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Randomized, Placebo-Controlled, Phase II Study of Veliparib in Combination with Carboplatin and Paclitaxel for Advanced/Metastatic Non–Small Cell Lung Cancer

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Abstract

Purpose: PARP plays an important role in DNA repair. Veliparib, a PARP inhibitor, enhances the efficacy of platinum compounds and has been safely combined with carboplatin and paclitaxel. The primary endpoint of this phase II trial determined whether addition of veliparib to carboplatin and paclitaxel improved progression-free survival (PFS) in previously untreated patients with advanced/metastatic non–small cell lung cancer.

Experimental Design: Patients were randomized 2:1 to carboplatin and paclitaxel with either veliparib or placebo. Veliparib (120 mg) or placebo was given on days 1 to 7 of each 3-week cycle, with carboplatin (AUC = 6 mg/mL/min) and paclitaxel (200 mg/m^2) administered on day 3, for a maximum of 6 cycles.

Results: Overall, 158 were included (median age, 63 years; male 68%, squamous histology 48%). Median PFS was 5.8 months in the veliparib group versus 4.2 months in the placebo group [HR, 0.72; 95% confidence interval (CI), 0.45–1.15; $P = 0.17$)]. Median overall survival (OS) was 11.7 and 9.1 months in the veliparib and placebo groups, respectively (HR, 0.80; 95% CI, 0.54–1.18; $P = 0.27$). In patients with squamous histology, median PFS (HR, 0.54; 95% CI, 0.26–1.12; $P = 0.098$) and OS (HR, 0.73; 95% CI, 0.43–1.24; $P = 0.24$) favored veliparib treatment. Objective response rate was similar between groups (veliparib: 32.4%; placebo: 32.1%), but duration of response favored veliparib treatment (HR, 0.47; 95% CI, 0.16–1.42; $P = 0.18$). Grade III/IV neutropenia, thrombocytopenia, and anemia were comparable between groups.

Conclusions: Veliparib combination with carboplatin and paclitaxel was well-tolerated and demonstrated a favorable trend in PFS and OS versus chemotherapy alone. Patients with squamous histology had the best outcomes with veliparib combination. *Clin Cancer Res; 23(8); 1937–44. ©2016 AACR.*

Introduction

PARP belongs to a family of proteins that play critical roles in several cellular functions (1). The most understood among these is the role of PARP in the base excision repair (BER) pathway, although its role has also been recognized in other DNA repair mechanisms such as nonhomologous end-joining, and other cellular processes beyond DNA repair (2). In response to single-strand breaks, PARP is among the first to be recruited to the site of DNA damage, where it mediates DNA repair by recruiting a number of proteins such as XRCC1, DNA glycosylase, AP endonuclease, etc. Several commonly used therapeutic agents against cancer, including platinum compounds and ionizing radiation act by inducing DNA damage. Activation of DNA repair pathways in response to these treatment modalities contributes to resistance (3). Therefore, pharmacologic inhibition of PARP has been developed as a therapeutic strategy against cancer.

Veliparib is an orally administered, potent inhibitor of PARP1 and 2 (4). In preclinical studies, veliparib has demonstrated increased cytotoxicity when given in combination with DNA-damaging agents such as platinum compounds, topoisomerase inhibitors, and alkylating agents (5–7). In early-phase studies, veliparib demonstrated robust inhibition of PARP levels in tumor

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Translational Relevance

This article is the first to describe a phase II study of veliparib, a PARP inhibitor, given in combination with carboplatin and paclitaxel in patients with advanced non–small cell lung cancer (NSCLC). These results demonstrate that veliparib administration results in clinically meaningful improvements in outcomes with carboplatin and paclitaxel when given as first-line therapy for advanced NSCLC. A phase III trial of veliparib is underway comparing carboplatin and paclitaxel given in combination with placebo versus veliparib in patients with advanced-stage squamous cell carcinoma of the lung.

tissue at the 25- and 50-mg dose, and veliparib 120 mg orally (*per os*) twice daily (BID) in combination with carboplatin and paclitaxel was safe and showed antitumor activity for patients with advanced-stage solid organ malignancies (8, 9). The activity observed in this phase I study was encouraging and warranted further evaluation of the regimen in platinum-sensitive cancers.

Platinum-based combinations form the cornerstone of chemotherapy for advanced non–small cell lung cancer (NSCLC) at the time of diagnosis or following targeted therapy in patients with EGFR mutation or ALK translocation (10). Strategies to improve the efficacy of chemotherapy are urgently needed as an efficacy plateau has been reached with combination chemotherapy in this patient population. In particular, there has been limited progress in the treatment of squamous cell lung cancer in several years. We therefore evaluated the combination of veliparib with carboplatin and paclitaxel in a randomized phase II study.

