg-7 d b.i.d. (grade 2 fatigue, $n = 1$); 120 mg-7 d b.i.d. (grade 3 thrombocytopenia, $n = 1$; grade 3 anemia, $n = 1$); 160 mg-7 d b.i.d. (grade 3 anemia and grade 3 myocardial infarction in same patient, $n = 1$); 240 mg-7 d (grade 2 decreased appetite, $n = 1$); 240 mg-14 d (grade 3/4 neutropenia, $n = 3$; grade 3/4 thrombocytopenia and grade 3 febrile neutropenia and grade 3 fatigue/decreased appetite in same patient, $n = 1$); 240 mg-cont (grade 3/4 neutropenia and grade 3 thrombocytopenia in same patient, $n = 1$).

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Table 3. Veliparib-related AEs of all grades in ≥20% of all patients or grade 3/4 in ≥10% of all patients during (A) combination therapy and (B) maintenance monotherapy

A

	80 mg b.i.d.-7 d (*n* = 4)		120 mg b.i.d.-7 d (*n* = 3)		160 mg b.i.d.-7 d (*n* = 4)		200 mg b.i.d.-7 d (*n* = 3)		240 mg b.i.d.-7 d (*n* = 8)		240 mg b.i.d.-14 d (*n* = 13)		240 mg b.i.d.-cont (*n* = 4)		Total (*n* = 39)	
***N* (%)**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**
Neutropenia[a]	0	0	1 (33%)	1 (33%)	2 (50%)	2 (50%)	1 (33%)	1 (33%)	4 (50%)	3 (38%)	11 (85%)	11 (85%)	4 (100%)	4 (100%)	23 (59%)	22 (56%)
Thrombocytopenia[b]	0	0	1 (33%)	1 (33%)	0	0	0	0	3 (38%)	2 (25%)	8 (62%)	7 (54%)	3 (75%)	3 (75%)	15 (39%)	13 (33%)
Fatigue	2 (50%)	0	3 (100%)	1 (33%)	1 (25%)	0	2 (67%)	0	3 (38%)	1 (13%)	3 (23%)	1 (8%)	1 (25%)	1 (25%)	15 (39%)	4 (10%)
Nausea	1 (25%)	1 (25%)	2 (67%)	0	0	0	1 (33%)	0	4 (50%)	0	6 (46%)	0	1 (25%)	0	15 (39%)	1 (3%)
Anemia	0	0	1 (33%)	1 (33%)	1 (25%)	1 (25%)	1 (33%)	1 (33%)	4 (50%)	2 (25%)	4 (31%)	2 (15%)	2 (50%)	1 (25%)	13 (33%)	8 (21%)
Leukopenia[c]	0	0	0	0	1 (25%)	0	1 (33%)	1 (33%)	2 (25%)	2 (25%)	2 (15%)	2 (15%)	2 (50%)	1 (25%)	8 (21%)	6 (15%)
Decreased appetite	1 (25%)	0	2 (67%)	0	0	0	0	0	1 (13%)	0	3 (23%)	1 (8%)	1 (25%)	0	8 (21%)	1 (3%)
Alopecia	1 (25%)	0	0	0	0	0	1 (33%)	0	1 (13%)	0	4 (31%)	0	1 (25%)	0	8 (21%)	0
Febrile neutropenia	1 (25%)	1 (25%)	0	0	0	0	1 (33%)	1 (33%)	1 (13%)	1 (13%)	2 (15%)	2 (15%)	1 (25%)	1 (25%)	6 (15%)	6 (15%)

