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# Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Patients With Advanced Non-Squamous Non-Small Cell Lung Cancer

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## Abstract

**Patients with advanced non-squamous non-small cell lung cancers without oncogenic drivers have poor treatment outcomes. Overall, no survival benefit was observed in patients (N = 595) receiving veliparib plus chemotherapy versus chemotherapy alone. However, in the LP52+ population (n = 80), patients receiving veliparib plus chemotherapy trended toward improved survival. The LP52 signature may help predict patients more likely to benefit from veliparib.**

**Background:** This open-label Phase III trial (NCT02264990) evaluated the PARP inhibitor, veliparib, combined with carboplatin/paclitaxel versus chemotherapy alone for first-line treatment of patients with advanced non-squamous non-small cell lung cancers (NSCLC). A 52-gene expression classifier (LP52) previously shown to identify patients more likely to respond to veliparib was evaluated as a planned correlative analysis. **Materials and Methods:** Adult current or former smokers with advanced non-squamous NSCLC were randomized 1:1 to veliparib (120 mg daily for 7 days/cycle) with carboplatin and paclitaxel or to investigators' choice of platinum doublet chemotherapy (up to 6, 21-day cycles), with optional pemetrexed maintenance. Prospective analysis of the LP52 signature was conducted using a clinical Qiagen/HTG assay. The primary endpoint was overall survival (OS) in LP52+ patients. **Results:** Overall, 595 patients received veliparib + carboplatin/paclitaxel (n = 298) or chemotherapy alone (n = 297); 13% (n = 40) in each arm were LP52+. The primary endpoint was not met; median OS was 11.2 months with veliparib + carboplatin/paclitaxel versus 9.2 months with chemotherapy alone in the LP52+ subgroup (hazard ratio [HR] 0.644, 95% confidence interval [CI]: 0.396-1.048; P = .113). In the overall population, median OS was 12.1 months in both arms (HR 0.986, 95% CI: 0.827-1.176; P = .846). No new safety signals were observed. **Conclusion:** In patients with non-squamous NSCLC, there was no significant improvement in OS with veliparib + carboplatin/paclitaxel versus chemotherapy alone, although a trend toward improved OS in the LP52+ population suggests this subgroup may benefit from veliparib. Statistical power was limited due to the small sample size.

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**Keywords:** NSCLC, PARP inhibitor, Overall survival, Combination therapy, Biomarkers

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## Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide and incidence rates are intrinsically linked to smoking.<sup>1</sup> The vast majority of lung cancers are non–small cell lung cancers (NSCLCs) which are divided into squamous and non–squamous histology. Non–squamous NSCLC include adenocarcinoma, which is the most common NSCLC subtype, and large cell carcinoma.<sup>2,3</sup> Targeted therapies are the current standard of care for patients with advanced, oncogene-driven non–squamous NSCLC.<sup>4</sup> However, for patients with advanced NSCLC who do not have actionable oncogene mutations, platinum-based chemotherapy is the mainstay of first-line treatment, and a substantial proportion of these patients die within 3 years of diagnosis.<sup>5–7</sup> Identifying optimal treatments for patients with non–squamous NSCLC that is not oncogene-driven is a key challenge in improving outcomes for these patients.

Poly (adenosine diphosphate-ribose) polymerase (PARP) enzymes facilitate the repair of DNA damage.<sup>8,9</sup> PARP inhibitors have shown benefit in patients with tumors that exhibit deficiency in homologous recombination DNA repair, including loss of *BRCA1/2* function<sup>10–14</sup> and more recently have demonstrated activity against homologous recombination-competent tumors, including NSCLC.<sup>15</sup> Veliparib is a potent, oral PARP1/2 inhibitor which has demonstrated antitumor activity as monotherapy<sup>16,17</sup> and in combination with chemotherapy where it has enhanced the activity of platinum-based agents in preclinical models and in patients with solid tumors.<sup>18–21</sup> A randomized, Phase II, placebo-controlled trial in patients with untreated advanced or metastatic NSCLC showed a trend toward improved progression-free survival (PFS) and overall survival (OS) with the addition of veliparib to carboplatin/paclitaxel,<sup>21</sup> particularly in patients who were smokers.<sup>21</sup>

