Veliparib in Combination With Platinum-Based Chemotherapy for First-Line Treatment of Advanced Squamous Cell Lung Cancer: A Randomized, Multicenter Phase III Study

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PURPOSE Squamous non–small-cell lung cancer (sqNSCLC) is genetically complex with evidence of DNA damage. This phase III study investigated the efficacy and safety of poly (ADP-ribose) polymerase inhibitor veliparib in combination with conventional chemotherapy for advanced sqNSCLC (NCT02106546).

PATIENTS AND METHODS Patients age ≥ 18 years with untreated, advanced sqNSCLC were randomly assigned 1:1 to carboplatin and paclitaxel with veliparib 120 mg twice daily (twice a day) or placebo twice a day for up to six cycles. The primary end point was overall survival (OS) in the veliparib arm versus the control arm in current smokers, based on phase II findings. Archival tumor samples were provided for biomarker analysis using a 52-gene expression histology classifier (LP52).

RESULTS Overall, 970 patients were randomly assigned to carboplatin and paclitaxel plus either veliparib (n = 486) or placebo (n = 484); 57% were current smokers. There was no significant OS benefit with veliparib in current smokers, with median OS 11.9 versus 11.1 months (hazard ratio [HR], 0.905; 95% CI, 0.744 to 1.101; *P* = .266). In the overall population, OS favored veliparib; median OS was 12.2 versus 11.2 months (HR, 0.853; 95% CI, 0.747 to 0.974), with no difference in progression-free survival (median 5.6 months per arm). In patients with biomarker-evaluable tumor samples (n = 360), OS favored veliparib in the LP52-positive population (median 14.0 *v* 9.6 months; HR, 0.66; 95% CI, 0.49 to 0.89), but favored placebo in the LP52-negative population (median 11.0 *v* 14.4 months; HR, 1.33; 95% CI, 0.95 to 1.86). No new safety signals were observed in the experimental arm.

CONCLUSION In current smokers with advanced sqNSCLC, there was no therapeutic benefit of adding veliparib to first-line chemotherapy. The LP52 signature may identify a subgroup of patients likely to derive benefit from veliparib with chemotherapy.

INTRODUCTION

Squamous non–small-cell lung cancer (sqNSCLC) accounts for 25%-30% of all NSCLC. Most patients present with locally advanced or metastatic disease, making this a particularly challenging population to treat.[1,2]

sqNSCLC is a genetically complex tumor type with a high mutation rate and evidence of DNA damage, including smoking-associated damage.[3-5] The low incidence of actionable driver mutations is a key differentiator from nonsquamous disease; as a result, targeted therapies are not useful for most patients with sqNSCLC.[2] Although chemotherapy options are limited in this setting,[1,6,7] chemotherapy plus immunotherapy (IO) represents a new standard treatment option.[8,9] Despite the availability of IO for sqNSCLC, many patients do not experience durable clinical benefit.[8,10,11] Novel treatments and reliable biomarkers to predict durable response are lacking[12-14]; sqNSCLC therefore remains an underserved patient population with unmet clinical need.

Poly (ADP-ribose) polymerase (PARP) enzymes play an important role in repairing DNA damage.[15,16] Inhibition of PARP1 has demonstrated synthetic lethality in susceptible tumor cells and augments the activity of DNA-damaging therapies in preclinical models and patients.[17-20] PARP inhibitor activity was originally established in *BRCA*-mutant tumors that exhibit

CONTEXT

Key Objective

Squamous non–small-cell lung cancer (sqNSCLC) has limited therapeutic options. This phase III study investigated the poly (ADP-ribose) polymerase inhibitor, veliparib, plus carboplatin and paclitaxel (C and P) versus placebo plus C and P (control) for advanced sqNSCLC, and explored outcomes with a potential gene-expression biomarker, LP52.

Knowledge Generated

There was no overall survival (OS) benefit with veliparib in current smokers; in the overall population, there was a trend for OS benefit with veliparib versus control (median 12.2 *v* 11.2 months), suggesting a subgroup of patients may derive greater benefit. In the LP52+ exploratory analyses, OS favored veliparib (median 14.0 *v* 9.6 months).

Relevance

Despite no benefit of adding veliparib to C and P in current smokers being observed, risk of death was decreased by 34% in the LP52+ population with veliparib versus placebo. These findings indicate that this biomarker-defined subgroup may derive greater benefit from poly (ADP-ribose) polymerase inhibition and support the use of biomarkers to identify treatment-sensitive subgroups.

homologous recombination deficiency; potential benefit has also been recognized in homologous recombination-competent tumors, including lung cancer.[20,21]

Veliparib is a potent, oral PARP1/2 inhibitor that enhances the activity of platinum-based chemotherapy regimens in solid tumors.[17,22-26] In a randomized phase II trial of veliparib or placebo in combination with carboplatin and paclitaxel (C and P) for advanced NSCLC, the most favored outcomes were observed in the veliparib arm in patients with a squamous histology (hazard ratio [HR] 0.54 and 0.73 for progression-free survival [PFS] and overall survival [OS], respectively), suggesting the addition of veliparib may benefit these patients.[23] Clinical benefit was also observed in current smokers (smoked within 12 months of study entry and had > 100 smoking events, eg, cigarettes, in their lifetime, also referred to as recent smokers), with improved PFS and OS in current smokers who received veliparib versus placebo (HR 0.38 and 0.43, respectively).[27]

These results prompted a phase III study to investigate veliparib with C and P in patients with previously untreated, advanced sqNSCLC; enrollment preceded the approval of IO as first-line treatment for sqNSCLC (first study visit, April 2014). Importantly, patients consented before treatment to provide tumor tissue samples for molecular biomarker evaluation.