B

	80 mg b.i.d.-7 d (*n* = 2)		120 mg b.i.d.-7 d (*n* = 3)		160 mg b.i.d.-7 d (*n* = 3)		200 mg b.i.d.-7 d (*n* = 1)		240 mg b.i.d.-7 d (*n* = 4)		240 mg b.i.d.-14 d (*n* = 10)		240 mg b.i.d.-cont (*n* = 2)		Total (*n* = 25)	
***N* (%)**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**	**All grade**	**G3/4**
Neutropenia[a]	1 (50%)	1 (50%)	1 (33%)	1 (33%)	2 (67%)	2 (67%)	0	0	3 (75%)	1 (25%)	10 (100%)	9 (90%)	2 (100%)	2 (100%)	19 (76%)	16 (64%)
Thrombocytopenia[b]	1 (50%)	0	1 (33%)	1 (33%)	1 (33%)	0	0	0	2 (50%)	1 (25%)	7 (70%)	3 (30%)	1 (50%)	0	13 (52%)	5 (20%)
Nausea	1 (50%)	1 (50%)	2 (67%)	0	0	0	0	0	2 (50%)	0	5 (50%)	0	0	0	10 (40%)	1 (4%)
Fatigue	1 (50%)	0	3 (100%)	1 (33%)	1 (33%)	0	1 (100%)	0	1 (25%)	0	2 (20%)	1 (10%)	0	0	9 (36%)	2 (8%)
Decreased appetite	1 (50%)	0	2 (67%)	0	0	0	0	0	1 (25%)	0	3 (30%)	1 (10%)	1 (50%)	0	8 (32%)	1 (4%)
Anemia	0	0	1 (33%)	1 (33%)	1 (33%)	1 (33%)	0	0	1 (25%)	1 (25%)	3 (30%)	1 (10%)	0	0	6 (24%)	4 (16%)
Dysgeusia	0	0	1 (33%)	0	0	0	0	0	1 (25%)	0	2 (20%)	0	1 (50%)	0	5 (20%)	0
Leukopenia[c]	1 (50%)	1 (50%)	0	0	1 (33%)	0	0	0	1 (25%)	1 (25%)	1 (10%)	1 (10%)	0	0	4 (16%)	3 (12%)

Abbreviation: G3/4, grade 3 or grade 4 AE.

[a]Includes neutrophil count decreased.

[b]Includes platelet count decreased.

[c]Includes white blood cell count decreased.

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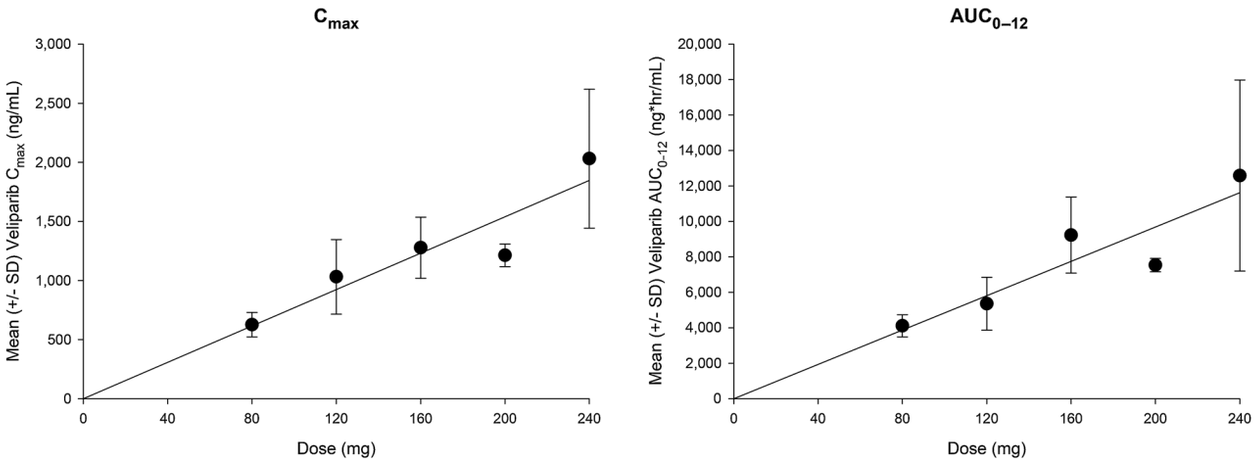

Figure 1.
Dose proportionality of veliparib. C_{max}, maximum plasma concentration; AUC_{0-12}, area under the plasma concentration–time curve from time 0 to 12 hours.