To facilitate the optimization of therapy, gene expression panel-based classification methods are being developed, validated, and applied, to better characterize poorly differentiated tumors, identify candidate prognostic biomarkers and direct targeted therapies.<sup>22,23</sup> Among these is a 57-gene lung subtyping panel (LSP) of 52 classification genes and 5 housekeeping genes which has demonstrated the ability to reproducibly differentiate squamous, adenocarcinoma, and neuroendocrine lung cancers, including poorly differentiated tumors.<sup>24–26</sup> The LSP was used to identify patients with poor prognosis in 3 independent NSCLC cohorts (N > 1000) which supports the potential for LSP as a gene expression-based prognostic marker in this population.<sup>25</sup>

The use of archived specimens from large perspective clinical trials has been proposed as a means to assess the medical utility of prognostic and predictive biomarkers.<sup>27</sup> We developed a new binary expression classification derived from the 52 classification genes of the LSP assay, referred to herein as Lung Panel 52 (LP52) (a list of the 52 genes included is provided in *Supplementary Methods 2, Table 1*). The predictive value of the LP52 classifier for improved efficacy with veliparib was initially identified in exploratory analyses of a Phase II veliparib trial in NSCLC (NCT01560104)<sup>21</sup> and was verified in a Phase III veliparib trial in squamous NSCLC, which demonstrated a potential benefit in overall survival (OS) in patients

with an LP52 positive (LP52+) status receiving veliparib.<sup>28</sup> Following prospective-retrospective verification of the LP52 classifier,<sup>27</sup> we hypothesized that this predictive value of LP52 to identify patients who have poorer outcomes and who may demonstrate an improved response to veliparib therapy may also be applicable to patients with non–squamous NSCLC.

This Phase III, randomized trial aimed to evaluate the efficacy and safety of veliparib combined with carboplatin/paclitaxel versus investigator's choice of standard chemotherapy as first-line treatment for patients with metastatic or advanced non–squamous NSCLC, including those who were LP52+. LP52 was evaluated prospectively as part of planned analyses. The study preceded the approval of immunotherapy as first-line treatment for non–squamous NSCLC, with the first visit occurring in September 2014 when platinum-based doublet chemotherapy, followed by maintenance treatment (such as pemetrexed), was standard of care.<sup>29</sup>

## Materials and Methods

### Patient Selection

Patients at least aged 18 years with a life expectancy of greater than 12 weeks and cytologically or histologically confirmed advanced or metastatic non–squamous NSCLC not amenable to surgical resection or radiation with curative intent at screening were eligible. Patients with mixed histology tumors were eligible if the tumor was predominantly non–squamous histology and did not include tumor cells with small cell histology. Recruitment was restricted to patients who were current or former smokers with at least 1 unidimensional measurable NSCLC lesion on a computed tomography scan as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, no history of brain metastases or evidence of central nervous system tumors at screening, and an Eastern Cooperative Oncology Group Performance Score (ECOG PS) of 0–1. Patients must have consented to provide archived tissue or a cytology sample of NSCLC tumor for analysis, if available.

Exclusion criteria included peripheral neuropathy of Grade 2 or above, squamous NSCLC or tumors with untreated *EGFR* mutation and/or *ALK* gene rearrangement, and a history of seizure within the last year. Prior cytotoxic chemotherapy or chemoradiotherapy for advanced NSCLC and recent radiotherapy were not permitted. Additional eligibility criteria are listed in *Supplementary Methods*.

### Study Design

This Phase III, randomized, open-label, multicenter study (NCT02264990) was conducted across 131 sites in 20 countries (enrolled from 2014 to 2016) and was performed in accordance with the protocol, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, applicable regulations and guidelines governing clinical study conduct, and ethical principles that have their origin in the Declaration of Helsinki. Each patient was required to give their informed consent.