We hypothesized that patients with sqNSCLC and molecular characteristics of adenocarcinoma may derive less clinical benefit from veliparib than patients with nonadenocarcinoma molecular characteristics. To test this, we developed a new binary gene expression classifier based on the gene content of an expression-based lung subtype panel (LSP),[28,29] referred to as LP52. We used the same gene content of the LSP but normalized within the cohort of squamous histology

samples and evaluated the association of LP52 status with clinical outcomes in exploratory analyses.

PATIENTS AND METHODS

Patient Selection

Patients were age ≥ 18 years with a life expectancy of > 12 weeks (per Investigator) and confirmed advanced or metastatic sqNSCLC not previously treated with chemotherapy. Full eligibility criteria are given in the Data Supplement (online only).

Study Design and Treatment

This randomized, double-blind, phase III study evaluated the efficacy, safety, and tolerability of veliparib with C and P versus placebo with C and P in patients with previously untreated advanced or metastatic sqNSCLC (NCT02106546). It was conducted in 218 sites across 37 countries between April 10, 2014, and November 20, 2019, in accordance with the Protocol (online only), 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. Patients provided informed consent that included provision of an archival tumor sample for biomarker analysis.

Patients were randomly assigned 1:1 to veliparib 120 mg twice daily (twice a day) or placebo twice a day, plus C and P. Random assignment was stratified by tumor stage, Eastern Cooperative Oncology Group performance status (ECOG-PS), geographic region, and smoking history (for further details, see stratification in Table 1). All patients received carboplatin (area under the curve 6 mg/mL/min) and paclitaxel (200 mg/m^2) IV infusion on day 1 of each 21-day cycle. Patients received oral veliparib or placebo on day −2

TABLE 1. Baseline Demographics and Disease Characteristics

Characteristic	Veliparib Plus C and P (n = 486)	Placebo Plus C and P (n = 484)
Sex		
Male	411 (85)	384 (79)
Female	75 (15)	100 (21)
Region		
Western Europe or Australia or Americas	242 (50)	239 (49)
Eastern Europe or Russia	244 (50)	245 (51)
Race		
White	471 (97)	477 (99)
Black	9 (2)	5 (1)
Asian	5 (1)	0
Other	1 (< 1)	2 (< 1)
Median age, years (range)	64 (36-83)	64 (33-84)
Age distribution, years		
< 65	261 (54)	256 (53)
≥ 65	225 (46)	228 (47)
Smoking status[a,b]		
Current smoker	276 (57)	276 (57)
Past smoker	181 (37)	181 (37)
Never smoked	29 (6)	27 (6)
Smoking exposure, median pack-years (range)	42 (< 1-179)	40 (2-180)
ECOG PS[a]		
0	166 (34)	165 (34)
1	320 (66)	319 (66)
Tumor stage[a]		
Locally advanced	114 (24)	112 (23)
Metastatic	372 (77)	372 (77)
Number of involved organ sites[c]		
1-2	298 (61)	310 (64)
> 2	188 (39)	173 (36)
Missing	0	1
Median tumor burden, mm (range)	87 (7-393)	91 (11-347)
Median time from diagnosis to first dose of study drug, months (range)	2 (< 1-157)	2 (< 1-326)

NOTE. Data are No. (%) unless otherwise stated; percentages calculated on nonmissing values.

Abbreviations: C, carboplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; P, paclitaxel.

[a]Based on interactive voice response system data and used for stratification in random assignment.

[b]Current smokers had > 100 lifetime smoking events (eg, cigarettes) and had smoked within the 12 months before study entry; past smokers had > 100 lifetime smoking events but had not smoked in the past 12 months; and never smokers had ≤ 100 lifetime smoking events.

[c]Collected from baseline tumor assessment.

(2 days before the start of C and P) through day 5 (7 consecutive days) of each cycle. Patients received six cycles of treatment (no maintenance therapy), unless they discontinued early because of toxicity or radiographic progression. Dose modifications or delays because of toxicities were permitted. After investigator-identified disease progression or other criteria were met for discontinuation of protocol-specified clinical assessments, patients moved to the survival follow-up portion of the study.

End Points and Assessments

The primary efficacy end point was OS in current smokers. Secondary end points included OS in the intention-to-treat (ITT) population (all randomly assigned patients), and PFS and overall response rate (ORR) in current smokers and the ITT population. Additional information regarding the primary end point is provided in the Data Supplement.

Clinical assessments including radiographic tumor assessments were conducted at baseline, before treatment on cycle 3 day 1 and cycle 5 day 1, every 6 weeks until 1 year after beginning treatment, and then every 12 weeks until radiographic progression, additional cancer treatment, or death. Radiographic data were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients no longer undergoing clinical assessments had survival information collected at 2-month intervals until death, loss to follow-up, or study termination. Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Statistical Analysis

The data cutoff for the primary end point was triggered by 400 OS events in current smokers and 667 events in the total ITT population (2017). All other end points were analyzed using the final locked clinical database (2019). Statistical significance was determined by a two-sided P value ≤ .05. Efficacy analyses were performed on the ITT population; safety analyses included all patients who received at least one dose of study drug (as-treated population). The distribution of OS was estimated for each treatment arm using Kaplan-Meier methodology and compared between arms using the log-rank test, stratified by tumor staging (locally advanced v metastatic) and ECOG-PS (0 v 1). Additional information regarding the statistical analysis is provided in the Data Supplement.