Tolerability of the combination cycles is summarized in Supplementary Table S1. Adverse events that led to veliparib interruption/reduction included febrile neutropenia, thrombocytopenia, neutropenia, and nausea. Ten of 39 patients experienced dose delays during combination therapy. The highest number of dose delays occurred for patients on 240 mg b.i.d. veliparib for 14 days (Table 2), with the highest-grade AEs reported as grade 3/4 neutropenia in 3 patients, and grade 3/4 thrombocytopenia, grade 3 febrile neutropenia, and grade 3 fatigue/decreased appetite in 1 patient (Table 2).

The most common adverse events related to veliparib during combination therapy were hematologic toxicities neutropenia (59%), thrombocytopenia (39%), and anemia (33%), and nausea and fatigue (39% each; Table 3A). Grade 3 or grade 4 adverse events related to veliparib included neutropenia (56%), thrombocytopenia (33%), anemia (21%), and febrile neutropenia and leukopenia (15% each). Many of the adverse events related to veliparib (e.g., nausea, fatigue, alopecia, anemia, neutropenia, thrombocytopenia) were also related to carboplatin and etoposide treatment.

Serious AEs not specifically attributed to veliparib included febrile neutropenia in 3 patients and hyponatremia in 2 patients. There were 2 fatal AEs; the causes of death were disease progression in 1 patient at 160 mg b.i.d. and nondisease progression (gastric perforation/abdominal sepsis) in 1 patient at 200 mg b.i.d.. These deaths were not considered related to veliparib, carboplatin, or etoposide.

Twenty-five of the 39 patients in combination cycles continued to veliparib monotherapy. AEs during maintenance monotherapy are presented in Table 3B. Treatment exposure during combination therapy was a median of 3 cycles (range: 1–25), and for maintenance treatment, median exposure was 6 cycles (range: 1–25).

Pharmacokinetics

Veliparib coadministered with carboplatin and etoposide exhibited approximately dose-proportional increases in C_{max} and AUC in the dose range of 80 to 240 mg b.i.d. (Fig. 1; Supplementary Table S2). Maximum veliparib concentrations were observed approximately 1 to 2 hours following veliparib administration (Supplementary Table S2). Etoposide PK were comparable when coadministered with and without veliparib (Supplementary Fig. S1 and Supplementary Table S3).

Efficacy

Fifty-six percent of all dosed patients (22/39) achieved a ≥30% decrease in the sum of tumor target lesion diameter from baseline (Fig. 2). Confirmed responses occurred in 44% [95% confidence interval (CI), 28–60; n = 17/39] of all patients. For patients with ED SCLC, a confirmed CR or PR was observed in 64% (95% CI, 43–82; n = 16/25) of patients across all dose levels, in 60% (n = 3/5) of patients on veliparib 240 mg b.i.d. for 7 days,

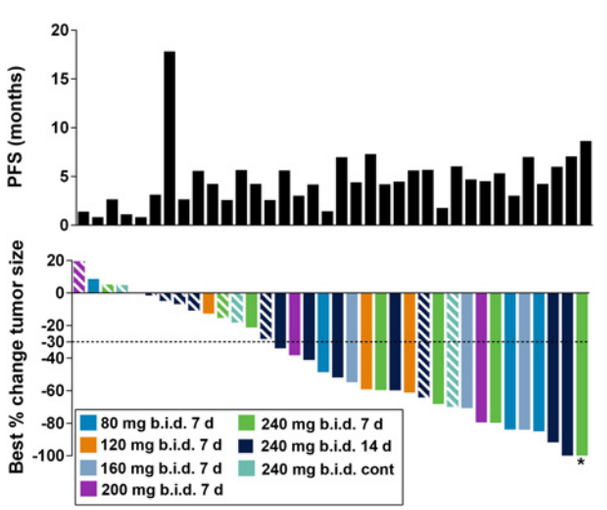

Figure 2.
Tumor size best percent change postbaseline and PFS. Individual patient data are shown for 36 patients with postbaseline assessment. Each column has PFS (black bars, top) and best percent tumor size change from baseline (colored bars, bottom) for the same individual patient. There was 1 patient with 0% change from baseline tumor size. Colored bars: solid colors indicate patients with extensive-stage small cell lung cancer; striped bars indicate patients with other solid tumors. Dashed line shows a threshold of 30% decrease in tumor size from baseline. Asterisk denotes 1 patient with a CR.