Patients were randomized 1:1 to receive veliparib + carboplatin/paclitaxel or chemotherapy alone (investigator's choice of carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed) by an interactive response technology system with use of permuted blocks within strata. Variable block sizes of 2 and 4 were used. Randomization was stratified by smoking

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# Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice

**Table 1** Baseline Demographics and Disease Characteristics

	LP52+ population		Overall population	
	Veliparib + carboplatin /paclitaxel N = 40	Chemotherapy alone N = 40	Veliparib + carboplatin /paclitaxel N = 298	Chemotherapy alone N = 297
Gender				
Male	29 (73)	28 (70)	206 (69)	207 (70)
Female	11 (28)	12 (30)	92 (31)	90 (30)
Ethnicity				
White	31 (78)	27 (68)	229 (77)	233 (78)
Black	3 (8)	3 (8)	11 (4)	11 (4)
Asian	6 (15)	10 (25)	57 (19)	53 (18)
Other	0	0	1 (< 1)	0
Median age, y (range)	61 (37-79)	68 (39-81)	63 (27-81)	64 (34-85)
Geographic region				
Japan	6 (15)	7 (18)	35 (12)	37 (12)
United States, Western Europe, Australia, and Canada	21 (53)	26 (65)	157 (53)	177 (60)
Eastern Europe/Russia	13 (33)	4 (10)	88 (30)	68 (23)
Asia (excluding Japan)	0	3 (8)	18 (6)	15 (5)
Smoking status <sup>a</sup>				
Current smoker <sup>b</sup>	24 (60)	21 (53)	152 (51)	153 (52)
Former smoker <sup>c</sup>	16 (40)	19 (48)	146 (49)	144 (48)
ECOG performance status <sup>a</sup>				
0	11 (28)	14 (35)	116 (39)	113 (38)
1	29 (73)	26 (65)	182 (61)	184 (62)
Number of involved organ sites <sup>d</sup>				
1-2	24 (60)	22 (55)	169 (57)	162 (55)
> 2	15 (38)	18 (45)	125 (43)	134 (45)
Missing	1	0	4	1
Tumor stage				
Locally advanced	8 (20)	4 (10)	38 (13)	38 (13)
Metastatic	32 (80)	35 (90)	257 (87)	255 (87)
Missing	0	1	3	4
Median tumor burden, mm (range)	68 (10-302)	78 (12-227)	73 (10-367)	75 (10-288)
Median time from diagnosis to randomization, mo (range)	2.4 (0.8-91.3)	1.7 (0.9-42.8)	2.0 (0.4-121.3)	1.9 (0.3-100.5)
LP52 status				
LP52+	40 (100)	40 (100)	40 (13)	40 (13)
LP52-	0	0	74 (25)	53 (18)
LP52 unknown/missing	0	0	184 (62)	204 (69)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LP52 = Lung Panel 52. Data reported as n (%), unless otherwise stated. Percentages calculated on non-missing values.

<sup>a</sup> Based on interactive response technology data and used for stratification in randomization.

<sup>b</sup> > 100 smoking events over lifetime and smoked within the last year.

<sup>c</sup> > 100 smoking events over lifetime and not smoked within the last year.

<sup>d</sup> Collected from baseline tumor assessment.

status (current vs. former), investigator's preferred platinum doublet therapy (carboplatin/paclitaxel vs. cisplatin/pemetrexed vs. carboplatin/pemetrexed), gender (male vs. female), and ECOG PS (0 vs. 1).

Oral veliparib was administered on Days -2-5 (7 days, beginning 2 days prior to the first dose of carboplatin/paclitaxel) at a

dose of 120 mg twice daily of each 21-day cycle. Carboplatin (area under the curve [AUC] 6 mg/mL/min) and paclitaxel (200 mg/m<sup>2</sup>) were administered on Day 1 of each 21-day cycle. Within the chemotherapy-alone arm, carboplatin (AUC 6 mg/mL/min) and paclitaxel (200 mg/m<sup>2</sup>), or cisplatin (75 mg/m<sup>2</sup>) and pemetrexed (500 mg/m<sup>2</sup>), or carboplatin (AUC 6 or AUC 5 mg/mL/min) and

pemetrexed (500 mg/m<sup>2</sup>) were administered on Day 1 of each 21-day cycle. Treatment was continued for a maximum of 6 cycles, or until discontinuation due to toxicity or radiographic progression. Dose delays or modifications due to study drug toxicities were permitted. Eligible patients were encouraged to receive maintenance pemetrexed (500 mg/m<sup>2</sup>) on Day 1 of each 21-day cycle following completion of platinum doublet therapy.