Materials and Methods

Study design and participants

This multicenter, randomized, double-blind, placebo-controlled, phase II study was conducted in 37 centers in 8 countries. All eligible patients were randomly assigned to receive veliparib or placebo in combination with carboplatin and paclitaxel. Patients with a confirmed diagnosis of NSCLC who had not received prior chemotherapy for advanced or metastatic stage disease (Stage IV, AJCC version 7) were included. The use of prior adjuvant chemotherapy for early-stage NSCLC was allowed if at least 12 months had elapsed. Other salient inclusion factors were age $\geq$18 years, life expectance > 12 weeks, presence of measureable disease, availability of archived tumor tissue, and performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale. Patients were required to have adequate liver [serum bilirubin $\leq$ 1.5 $\times$ upper limit of normal (ULN) and transaminases $\leq$ 2.5 $\times$ ULN] and renal function (serum creatinine $\leq$ 1.5 $\times$ ULN or creatinine clearance > 50 mL/min/1.73 m^2 for those with creatinine levels above normal range). Patients with hepatic metastasis could have elevated serum transaminase up to 5$\times$ ULN. Acceptable peripheral blood counts were an absolute neutrophil count $\geq$ 1,500/mm^3, platelets $\geq$ 100,000/mm^3, and serum hemoglobin $\geq$ 9 g/dL. Patients with brain metastasis were excluded because of the potential risk of seizures associated with veliparib in this patient population. Other exclusion factors were peripheral neuropathy $\geq$ grade II, receipt of external beam radiotherapy within 8 weeks, pregnancy, prior therapy with a PARP inhibitor and severe uncontrolled co-morbid conditions. All patients were required to sign a written informed consent approved by the institutional review board of the participating site. The study was performed according to the GCP guidelines and the declaration of Helsinki (Trial registration ID: NCT01560104).

Study procedures

Baseline assessments included medical history and physical exam, vital signs, documentation of performance status, staging, activated partial thromboplastin time, international normalized ratio, smoking history, symptoms, and prior treatment history. A complete blood count with differential, serum chemistry tests, urinalysis, performance tests, QLQ-CIPN20, and quality-of-life questionnaires (EORTC QLQ-C15-PAL/LC13) were also performed at baseline, cycle 1 day 1, and on day 1 of each subsequent cycle. A 12-lead electrocardiogram was performed at baseline and repeated on day 3 of each cycle. A serum pregnancy test was done for women of childbearing potential before study treatment was initiated. MRI of the brain was done at baseline to exclude brain metastasis. Tumor assessments were done with computerized axial tomography scans of the involved areas at baseline and every 6 weeks during study treatments. Archived tumor tissue was collected from patients at baseline along with peripheral blood samples for pharmacokinetic (PK) studies on day 3 of the first 4 treatment cycles. Peripheral blood samples were also collected for exploratory correlative science studies on day 1 of cycles 1, 3, and 5.

Eligible patients were treated with veliparib or placebo at 120 mg *per os* twice daily on days 1 to 7 of each 3-week cycle. The first 2 patients received veliparib at a dose of 80 mg twice daily per protocol. The protocol was amended to increase the dose to 120 mg *per os* twice daily for the remainder of the study when the dose was demonstrated to have an acceptable safety profile in a parallel ongoing phase I study. Carboplatin and paclitaxel were given on day 3 of each treatment cycle. Carboplatin was administered as a 30-minute intravenous infusion, whereas paclitaxel was given intravenously over 3 hours. Carboplatin was dosed to achieve an area under the concentration (AUC) versus time curve of 6 mg/mL/min on the basis of the Calvert formula and paclitaxel was given at a dose of 200 mg/m^2. Blood samples for veliparib PK assessment were collected before dosing and at 0.5, 1, 2, and 3 hours after the morning veliparib or placebo dose on day 3 of cycle 1. Blood samples for paclitaxel and carboplatin PK assessment were taken at 2 hours 55 minutes and 25 minutes after the start of paclitaxel and carboplatin infusions, respectively, on day 3 of cycles 2 through 4. Plasma concentrations of veliparib and paclitaxel were assessed using validated liquid chromatography methods with tandem mass spectrometry. Plasma concentrations of unbound platinum were determined using an inductively coupled plasma mass spectrometry. PK parameters of veliparib were determined using noncompartmental methods. Premedications for carboplatin and paclitaxel were given on the basis of local institutional guidelines. Treatments were continued to a maximum of 6 cycles. Patients who completed 6 cycles of treatment remained on study (off study drugs) until disease progression. Maintenance therapy was not allowed until disease progression occurred. Treatments were discontinued in the event of disease progression, clinical deterioration of the patient, pregnancy, withdrawal of informed consent, concomitant medical conditions that limit further therapy or investigator's decision to discontinue therapy based on the best interests of the patient.