Biomarker Analysis

Available patient tissue samples were used to evaluate putative biomarkers of efficacy in exploratory analyses. Whole transcriptome sequencing was performed at the Washington University Genome Technology Access Center on formalin-fixed, paraffin-embedded tumor samples from diagnosis that met the specified tumor content and nucleic

acid requirements for the assay. RNA-seq reads were aligned to the Ensembl release 76 assembly with START version 2.0.4b. Sequencing files were processed as previously described.[30] A specific informatic LP52 classifier was developed using independently derived RNA-seq data from a training cohort of 120 tumors representing a diverse set of NSCLC subtypes (data not shown). As expected,[29] three distinct clusters were identified from the 52-gene LSP panel on log-transformed and Z-score normalized reads per kilobase of transcript; per million mapped reads (RPKM) data and molecular expression signatures were thereby defined for adenocarcinoma, squamous, and neuroendocrine histologies.

To assess whether veliparib exerts greater clinical benefit in sqNSCLC tumors with nonadenocarcinoma molecular characteristics compared with adenocarcinoma characteristics, we developed a new binary expression classifier called LP52 to identify these patients, using training cohort as mentioned above with the same informative gene content as the LSP (Data Supplement).[28,29] While the LSP classifier has three centroids (adenocarcinoma, squamous, and neuroendocrine), LP52 has two (adenocarcinoma v

nonadenocarcinoma) and each gene was normalized within a cohort of squamous histology samples. LP52 positivity was assigned to tumors with nonadenocarcinoma characteristics whereby the cutoff for LP52+ assignment was based on the predicted probability of nonadenocarcinoma with a cutoff > 0.6. In this study, batch-wise Z-score normalization was applied to the $\log_2$-transformed RPKM data and the LP52 classifier applied to determine class.

OS for patients with evaluable gene expression data were compared with OS for the ITT population across stratification factors. Additional details are included in the Data Supplement.

RESULTS

Patient Characteristics

In total, 970 patients were randomly assigned to veliparib (n = 486) or placebo (n = 484) in combination with C and P, and 967 received ≥ 1 dose of veliparib or placebo. The planned six cycles were delivered to > 50% of patients (59% and 55% in the veliparib and placebo arms, respectively); the remainder discontinued early. The main
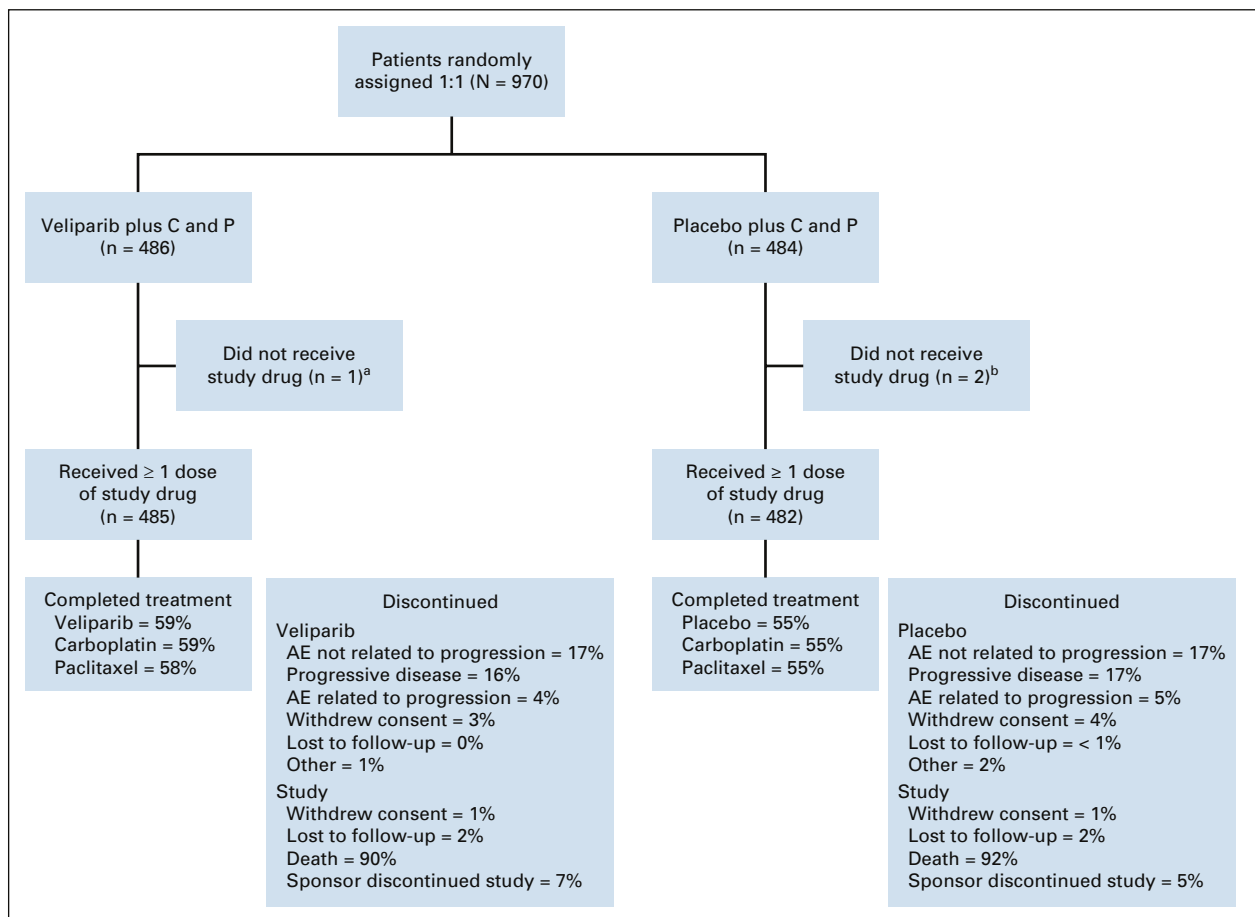
FIG 1. CONSORT diagram of patient disposition. [a]One patient randomly assigned to veliparib plus C and P did not receive treatment because of clinical disease progression. [b]Two patients randomly assigned to placebo plus C and P did not receive treatment: one was found to be ineligible for the study after random assignment, and one died before receiving the first dose. AE, adverse event; C, carboplatin; P, paclitaxel.

reasons for treatment discontinuation were progressive disease and AEs not considered related to progressive disease (Fig 1).