Tumor assessments were conducted at baseline, prior to Cycles 3 and 5, and every 9 weeks during maintenance therapy until unacceptable toxicity or disease progression. Patients who did not receive maintenance therapy were assessed every 9 weeks for 1 year, then every 12 weeks until progression. During survival follow-up, all patients were contacted every 2 months until death, loss to follow-up, or study termination.

### Biomarker-defined Population

LP52 analysis was carried out on available tumor samples as previously described.<sup>24,28</sup> The current analysis used the same set of genes as the LP52 classifier assay in M11-089 and the original LSI.<sup>24,28</sup> While retrospective use of LP52 in M11-089 was based on an RNA sequencing (RNAseq) platform normalized within M11-089 samples, to define LP52+ patients for the primary analysis of M14-359, we collaborated with Qiagen (Hilden, Germany), and HTG Molecular Diagnostics (Tucson, AZ) to develop an Investigational Use Only (IUO) RNA assay for LP52 classification. The IUO version of LP52 is based on HTG EdgeSeq (or HTGseq) technology, which uses a quantitative nuclease protection assay chemistry combined with next-generation sequencing to produce a simple and reproducible platform that is more compatible with clinical use than RNAseq. The evolution of LP52 is illustrated in *Supplementary Figure 1*.

To develop the HTGseq-based IUO assay, a cohort of 422 lung cancer tissues of known histology were procured and profiled with both RNAseq and HTGseq. This cohort was divided into independent training ( $n = 327$ ) and testing ( $n = 95$ ) sets. An HTGseq-based classifier was developed using the training set to maximize the concordance of the LP52 assignment between the 2 platforms. The concordance rate, assessed using the testing set, is 85.7% in squamous histology, and 75.0% in adenocarcinoma histology. Unlike RNAseq-based calling, the IUO calling for each sample does not require clinical histology information and does not require batch normalization.

Additional information on the LP52 assay composition, development, and verification is provided in *Supplementary Methods 2*.

### Endpoints

The primary endpoint was OS with veliparib + carboplatin/paclitaxel compared with chemotherapy alone in LP52+ patients. OS was defined as the number of days from the date of randomization to the date of death. The primary endpoint was amended from OS in the current smoker population after all patients had been randomized, but prior to analysis of outcomes, and before results of the LP52 assay were available. This change was to enable the prospective application of a biomarker assay following the emergence of data from a Phase II study of veliparib + carboplatin/paclitaxel in NSCLC (M10-898; NCT01560104) and a

Phase III study of veliparib + chemotherapy in squamous NSCLC (M11-089; NCT02106546) that suggested the assay may have utility across NSCLC subtypes, with LP52 positivity identifying patients more likely to benefit from veliparib treatment.<sup>28</sup>

Secondary endpoints included OS in the overall population, PFS in LP52+ patients and the overall population, and objective response rate (ORR) in LP52+ patients and the overall population with veliparib + carboplatin/paclitaxel versus chemotherapy alone. PFS was defined as the time from randomization to disease progression (within 26 weeks from last tumor assessment) or death from any cause (within 12 weeks of the last tumor assessment) according to RECIST version 1.1, as assessed by the local investigator. Other efficacy endpoints were duration of response (DoR), depth of response, change in ECOG PS from baseline, and change from baseline in quality of life (QoL) scores compared between the 2 study arms in LP52+ patients and the overall population. Safety parameters were evaluated continuously during the study and adverse events (AEs) were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