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The use of prophylactic granulocyte growth factor was allowed according to the investigator's standard practice or the American Society of Clinical Oncology guidelines. The dose of study drugs was modified for toxicity (carboplatin reduced to AUC 5 and 4 mg/mL/min; paclitaxel reduced by decrements of 25 mg/m^2; veliparib reduced to 80 mg twice daily and subsequently to 40 mg twice daily). If carboplatin and paclitaxel were discontinued, veliparib or placebo was to be discontinued as well. All dose reductions were considered permanent.

Objectives

The primary objective was to assess whether the addition of veliparib to carboplatin and paclitaxel would improve progression-free survival (PFS) compared with placebo plus carboplatin and paclitaxel. The secondary objectives included assessment of overall survival (OS), objective response rate (ORR), duration of overall response (DOR), safety and tolerability, and to conduct exploratory biomarker analyses. Responses were assessed by central independent review according to the RECIST criteria version 1.1 (11). Toxicity was graded according to the National Cancer Institute Common Terminology Criteria version 4.0. Imaging studies were done every 6 weeks for patients who discontinued therapy before progression of disease until documentation of disease progression.

Statistical methods

Patients were randomized 2:1 to treatment with carboplatin and paclitaxel with either veliparib or placebo. The stratification factors were histology (squamous vs. nonsquamous) and smoking history (current vs. former vs. never smokers). Assuming the true HR in favor of the veliparib group was 0.51, a total of 78 PFS events were required for the study to have approximately 80% power at one-sided α level of 0.025 to detect a statistically significant treatment effect using the log-rank test for PFS. PFS results are reported at the time of 78 PFS events. The estimated sample size was 135 patients. At final analysis, 158 patients were randomized in the study. The log-rank test, stratified by histology (squamous cell vs. nonsquamous cell) was used to compare PFS determined by central imaging review, OS between treatment groups, and DOR. Data cutoff date for PFS, ORR, and DOR are at 78th PFS events and all based on central imaging review. OS are reported from all 158 patients. The distribution of PFS, OS, and DOR was estimated for each treatment group using Kaplan–Meier methodology. ORR was estimated and compared between the 2 treatment groups using Cochran–Mantel–Haenszel (CMH) test, stratified by histology (squamous cell vs. nonsquamous cell). An exploratory analysis of a Cox proportional hazard model adjusting imbalanced baseline factors (gender and ECOG performance status) was performed for PFS and OS endpoints in the subgroup analyses. An independent data monitoring committee (IDMC) reviewed the unblinded safety data when approximately 18 patients had completed at least 2 cycles of treatment, reached an event of disease progression, or discontinued the study drug due to other reasons. The IDMC recommended continued accrual to the study.

Results

Characteristics

One hundred and sixty patients were enrolled between May 2012 and May 2013 at 37 centers in 8 countries. The first 2 patients were treated at the 80 mg *per os* twice daily dose of veliparib or placebo and 158 were randomized at 120 mg *per os* twice daily veliparib or placebo and included in the efficacy analysis. The median age was 63 years, and more than two thirds of the patients were male. Demographics and baseline characteristics are shown in Table 1 (characteristics by histology, Supplementary Tables S1 and S2); Fig. 1 is a consort diagram. Nearly half the patients (48%) had squamous cell histology and 87% were current or former smokers. The EGFR status was documented as wild-type in 89% of the patients; information was not available for 18 patients.

Table 1. Demographics and baseline characteristics

Characteristic	Placebo BID and carbo/paclitaxel ($N = 53$)	Veliparib BID and carbo/paclitaxel ($N = 105$)
Median age (range), y	62 (46–79)	63 (33–84)
Sex, *n* (%)		
Male	32 (60)	75 (71)
Female	21 (40)	30 (29)
Race		
White	52 (98)	102 (97)
Black	1 (2)	2 (2)
American Indian/Alaskan Native	0 (0)	1 (1)
Histology, *n* (%)		
Squamous	25 (47)	51 (49)
Nonsquamous	28 (53)	54 (51)
Smoking history, *n* (%)		
Current	31 (58)	64 (61)
Former	14 (26)	28 (27)
Never	8 (15)	13 (12)
EGFR status, *n* (%)		
Wild-type	49 (92)	91 (87)
Missing	4 (8)	14 (13)
Tumor burden at time of enrollment, *n* (%)		
Locally advanced	15 (28)	22 (21)
Metastatic	38 (72)	83 (79)
Baseline ECOG, *n* (%)		
0	17 (32)	35 (33)
1	36 (68)	70 (67)

Abbreviations: carbo, carboplatin.