Most patients were male (82%) with a median age of 64 years (range, 33-84 years). Current smokers accounted for 57% of the study population. There were no clinically meaningful differences in baseline demographics or disease characteristics between treatment arms (Table 1).

Efficacy

At the time of the primary data cut-off, median OS follow-up was 19.3 months and 20.6 months for current smokers within the veliparib plus C and P and placebo plus C and P arms, respectively. There was no statistically significant survival benefit with the addition of veliparib to chemotherapy in current smokers; median OS was 11.9 versus 11.1 months; HR for death was 0.905 (95% CI, 0.744 to 1.101; $P = .266$; Fig 2).

Additional analyses were performed descriptively, using the final locked database. OS in the ITT population favored veliparib over placebo, with median OS 12.2 versus 11.2 months (HR, 0.853; 95% CI, 0.747 to 0.974; nominal $P = .032$; Fig 3A). The treatment effect was observed shortly after completion of study drugs and retained through most of the follow-up period; median follow-up at the final analysis was approximately 4 years (47.1 and 49.8 months in the veliparib and placebo arms, respectively). Median PFS in the ITT population was 5.6 months in both arms (HR, 0.897; 95% CI, 0.779 to 1.032; nominal $P = .107$; Fig 3B). Subgroup analyses were also performed in the ITT population according to sex, age ($< 65 \ v \geq 65$ years), ECOG PS (0 v 1), and region (Western Europe or Australia or Americas v Eastern Europe or Russia). The results were consistent across subgroups for OS and PFS.

The ORR (confirmed complete response plus partial response) was 37% in the veliparib arm and 37% in the placebo arm. Complete response was achieved by eight (2%) and four patients ($< 1\%$) in the veliparib and placebo arms, and partial response was achieved by 172 (35%) and 176 patients (36%), respectively (Data Supplement).

No clinically meaningful differences were observed between arms for duration of response, depth of response, quality of life, or changes in ECOG-PS (data not shown). Among patients who achieved an overall response (n = 180 per arm), median duration of response was 5.4 months with veliparib and 5.5 months with placebo. Mean tumor shrinkage from baseline was −35.1% with veliparib and −31.0% with placebo.

Approximately half of all patients received post-treatment anticancer therapy, which was comparable between treatment arms (Data Supplement).

Biomarker Analysis

LP52 status could be determined in tumor tissue samples from 360 patients. Overall, 202/360 (56%) patients were LP52+ (94 in the veliparib group and 108 in the placebo group), and 158 were LP52− (85 in the veliparib group and 73 in the placebo group). Baseline characteristics were similar between LP52+ and LP52− populations within both treatment arms and were comparable to the overall population. Minor imbalances were noted for sex and ECOG-PS (Data Supplement). Evaluated using the final clinical database, OS in the LP52+ population favored the veliparib arm (median OS, 14.0 v 9.6 months; HR, 0.66; 95% CI, 0.49 to 0.89; Fig 4A). The trend was reversed in the LP52− population with OS favoring the placebo arm (median OS, 11.0 v 14.4 months; HR, 1.33; 95% CI, 0.95 to 1.86; Fig 4B). Within the placebo arm, OS favored the LP52− population (HR, 1.6; 95% CI, 1.15 to 2.22]). Similarly, PFS in the LP52+ population favored the veliparib arm (median PFS, 5.78 v 5.62 months; HR, 0.79; 95% CI, 0.57 to 1.08), whereas in the LP52− population, PFS favored the

Parameter	Veliparib plus C and P	Placebo plus C and P
Events	197/276	205/276
Median OS, months (95% CI)	11.9 (10.5 to 13.5)	11.1 (9.6 to 12.6)
HR (95% CI); stratified log-rank P	0.905 (0.744 to 1.101); .266	