### Statistical Analysis

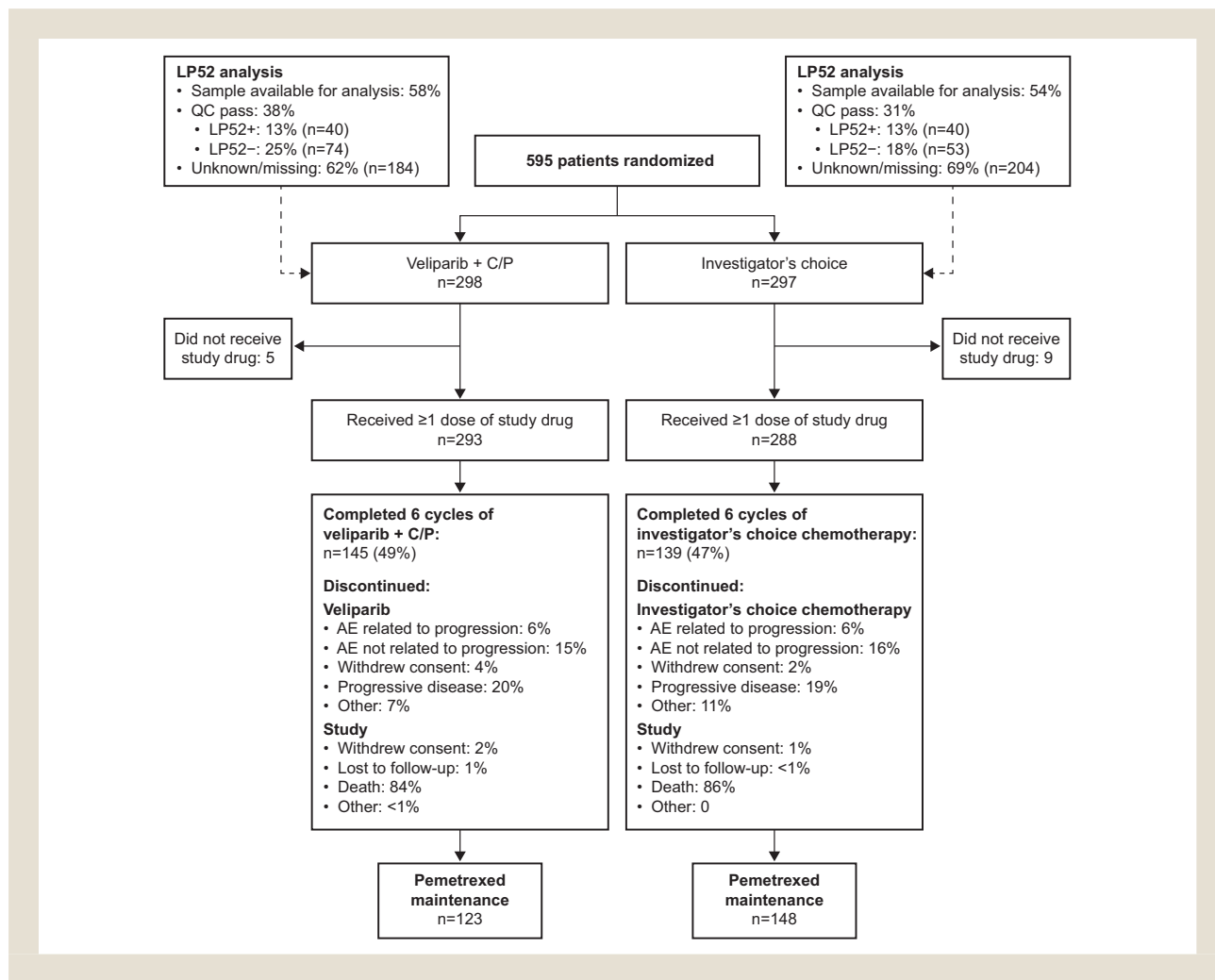
The study's original statistical design aimed to enroll 300 current smoker patients to accrue 210 OS events to provide at least 90% power at a 1-sided 0.025  $\alpha$  level (assuming a hazard ratio [HR] of 0.64) to detect a significant treatment effect. It was anticipated that 225 former smokers would be enrolled alongside current smokers for a total of approximately 525 patients.

The primary endpoint was amended from a non-biomarker selected non-squamous NSCLC population to the LP52+ population after the trial was fully enrolled. Accordingly, approximately 76% of total enrolled patients were estimated to have evaluable tumor tissue sample available for LP52 profiling with 50% LP52 positivity rate. Assuming 80% OS event rate, 180 OS events were expected that would give 82% power to detect significant treatment effect in LP52+ population. The data cutoff for the efficacy analyses reported in this manuscript was July 15, 2019. For all other analyses, all data accrued up to the database lock date of November 14, 2019 were used.