Safety and pharmacokinetics

The median number of cycles of chemotherapy administered in the placebo group was 6 (range, 1–6) for both carboplatin and paclitaxel. In the veliparib group, patients received a median of 6 cycles of carboplatin (range, 1–6) and 5 cycles of paclitaxel (range, 1–6). Veliparib was rapidly absorbed and exhibited moderate interpatient PK variability with about 40% coefficient of variation in maximum concentration observed (C_{max}) and AUC. Veliparib PK exposure was similar to that seen in previous studies (Supplementary Table S3). The PK exposure of carboplatin and paclitaxel appeared to be comparable between the placebo and veliparib groups (Supplementary Table S4). Median number of days on veliparib or placebo per cycle were 7.0 days (range, 1–8.5) and 7.0 days (range, 3–8.5), respectively. Serious adverse events (SAE) were observed in 28 (27%) and 12 (23%) of patients in the veliparib and placebo groups, respectively. AEs are summarized in Table 2. The increase in neutropenia (all grade) with the addition of veliparib to carboplatin and paclitaxel was less than 10%, and the grade III/IV neutropenia rate was balanced between the 2 arms. The number of patients with neither dose reduction nor interruption of veliparib or placebo were 103 (98.1%) and 49 (94.2%), respectively. Dose reduction was required for carboplatin in 14 (13.7%) and 3 (5.9%) of patients in the veliparib and

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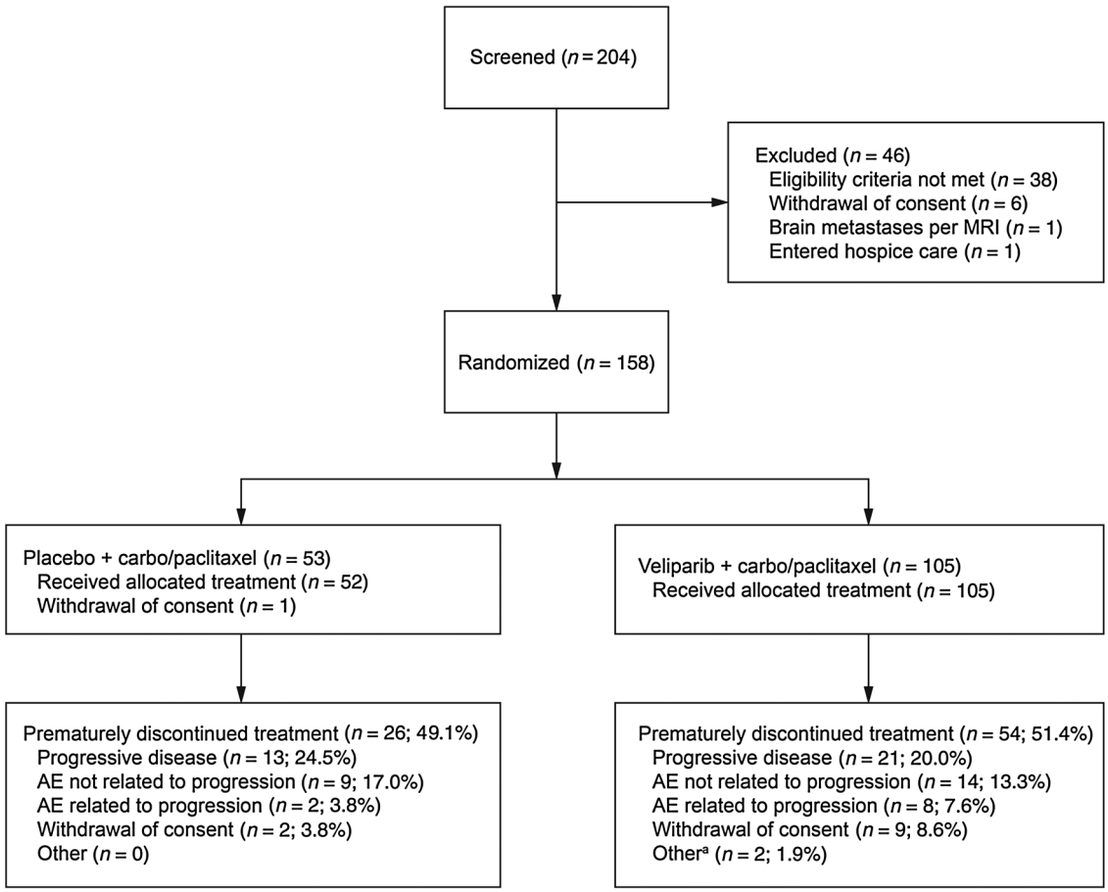