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Table 4. ORR and best response by RECIST 1.1 criteria

N (%)	All ED SCLC patients (*n* = 25)	ED SCLC patients at RP2D (*n* = 6)	All other solid tumor patients (*n* = 14)	Other solid tumor patients at RP2D (*n* = 7)
Objective response[a] (95% CI)	16 (64%) (42.5–82.0)	5 (83%) (35.9–99.6)	1 (7%) (0.4–57.9)	1 (14%) (0.4–57.9)
Confirmed CR	1 (4%)	0	0	0
Confirmed partial response	15 (60%)	5 (83%)	1 (7%)	1 (14%)
Best response				
CR	1 (4%)	0	0	0
Partial response	20 (80%)	6 (100%)	1 (7%)	1 (14%)
Stable disease	3 (12%)	0	10 (71%)	5 (71%)
Progressive disease	0	0	1 (7%)	0
Incomplete data	1 (4%)	0	2 (14%)	1 (14%)

Abbreviation: RP2D, recommended phase II dose of 240-mg veliparib b.i.d. as 14-day treatment.
[a]Objective response, confirmed CR + confirmed PR.

and in 83% (95% CI, 36–100; $n = 5/6$) of patients on veliparib 240 mg b.i.d. for 14 days (Table 4). Confirmed responses for other tumor types were observed in 7% (95% CI, 2–40) of patients ($n = 1/14$; 1 neuroendocrine) across all dose levels and in 14% (95% CI, 0–58; $n = 1/7$; neuroendocrine) at the RP2D.

In patients with prior carboplatin, cisplatin, and/or etoposide treatment, 1 patient with ED SCLC had a partial response, and 3 patients with other solid tumors had stable disease. No patient with ED SCLC in the RP2D treatment group had received prior chemotherapy.

Median PFS (mPFS) of the RP2D treatment group ($n = 13$) was 5.6 months, and 4.5 months for other cohorts (all doses excluding RP2D, $n = 26$). Patients in the 240 mg b.i.d. cohorts had the longest duration on study, including 1 patient with a CR and 1 patient with stable disease who remained on study over 18 months (Supplementary Fig. S2). mPFS for all dosed patients ($n = 39$) was 5.3 months (95% CI, 4.2–5.7; Supplementary Fig. S3). There were 28 events (72% of patients) with radiologic progression and death. mPFS was 5.3 months for patients with ED SCLC across all dose levels ($n = 25$) versus 5.8 months at the RP2D ($n = 6$). mPFS for patients with other solid tumors was 5.6 months across all doses ($n = 14$).

The median time to response for all dosed patients was 1.4 months (range, 1.3–4.3). The median duration of response for all dosed patients was 5.0 months (range, 1.4–8.6) and 5.7 months (range, 4.2–7.1) for all patients at the RP2D ($n = 13$).

Biomarkers

Whole transcriptome RNA-seq was successfully conducted on pretreatment tumor tissues from 25 patients with confirmed clinical efficacy data. Tumor type, treatment regimen, and response status are shown in Supplementary Table S4. Of these patients, 17 patients had SCLC, 2 had large cell neuroendocrine carcinoma of the lung, and 6 had other solid tumors. Partial response was observed in 59% of SCLC patients ($n = 10/17$), and no response was observed for patients with other types of tumors ($n = 0/8$). Biomarker cohort mirrors efficacy findings from overall cohort.

Because of the small sample size and heterogeneous veliparib dose, unsupervised genome-wide clustering analysis failed to form clusters that are enriched with clinical response (data not shown). We further analyzed genes of interest that included *PARP* family genes, *E2F1*, *SLFN11*, and Byers DNA-damaging signature genes (4). There is a trend that high *E2F1* tends to associate with response in SCLC patients ($P = 0.129$ from 2-sided group t test, $n = 17$; Supplementary Fig. S4).