No. at risk:
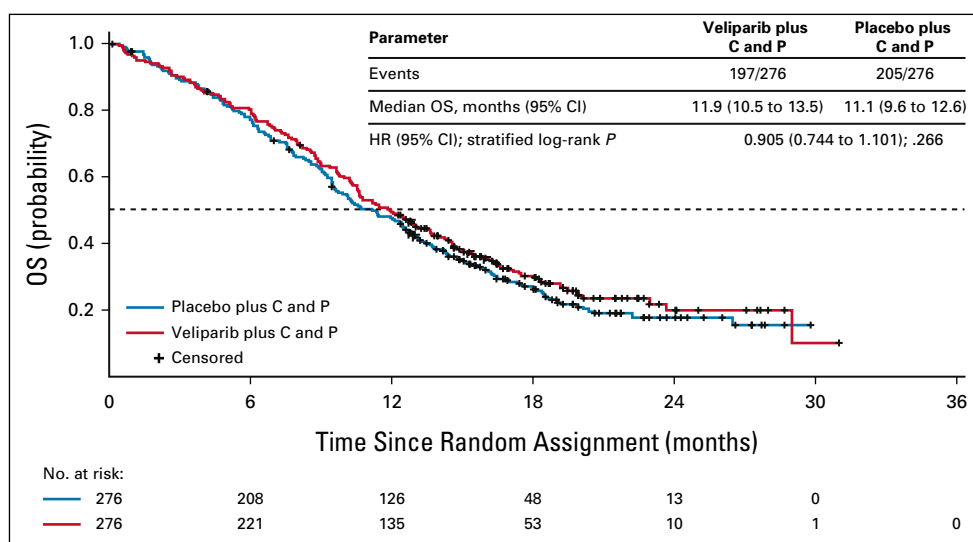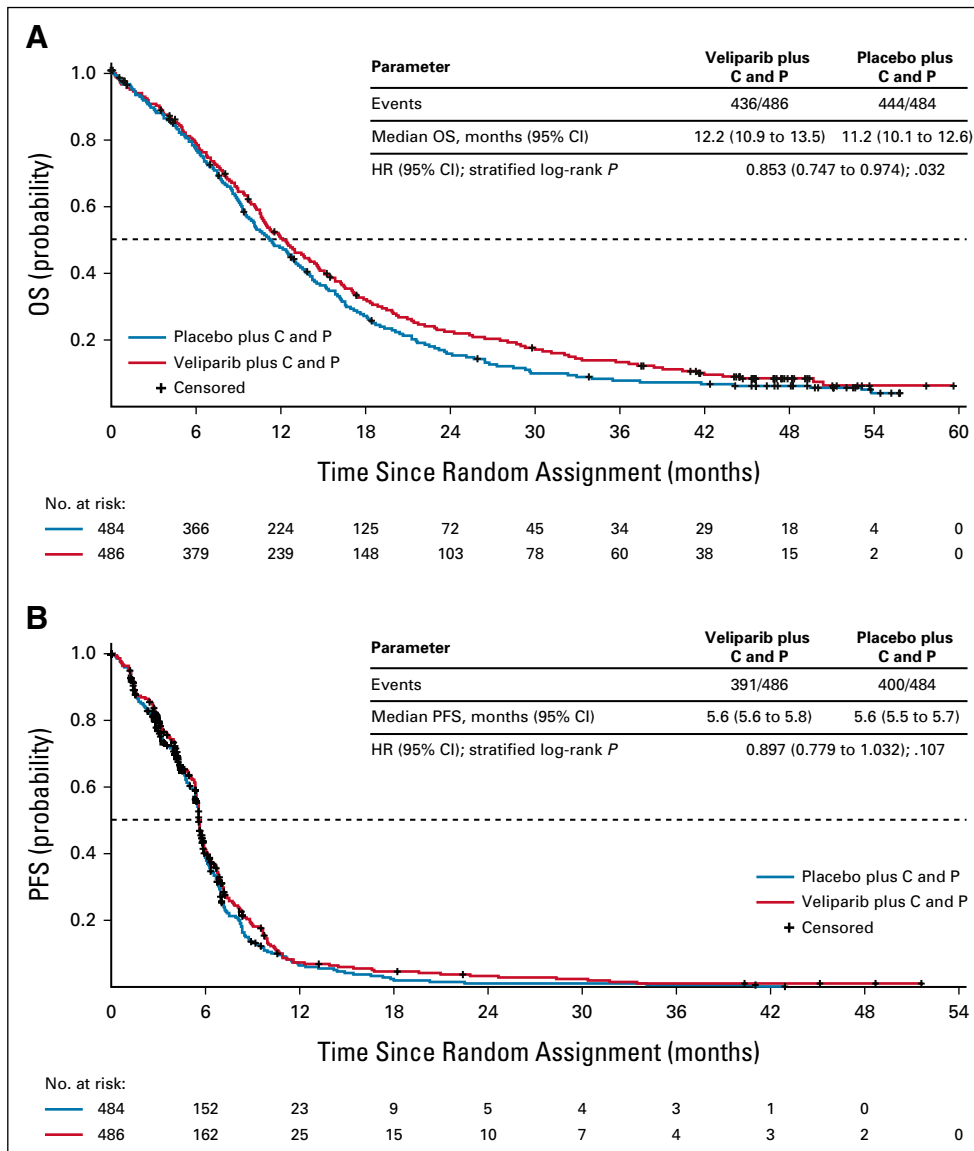|						
276	208	126	48	13	0	
276	221	135	53	10	1	0

FIG 2. OS in current smokers. C, carboplatin; HR, hazard ratio; OS, overall survival; P, paclitaxel.

FIG 3. (A) OS and (B) PFS in all patients (ITT). C, carboplatin; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; P, paclitaxel; PFS, progression-free survival.

placebo arm (median PFS, 5.59 v 5.88 months; HR, 1.38; 95% CI, 0.97 to 1.98; Fig 5). In LP52+ population, ORR was slightly higher in veliparib arm than in placebo; however, higher ORR was observed in placebo arm within the LP52− population (Data Supplement).

Molecular characterization of LP52+ and LP52− subgroups from RNA-seq data revealed a significantly higher stem score ($P < .0001$), a significant enrichment of TP53 inactivation score ($P = .0001$), as well as a low immune infiltrate in the LP52+ group (Data Supplement).

Safety

Treatment exposure was similar between arms; mean total dosed days was 34.2 for veliparib and 33.5 for placebo. Patients in both arms received a median of 6.0 cycles of veliparib or placebo, carboplatin, and paclitaxel. Relative dose intensity (RDI) was > 95% for all study drugs, and the relative dose intensity was similar between treatment arms. Mean veliparib predose concentrations were consistent between cycles 2-4.