Figure 1.
CONSORT diagram. [a]One declining performance status; 1 death. Carbo, carboplatin.

placebo groups, respectively. For paclitaxel, dose reductions were required in 20 (19.2%) and 10 (19.6%) of patients in the 2 groups, respectively. Disease progression was the most common primary reason for discontinuation from veliparib/placebo with 20.0% and 24.5% of patients in the veliparib and placebo groups having progression of disease, respectively (Table 3).

Efficacy

The median PFS was 5.8 months [95% confidence interval (CI), 4.3–6.5] with the addition of veliparib to chemotherapy versus 4.2 months (95% CI, 3.1–5.6) with placebo (HR, 0.72; 95% CI, 0.45–1.15; $P = 0.17$; Table 4). Median OS in the veliparib group (11.7 months; 95% CI, 8.8–13.7) was not statistically significant in comparison to the placebo group (9.1 months; 95% CI, 5.4–12.3), with an HR of 0.80 (95% CI, 0.54–1.18; $P = 0.27$). Best tumor response according to RECIST version 1.1 criteria is presented in Fig. 2 for carboplatin and paclitaxel with either veliparib (Fig. 2A) or placebo (Fig. 2B). The ORR for the veliparib and placebo groups was 32.4% (95% CI, 23.6–42.2) and 32.1% (95% CI, 19.9–46.3), respectively.

Complete and partial responses were achieved by 2 (1.9%) and 32 (31%) patients, respectively, in the veliparib group; no patients had a complete response in the placebo group, and 17 (32%) patients achieved a partial response. Stable disease was achieved in 42 (40%) and 22 (42%) patients in the veliparib and placebo groups, respectively. Median DOR was 6.9 months (95% CI, 4.5–7.0) with the addition of veliparib to chemotherapy versus 4.3 months [95% CI, 2.8–not available (NA)] with placebo (HR, 0.47; 95% CI, 0.16–1.42; $P = 0.18$). Outcomes of an exploratory time-to-event analysis in responder and nonresponder groups are shown in Supplementary Fig. S1.

Analysis was also performed by histology groups (Table 4). In the subset of patients with squamous cell histology, median PFS was 6.5 months (95% CI, 4.4–8.4) with veliparib versus 4.1 months (95% CI, 2.8–NA) with placebo (HR, 0.54; 95% CI, 0.26–1.12; $P = 0.098$). In patients with nonsquamous histology, there was no difference in median PFS between the 2 groups (HR, 0.87; 95% CI, 0.48–1.59; $P = 0.65$). Similar to the PFS results, median OS in patients with squamous cell carcinoma was favored in the veliparib arm (10.3 months; 95% CI, 8.3–13.2) versus placebo arm (8.4 months; 95% CI, 5.0–12.9), with an HR of 0.73 (95% CI, 0.43–1.24; $P = 0.24$).

Post-study therapy was administered to patients in both treatment arms. A higher proportion of patients randomized to the veliparib arm received treatment with pemetrexed [21 (20.0%) vs. 5 (9.4%)], docetaxel [14 (13.3%) vs. 5 (9.4%)], and erlotinib [14 (13.3%) vs. 2 (3.8%); Table 5], agents currently approved for second- and third-line treatment in advanced NSCLC.