Discussion

This phase I study evaluated veliparib in combination with carboplatin and etoposide in patients considered suitable for this regimen by the investigators, with an emphasis on patients with ED SCLC. Veliparib plus carboplatin and etoposide had an acceptable safety profile, with an RP2D of 240 mg b.i.d. for 14 days based on long-term tolerability. Continuous dosing of veliparib at 240 mg b.i.d. with carboplatin and etoposide resulted in excessive carboplatin and etoposide dose delays due to hematologic toxicity, predominantly grade 3/4 neutropenia, and grade 3/4 thrombocytopenia in ≥75% to 100% of patients. Because we could not maintain continuous dosing, RP2D was based more on long-term safety than on DLTs. The 3+3 design and also the "up-and-down" and "short-and-extended" veliparib dosing may have helped to contour toxicity and better define the RP2D, as the preplanned MTD for the 7-day schedule was not reached. The RP2D was selected based on the maximal achievable dose intensity of veliparib in combination with carboplatin and etoposide which did not compromise dose intensity of the carboplatin and etoposide regimen itself.

In a previous phase I study, RP2D of veliparib in combination with cisplatin and etoposide was established at 100 mg b.i.d. in a 7-day schedule (11). In the current trial, we achieved an RP2D of 240 mg b.i.d. in a 14-day schedule for veliparib plus carboplatin and etoposide based on long-term tolerability. Doublet chemotherapy with carboplatin/etoposide is known to be as effective as cisplatin/etoposide in untreated SCLC patients with a more favorable toxicity profile than the cisplatin-containing regimen (25). This could be an explanation for achieving a higher RP2D of veliparib in our trial with longer treatment duration.

The lack of PK drug–drug interaction between veliparib and etoposide was anticipated. Veliparib is a Biopharmaceutical Classification System Class 1 compound primarily eliminated via renal excretion and to a lesser extent by metabolism by cytochrome P450 enzymes (primarily CYP2D6 and to a lesser extent by CYP3A4), and it has not been shown to inhibit or induce major drug-metabolizing enzymes or transporters at therapeutic levels (26–28). Etoposide is cleared by both renal and nonrenal paths; approximately 56% of the dose was excreted unchanged in urine as parent and metabolites, biliary excretion of unchanged drug constitutes 44% on the dose, and CYP3A4 is primarily responsible for its metabolism (29). In the current study, coadministration of veliparib with carboplatin and etoposide had no effect on etoposide PKs, suggesting no interaction in the metabolism/elimination of these 2 compounds. Veliparib has been previously shown to not affect carboplatin PKs (30) and hence was not

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explicitly evaluated in the current study. Veliparib PK parameters were approximately dose proportional in the dose range of 80 mg to 240 mg b.i.d. and are consistent with previous studies (30, 31).

Responses were seen across all dose levels. Confirmed responses were observed in 64% of patients with ED SCLC across all dose levels, in 60% of ED SCLC patients on veliparib 240 mg b.i.d. for 7 days, and in 83% of ED SCLC patients on 240 mg b.i.d. for 14 days. In patients with prior carboplatin, cisplatin, and/or etoposide, 1 patient with ED SCLC had a partial response and 3 patients with other solid tumors had stable disease. Median PFS was 5.3 months for all dosed patients, and 5.3 and 5.8 months for patients with ED SCLC across all dose levels and at the RP2D, respectively. However, the relative small numbers for each group make it impossible to draw any formal conclusion on the interaction of veliparib dose level with efficacy. A preclinical study demonstrated that SCLC cell lines were highly sensitive to PARP inhibition when treated for 14 days (4). Thus, the RP2D of 240 mg veliparib for 14 days added to the known doublet chemotherapy has the potential to improve treatment outcome. However, historical data with platinum-based doublet chemotherapy showed a mPFS ranging between 4.6 and 12 months (32). Considering relatively high response rate of the doublet chemotherapy, superiority of addition of veliparib to established regimen can only be investigated in a larger 2-arm phase II trial. The phase II, randomized, double-blind part of this study of veliparib in combination with carboplatin and etoposide is ongoing in first-line patients with ED SCLC.