Most patients experienced ≥ 1 AE (96% in both arms; Table 2). In total, 21% of patients in the veliparib arm and 23% in the placebo arm experienced an AE leading to discontinuation of veliparib or placebo. AEs leading to dose interruptions occurred in 24% and 23% of patients in the veliparib and placebo arms, respectively, and there were few dose reductions (Data Supplement).

AEs deemed related to study drug occurred in 45% of patients in the veliparib arm and 45% in the placebo arm; the most common were anemia, fatigue, and neutropenia
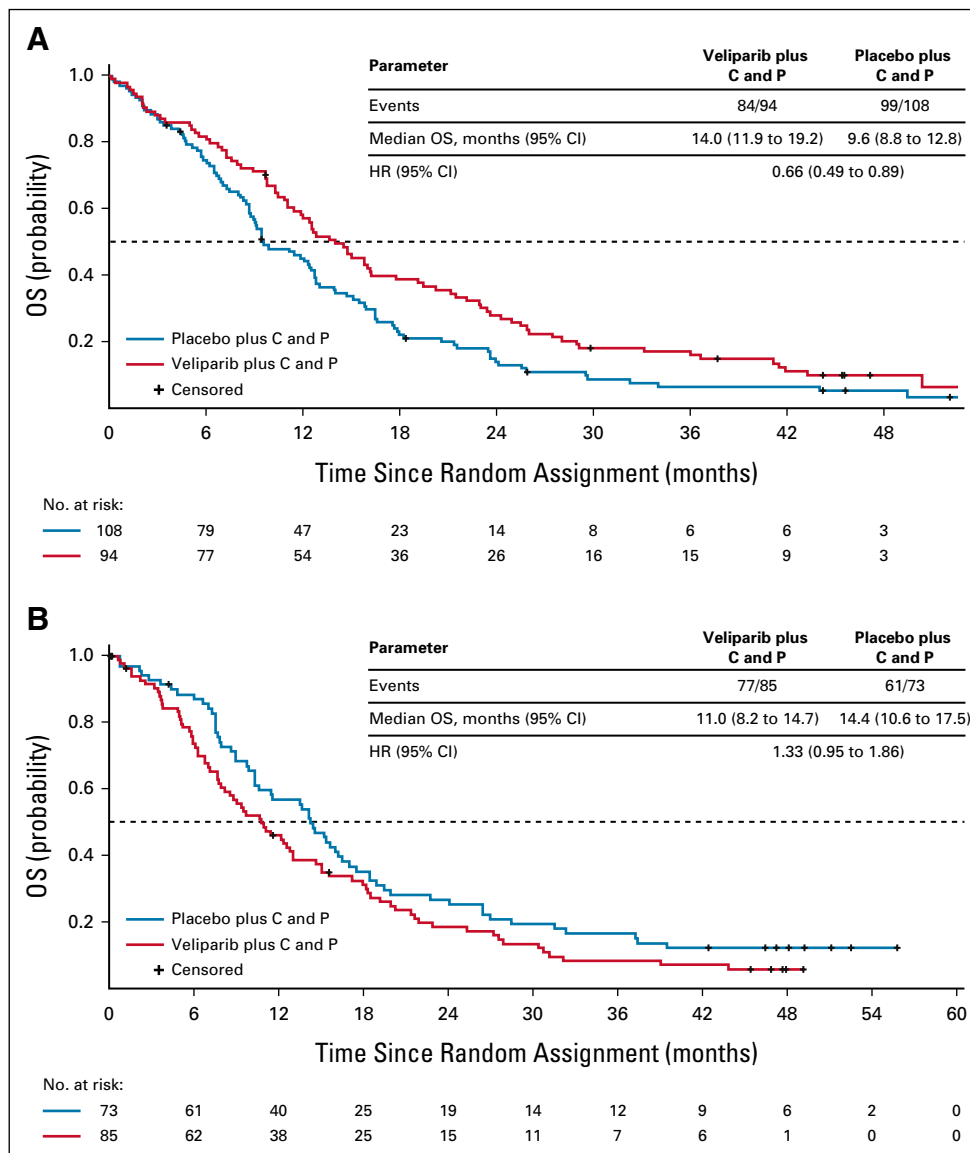
FIG 4. OS in (A) LP52+ and (B) LP52− populations of both treatment arms. C, carboplatin; HR, hazard ratio; OS, overall survival; P, paclitaxel.

(Data Supplement). Grade ≥ 3 AEs were reported in 60% of patients in the veliparib arm and 58% in the placebo arm; most were hematologic (Table 2). Grade 3 or 4 AEs considered related to study drug were experienced by 20% of patients in both treatment arms, the most frequent being neutropenia (9% in both arms). Serious AEs occurred in 32.0% of patients in the veliparib arm and 34.0% in the placebo arm, with pneumonia, febrile neutropenia, and anemia the most commonly reported in both arms (all ≤ 5% of patients).

Most thrombocytopenia events were nonserious, and hemorrhage events occurring within 14 days of thrombocytopenia were mostly minor (4/4 in the veliparib arm and 7/8 in the placebo arm were nonserious). Most neutropenia events were nonserious and infections were infrequent

within 14 days of a neutropenia event (6.8% and 6.0% in veliparib and placebo arms, respectively). AE-related deaths occurred in 38 (7.8%) patients in the veliparib arm and 44 (9.1%) in the placebo arm, and most were considered unrelated to study drugs.