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Table 2. Summary of AEs

AEs	Placebo BID and carbo/paclitaxel ($N = 52$)	Veliparib BID and carbo/paclitaxel ($N = 105$)
Any grade AE, *n* (%)	46 (89)	101 (96)
Any grade ≥3 AE, *n* (%)	30 (58)	72 (69)
Any SAE	12 (23)	28 (27)
Alopecia	22 (42)	41 (39)
Neutropenia	15 (29)	38 (36)
Anemia	21 (40)	33 (31)
Nausea	13 (25)	29 (28)
Peripheral neuropathy	13 (25)	25 (24)
Fatigue	13 (25)	24 (23)
Arthralgia	7 (13)	20 (19)
Dyspnea	6 (12)	16 (15)
Decreased appetite	9 (17)	14 (13)
Diarrhea	8 (15)	13 (12)
Thrombocytopenia	8 (15)	13 (12)
Myalgia	4 (8)	13 (12)
Pain	6 (12)	12 (11)
Constipation	7 (13)	9 (9)
Cough	8 (15)	8 (8)
Unbalanced AE, *n* (%)		
Leukopenia	0 (0)	12 (11)
Grade ≥3 AEs, *n* (%)		
Neutropenia	12 (23)	20 (19)
Anemia	5 (10)	11 (10)
Alopecia	3 (6)	7 (7)
Leukopenia	0 (0)	6 (6)
Thrombocytopenia	3 (6)	5 (5)
Nausea	0 (0)	4 (4)
Hyperkalemia	1 (2)	4 (4)
Arthralgia	0 (0)	3 (3)
Fatigue	0 (0)	3 (3)
Hypersensitivity	0 (0)	3 (3)
Hyponatremia	1 (2)	2 (2)
Myalgia	0 (0)	2 (2)
Weight loss	0 (0)	2 (2)

NOTE: Analyses of safety were performed using data from the 157 patients who received at least 1 dose of study drug. Toxicity of any grade occurring in ≥10% of patients and grade ≥3 occurring in >1 patient are reported.
Abbreviations: carbo, carboplatin; SAE, serious adverse event.

Discussion

The majority of the patients with advanced NSCLC do not harbor a targetable driver mutation. For these patients, front-line systemic chemotherapy is the current standard of care. However, strategies to improve the efficacy of chemotherapy are an unmet need for this patient population. PARP inhibitors have demonstrated anticancer activity when used in tumors that accumulate DNA damage, either due to inherent deficits in DNA repair or through combination therapy with DNA-damaging agents (5, 12–14). Mutations in DNA repair pathways are not associated with lung cancer; therefore, PARP inhibitors are more suited for evaluation as combination therapy in NSCLC.

Table 3. Reasons for discontinuation of study drug

Primary reason for veliparib/placebo discontinuation	Placebo BID and carbo/paclitaxel ($N = 53$)	Veliparib BID and carbo/paclitaxel ($N = 105$)
Completed treatment	27 (50.9%)	51 (48.6%)
Progression of disease	13 (24.5%)	22 (21.0%)
Adverse event related to progression	2 (3.8%)	8 (7.6%)
Adverse event not related to progression	10 (18.9%)	14 (13.3%)
Withdrew consent	2 (3.8%)	9 (8.6%)
Lost to follow-up	0	1 (1.0%)
Other	1 (1.9%)	6 (5.7%)

Abbreviation: carbo, carboplatin.

The combination of PARP inhibitors with platinum-based chemotherapy has been associated with improved efficacy in preclinical studies. However, with several PARP inhibitors, toxicity has limited the ability to develop novel combinations with cytotoxic agents (15). Veliparib, on the other hand, has proven to be a well-tolerated agent when given with platinum-based chemotherapy (8). The use of veliparib for only 7 days in each cycle, primarily to enhance DNA damage in the setting of platinum-based therapy, may have contributed to the manageable tolerability profile of the regimen utilized in our study. Of note, the design and accrual of this trial was conducted prior to widespread use of maintenance therapy for patients with nonsquamous NSCLC. Maintenance of veliparib therapy was not included in the design because of the lack of evidence for monotherapy efficacy of PARP inhibitors in sporadic tumors not known to have deficiencies in DNA repair, such as NSCLC. Although the primary endpoint of the current study was not met, the study demonstrates that veliparib, a potent inhibitor of PARP, was associated with clinically meaningful improvements in outcomes when combined with carboplatin and paclitaxel and given as first-line therapy for advanced NSCLC. Limitations of the reported study include issues with statistical analyses [e.g., very high assumption (HR, 0.51) and poor power (0.8)]; post-study therapy was more frequent in the veliparib arm (e.g., pemetrexed); and the relatively poor performance of the control arm in a selected patient population (ECOG performance status, 0–1).