E2F1 is known to have an important role in cell-cycle progression and the induction of apoptosis in response to DNA damage with increased levels of E2F1, triggering invasion and tumor growth. PARP1 has been identified as an important coactivator of E2F1 (22). Thus, inhibition of PARP1 can have a dual antiproliferative effect by directly targeting DNA repair and other E2F1-regulated DNA repair proteins. This is supported by the study of Byers and colleagues (4) in which protein lysate from SCLC cell lines treated with PARP inhibitors showed a decrease in DNA repair proteins and E2F1 target proteins over time. In terms of identifying predictive biomarkers in this study, preliminary results indicate that responder patients with SCLC tend to have high E2F1 levels. E2F1 regulates expression of PARP and other DNA repair targets, and PARP may cause a positive feedback loop on E2F1 (4), which may explain this observation. However, there was not a complete distinction between responders and nonresponders based on an identifiable E2F1 level, and in a single-arm study including active chemotherapy within the combination, the significance of these results remains uncertain. Because most of the patients included in the trial showed some degree of response, a true comparator including patients with progressive disease as best response is lacking, limiting the validation of the results. Without a randomized control arm, it is hard to determine whether E2F1 or any other biomarker is associated with veliparib effect specifically or a combination therapy effect. They may be worthy of exploration in later randomized trials. In this biomarker analysis, the role for veliparib cannot be established as the chemotherapy may also select for higher E2F1-expressing cells.

In conclusion, we have established a relatively high RP2D of the PARP1 inhibitor veliparib in combination with a bone marrow toxic doublet chemotherapy with a longer treatment schedule (14-day schedule) than previous trials. PARP inhibitors investigated in other trials with cytotoxic agents included compounds with a strong PARP-trapping ability (33–37) limiting the combination with chemotherapy. Less potent PARP inhibitors with mainly catalytic PARP inhibition properties like veliparib are more suitable for combination therapy with cytotoxic agents. Thus, selecting PARP inhibitors based on their PARP inhibition potency does matter for selecting as monotherapy or in combination therapy. Due to phase I study design, the small sample size, and small number of samples for biomarker testing, data from a larger phase II trial are necessary to support enhanced efficacy.

The additional toxicity on top of those from full-dose carboplatin and etoposide was mainly without DLT (except grade 3 event in 1 patient) leading to a recommended veliparib dosing of 240 mg b.i.d. for 14 days during chemotherapy followed by maintenance dosing of 400 mg b.i.d.. As this schedule is well tolerated and a high number of responses were seen, it should be explored further, especially in SCLC where there is ample activity.

Availability of Data and Material

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Disclosure of Potential Conflicts of Interest

H.J.M. Groen reports receiving commercial research grants from MSD and Roche, other commercial research support from Bristol-Myers Squibb, Novartis, and Pfizer, and is a consultant/advisory board member for Takeda. E. Garralda is a consultant/advisory board member for Janssen, NeoMed Therapeutics, and Roche. R.S. Sangha is a consultant/advisory board member for Abbvie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Novartis, Roche, and Takeda. S. Viteri reports receiving speakers bureau honoraria from Bristol-Myers Squibb and Roche, and is a consultant/advisory board member for Abbvie and Roche. Y.K. Chae reports receiving commercial research grants from Abbvie and Bristol-Myers Squibb, speakers bureau honoraria from AstraZeneca, Biodesix, Foundation Medicine, Guardant Health, Immuneoncia, Merck, Roche, and Takeda, and is a consultant/advisory board member for Genentech. N.Y. Gabrail reports receiving speakers bureau honoraria from Amgen, Bayer, Heron, Janssen Pharmaceuticals, and Taiho. S. Nuthalapati, E. Hoening, and P. Komarnitsky hold ownership interest (including patents) in AbbVie. No potential conflicts of interest were disclosed by the other authors.

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Other (patient accrual): M.P. Lolkema

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Clinical Cancer Research

A Phase I Dose-Escalation Study of Veliparib Combined with Carboplatin and Etoposide in Patients with Extensive-Stage Small Cell Lung Cancer and Other Solid Tumors

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