DISCUSSION

This study did not meet its primary end point of improved OS in current smokers with veliparib plus C and P versus placebo plus C and P, despite this being a key observation in the phase II study of the same regimen and treatment schedule.[27] Thus, subsequent end points were evaluated in a descriptive manner. In the overall ITT population, median OS was slightly longer in the veliparib arm. The modest but consistent trend was seen from 6 months and retained for
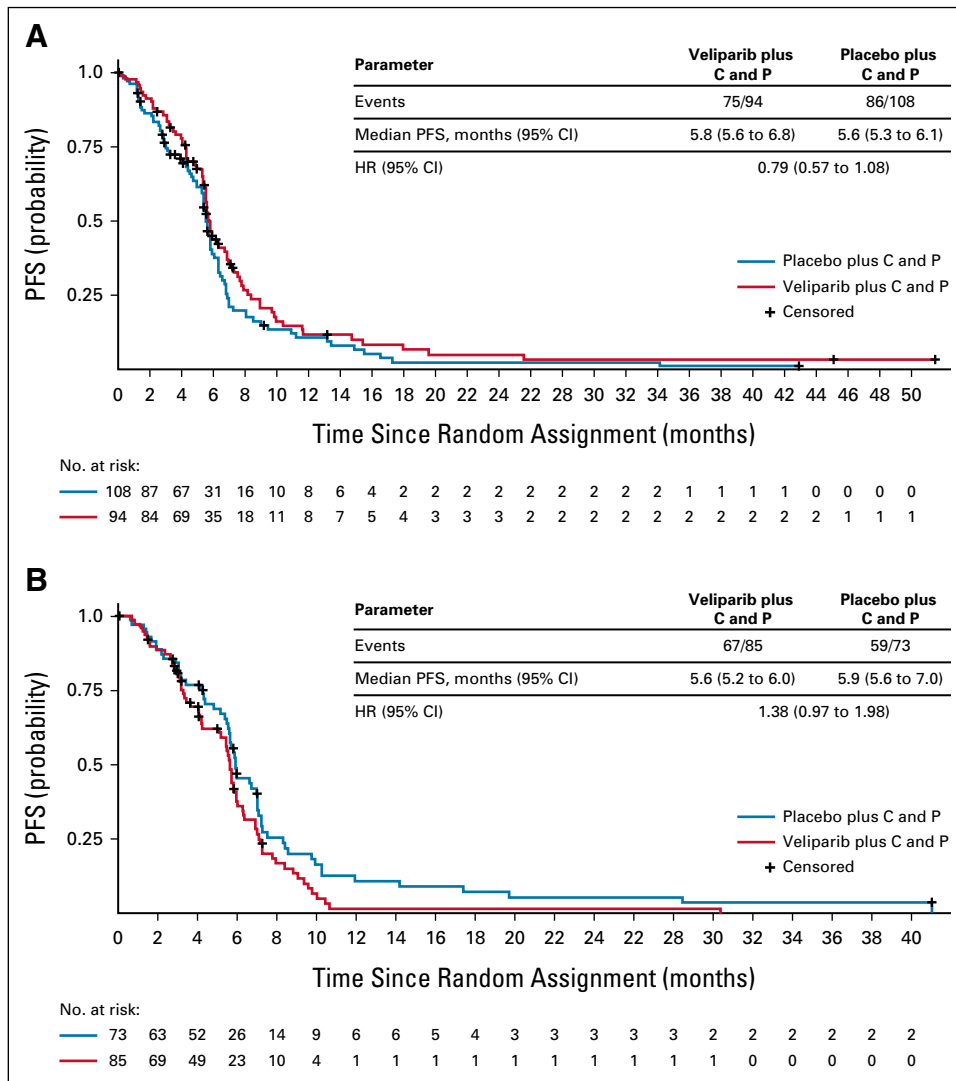
FIG 5. PFS in (A) LP52+ and (B) LP52− patients. C, carboplatin; HR, hazard ratio; P, paclitaxel; PFS, progression-free survival.

over 3 years with an overall decrease in risk of death of approximately 15% (HR, 0.853; 95% CI, 0.747 to 0.974). This suggests that within the overall ITT population, there may be a subgroup of patients more likely to derive benefit from veliparib, such as a biomarker-selected population. The exploratory LP52 biomarker analysis among 360 patients with evaluable tumor samples defined two populations with distinct molecular characteristics. Notably, there was a consistent trend for improved OS for the LP52+ population treated with veliparib plus C and P, with approximately 34% decrease in the risk of death compared with the control arm, suggesting this subgroup is deriving greater benefit from veliparib. The results for other efficacy parameters were generally similar between treatment arms in the ITT population, including PFS and ORR.

In the phase II study, improved PFS and OS was observed in current smokers, defined by patient-reported history, who received veliparib versus placebo (HR 0.38 and 0.43, respectively); current smokers also had greater ORR and depth of response. This treatment effect was also observed in patients with chemical evidence of recent smoking, defined as plasma cotinine > 10 ng/mL (HR of 0.38 and 0.52, respectively), which provided further support for the hypothesis that current smokers were most likely to benefit from veliparib treatment (although cotinine was not evaluated in this phase III study).[27] The hypothesis generated from the phase II study was not confirmed in the phase III study. The phase II study had a relatively small sample size (N = 158), used a 2:1 random assignment ratio, and enrolled both squamous and nonsquamous NSCLC patients, which may have led to spurious results in subgroup analyses. Additionally, the results for the control arm in the phase II (PFS and OS of 4.2 and 9.1 months, respectively) were worse than historical benchmarks for C and P in this population, suggesting that the treatment comparisons may partially reflect an underperforming control arm.