The improvement in efficacy was noted primarily in patients with squamous histology. The improvement in PFS in patients with squamous histology was also associated with a favorable trend in OS, although the study was not powered to detect differences in survival. When comparisons were adjusted for imbalances in baseline factors identified in the subgroup analyses (gender and ECOG performance status), the improvement in PFS associated with veliparib treatment was more pronounced (overall population: HR, 0.56; 95% CI, 0.35–0.90; $P = 0.017$; squamous histology: HR, 0.43; 95% CI, 0.20–0.94; $P = 0.034$). The reasons behind the efficacy in squamous cell carcinoma may be related to the higher genomic instability observed in this patient population, which is more vulnerable to targeting with agents that enhance DNA damage (16–18). Another salient observation is that the DOR favored the veliparib combination despite the absence of improvement in ORR. This indicates that the responses are "deeper" with the addition of veliparib to platinum-based chemotherapy. Indeed, preclinical studies have demonstrated this phenomenon of PARP inhibition being synergistic with platinum compounds in platinum-sensitive cell lines, but not in refractory cells (19, 20). This observation calls for identification of biomarkers to determine platinum sensitivity to identify patients likely to benefit from PARP inhibition. Biomarker evaluations conducted in the trial and results from responsive patient subsets will be fully reported in a future article. It is possible that the discordance in the use of post-study therapies could have influenced the secondary endpoint of OS in favor of the veliparib arm, but the overall proportion that received them is consistent with recently reported clinical trials (21–23).

The promising results from our study have provided the basis for a phase III study to compare carboplatin and paclitaxel given in combination with placebo versus veliparib in patients with advanced-stage squamous cell carcinoma of the lung

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Table 4. Overview of results for primary and secondary endpoints

	PFS median (95% CI), mo	OS median (95% CI), mo	ORR, % (95% CI)	DOR median (95% CI), mo
Placebo BID and carbo/paclitaxel ($N = 53$)	4.2 (3.1–5.6)	9.1 (5.4–12.3)	32.1 (19.9–46.3)	4.3 (2.8–NA)
Squamous ($n = 25$)	4.1 (2.8–NA)	8.4 (5.0–12.9)		
Nonsquamous ($n = 28$)	5.0 (2.8–5.7)	11.1 (4.8–14.6)		
Veliparib BID and carbo/paclitaxel ($N = 105$)	5.8 (4.3–6.5)	11.7 (8.8–13.7)	32.4 (23.6–42.2)	6.9 (4.5–7.0)
Squamous ($n = 51$)	6.5 (4.4–8.4)	10.3 (8.3–13.2)		
Nonsquamous ($n = 54$)	5.6 (2.8–6.4)	12.8 (8.0–17.2)		
HR (95%CI)				
All patients ($N = 158$)	0.72 (0.45–1.15)	0.80 (0.54–1.18)		0.47 (0.16–1.42)
Squamous ($n = 76$)	0.54 (0.26–1.12)	0.73 (0.43–1.24)		
Nonsquamous ($n = 82$)	0.87 (0.48–1.59)	0.90 (0.51–1.58)		
Adjusted HR[a] (95% CI)				
All patients ($N = 158$)	0.56 (0.35–0.90)	0.72 (0.49–1.07)		
Squamous ($n = 76$)	0.43 (0.20–0.94)	0.70 (0.39–1.21)		
Nonsquamous ($n = 82$)	0.73 (0.39–1.36)	0.77 (0.43–1.37)		

Abbreviation: carbo, carboplatin.

[a]HR adjusted for ECOG performance status and gender.

(NCT02106546). The use of veliparib is also of interest in combination with chemoradiotherapy in stage III disease for patients with surgically unresectable disease (NCT01386385). Another randomized study will evaluate the addition of veliparib to cisplatin and etoposide combination in patients with extensive stage small-cell lung cancer (SCLC; NCT01642251).