Unless otherwise noted, statistical significance was determined by a 2-sided  $P$  value  $\leq .05$  (corresponding to 1-sided  $\alpha$  level of 0.025) for all statistical analyses. Efficacy analyses were performed on the intention to treat (ITT) population including all randomized patients. Safety analyses were performed on the as-treated population including all randomized patients who received at least 1 dose of study drug. For the primary analysis, between-group differences were determined with a 2-sided log-rank test, stratified by ECOG PS (0, 1), investigator's preferred chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, carboplatin/pemetrexed), and gender. HRs and 95% confidence intervals (CI) were estimated using a stratified Cox proportional hazard model. The Kaplan-Meier method was used to generate time-to-event curves and to calculate median values. If statistical significance was shown for the primary endpoint analysis (ie, OS in LP52+ patients), secondary endpoints were to be tested using a fixed-sequence testing procedure in the following order: PFS in

# Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice

**Figure 1** Patient disposition. Abbreviations: AE = adverse event; C/P = carboplatin/paclitaxel; LP52 = Lung Panel 52; QC = quality control.



LP52+ patients, ORR in LP52+ patients, OS in all patients, PFS in all patients, and ORR in all patients. HRs were estimated using a covariate-adjusted Cox regression model with covariates being ECOG PS, investigator's preferred chemotherapy, and gender.

Analyses were done with SAS (Cary, NC) version 9.4 under the UNIX operating system.

## Results

### Patients

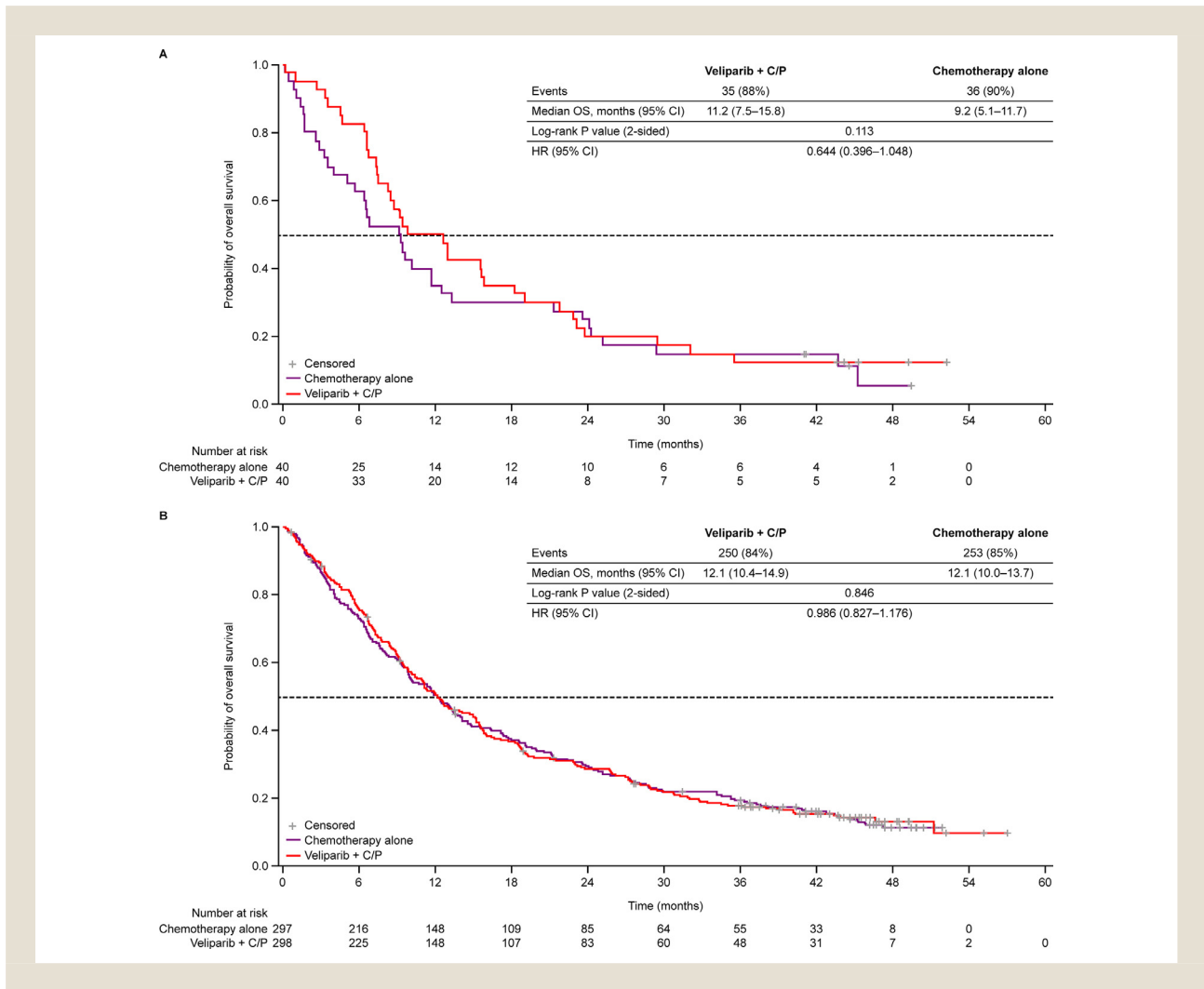
In total, 595 patients were randomized to receive veliparib + carboplatin/paclitaxel (n = 298) or chemotherapy alone (n = 297). Of those who received chemotherapy alone, 71 (24%) received carboplatin/paclitaxel, 95 (32%) received cisplatin/pemetrexed, and 131 (44%) received carboplatin/pemetrexed. Just under half of the patients in each arm completed the maximum 6 cycles of scheduled therapy; the primary reason for early discontinuation was progressive disease (Figure 1). Pemetrexed maintenance therapy was received by 123 (41%)