TABLE 2. Overview of All TEAEs Occurring in ≥ 10% of Patients and Grade 3 or 4 TEAEs Occurring in ≥ 5% of Patients in Either Arm

TEAE	Veliparib Plus C and P (n = 485)		Placebo Plus C and P (n = 482)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any TEAE	465 (96)	292 (60)	462 (96)	281 (58)
Alopecia	232 (48)	—	220 (46)	—
Anemia	169 (35)	46 (10)	167 (35)	52 (11)
Neutropenia	160 (33)	116 (24)	145 (30)	95 (20)
Peripheral sensory neuropathy	154 (32)	—	149 (31)	—
Nausea	116 (24)	—	116 (24)	—
Fatigue	101 (21)	—	108 (22)	—
Thrombocytopenia	95 (20)	28 (6)	102 (21)	33 (7)
Diarrhea	85 (18)	—	81 (17)	—
Constipation	75 (16)	—	84 (17)	—
Decreased appetite	69 (14)	—	78 (16)	—
Asthenia	71 (15)	—	72 (15)	—
Dyspnea	74 (15)	—	61 (13)	—
Arthralgia	65 (13)	—	67 (14)	—
Cough	62 (13)	—	69 (14)	—
Myalgia	56 (12)	—	43 (9)	—
Vomiting	44 (9)	—	54 (11)	—
Leukopenia	55 (11)	—	34 (7)	—

NOTE. Data are No. (%) unless otherwise stated.
Abbreviations: C, carboplatin; P, paclitaxel; TEAE, treatment-emergent adverse event.

Treatment exposure was similar between arms, consistent with other studies of veliparib with C and P[18,23,31]; however, planned veliparib exposure was lower than in studies where veliparib was administered continuously, given until disease progression, or as a monotherapy.[18,31,32] There were no new safety signals recorded for veliparib during this study and AEs were consistent with known safety profiles of the study drugs. The control arm performed as expected, with outcomes generally similar to the chemotherapy-only control arms of recent studies in similar populations, such as KEYNOTE-407.[8]

A unique feature of this large study was the provision of tumor samples for prospective biomarker analysis. Consistent with a previous analysis demonstrating the LSP signature as a negative prognostic indicator in NSCLC,[33] exploratory analyses in our study demonstrate potential for LP52+ as a negative prognostic indicator. In the control arm, shorter OS was observed in patients with LP52+ tumors compared with LP52− tumors (median OS 9.6 v 14.4 months) and was also shorter than the control arm overall (11.2 months). However, the data also suggest that LP52+ may be predictive of an OS benefit with veliparib plus C and P in these patients with a poor prognosis and currently limited treatment options. In an analogous pattern to the overall population, the LP52+ OS curves separated early and remained separate throughout follow-

up. It is noteworthy that these trends were not as evident for PFS, which may limit interpretation of such subgroup analyses. Nonetheless, these data warrant further investigation regarding the use of biomarkers to identify populations more sensitive to treatment effect.

The molecular characteristics of LP52+ tumors in this study were consistent with those previously reported for metastatic or aggressive tumors, namely a high stem score,[34] high p53 inactivation,[35] and low immune infiltrate (Data Supplement). Stem-cell properties are intrinsically linked to tissue lineage and differentiation status, and certain cancers may revert to a molecular state reminiscent of tissue or embryonic stem cells as they become more aggressive. PARP1/2 enzymes play a role in maintaining the self-renewal potency of embryonic cells.[36,37] Although the reason for the favorable outcome with veliparib in the LP52+ group is not known, we postulate that selective targeting of the cancer stem component, which is enriched in this group, may play a role. It is feasible that the targeting of tumor stem cells by PARP inhibition may enhance sensitivity of tumors to subsequent IO; however, our findings do not provide direct evidence of this. Interestingly, LP52 positivity was associated with a uniformly cold tumor immune microenvironment, creating an inverse relationship between high stem-cell score and low immune infiltrate, consistent with a previous report.[34] Such a molecular profile suggests that patients with LP52+ tumors may not respond

as well to anti–programmed cell death ligand-1 (PD-L1) therapy as their LP52− counterparts, a concept that warrants further investigation. Since this study was initiated, other studies of programmed cell death-1 (PD-1)/PD-L1–directed therapy in combination with platinum doublet chemotherapy have demonstrated a breakthrough in durable clinical benefit for a subset of patients with sqNSCLC, but reliable treatment-predictive biomarkers are still needed. Furthermore, observations in SCLC and other tumor types indicate that PARP inhibitors may augment the activity of PD-L1 inhibitors and enhance the antitumor immunity through activation of the STING innate pathway, essentially driving the conversion of an immune cold environment into a hot one.[38-40] An ongoing phase III study (NCT03976362) investigating the programmed cell death-1 inhibitor,

pembrolizumab, with olaparib or placebo as maintenance following pembrolizumab plus carboplatin and a taxane induction therapy, for the first-line treatment of metastatic sqNSCLC may shed further light on this potential treatment combination.[41]

Overall, we observed no therapeutic benefit of adding veliparib to C and P when using a clinical enrichment strategy focused on current smokers; however, exploratory biomarker analyses suggest that the LP52 signature may define a subgroup more likely to benefit from veliparib. These data support a role for biomarker-guided utilization of PARP inhibition with veliparib in a subset of sqNSCLC; further studies are warranted to confirm the predictive potential of this novel biomarker.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Veliparib in Combination With Platinum-Based Chemotherapy for First-Line Treatment of Advanced Squamous Cell Lung Cancer: A Randomized, Multicenter Phase III Study

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