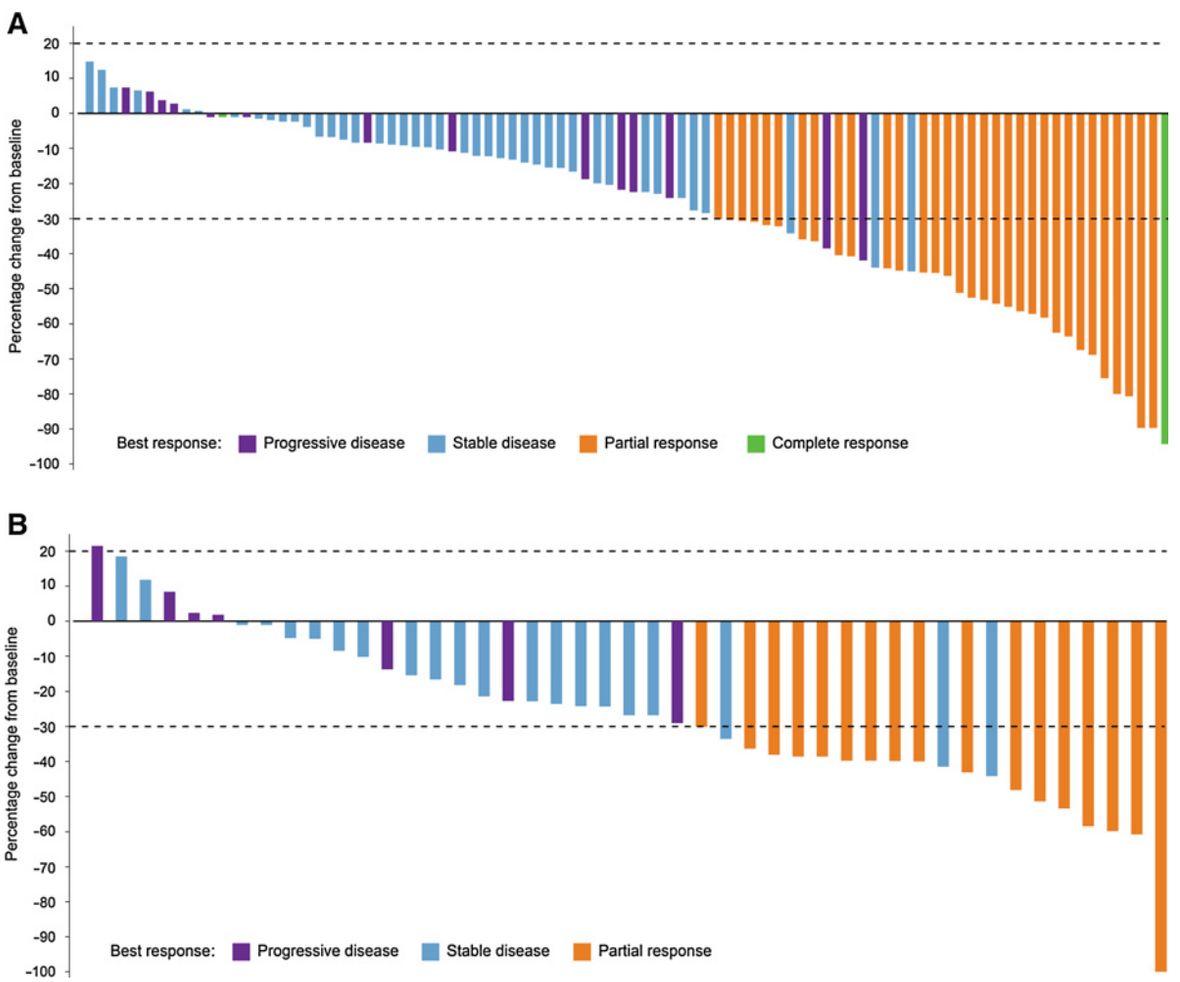

Figure 2.

Best percentage change in the sum of target lesions sizes. **A,** Veliparib BID and carbo/paclitaxel (ORR, 32.4%; 95% CI, 23.6–42.2). **B,** Placebo BID and carbo/paclitaxel (ORR, 32.1%; 95% CI, 19.9–46.3). Carbo, carboplatin.

Table 5. Post-study therapies

Post-study therapy	Placebo BID and carbo/paclitaxel ($N = 53$)	Veliparib BID and carbo/paclitaxel ($N = 105$)
Without any therapy	31 (58.5%)	46 (43.8%)
With at least one therapy	22 (41.5%)	59 (56.2%)
Type of medications in post-study therapy[a]		
Docetaxel	5 (9.4%)	14 (13.3%)
Erlotinib	2 (3.8%)	14 (13.3%)
Gemcitabine	4 (7.5%)	14 (13.3%)
Pemetrexed	5 (9.4%)	21 (20.0%)
Other	12 (22.6%)	40 (38.1%)

Abbreviation: carbo, carboplatin.
[a]Patients who were on multiple medications in a therapy are counted under each medication.

Promising results in SCLC with another PARP inhibitor, BMN 673 (24), have also resulted in enthusiasm for the development of this group of agents in a variety of settings for patients with lung cancer.

Disclosure of Potential Conflicts of Interest

S.S. Ramalingam is a consultant/advisory board member for AbbVie. M. Reck reports receiving speakers' bureau honoraria from and is a consultant/advisory board member for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Hoffmann-La Roche, Lilly, MSD, Novartis, and Pfizer. C.M. Jones reports receiving speakers' bureau honoraria from Bristol-Myers Squibb and is a consultant/advisory board member for Baxalta. J. Qian has ownership interest (including patents) in AbbVie. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

AbbVie participated in the design, study conduct, analysis, and interpretation on of data as well as the writing, review, and approval of the manuscript.

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