patients in the veliparib + carboplatin/paclitaxel arm and 148 (50%) patients in the chemotherapy-alone arm.

The percentage of patients who were able to provide a tumor tissue sample for analysis was less than the 76% that was estimated; 331 patients (56%) in the overall population provided a tumor tissue sample sufficient for LP52 evaluation (including > 50% tumor content), and 207 of these yielded analytically valid results (classified as LP52+ or LP52-); 388 patients were not able to provide tumor tissue that met these criteria and were classified unknown/missing. Among the total enrolled patients in each treatment arm, 13% were LP52+ in both the veliparib + carboplatin/paclitaxel arm and the chemotherapy-alone arm; 25% and 18% were LP52- in the veliparib + carboplatin/paclitaxel arm and the chemotherapy-alone arm, respectively.

The majority of patients were male (69%) and White (78%), and approximately half were current smokers (51%). There were no clinically meaningful differences in baseline demographics or disease characteristics between treatment arms in the overall or LP52+ populations (Table 1). Baseline demographics and charac-

**Figure 2** Kaplan–Meier curves for OS in the (A) LP52+ population and (B) Overall Population. Abbreviations: C/P = carboplatin/paclitaxel; CI = confidence interval; HR = hazard ratio; LP52 = Lung Panel 52; OS = overall survival.



teristics were also balanced between the 3 regimens within the chemotherapy-alone group, with the exception of a higher proportion of patients enrolled from Eastern Europe and Russia in the carboplatin/paclitaxel group (*Supplementary Table 1*).

### Efficacy

At the time of the primary data cutoff (July 15, 2019), median OS follow up within the veliparib + carboplatin/paclitaxel and chemotherapy-alone arms was 45.3 months and 44.5 months, respectively, in the LP52+ population, and 44.6 and 45.4 months in the overall population. There were 71 OS events in the 80 LP52+ patients across both treatment arms, representing 89% maturity.

The primary efficacy endpoint of OS in LP52+ patients was not met; there was no statistically significant OS benefit for the patients with LP52 positivity who received veliparib + carboplatin/paclitaxel ( $n = 40$ ) compared with chemotherapy alone ( $n = 40$ ), despite an early and consistent separation of survival curves. Median OS was 11.2 months in the veliparib + carboplatin/paclitaxel arm and

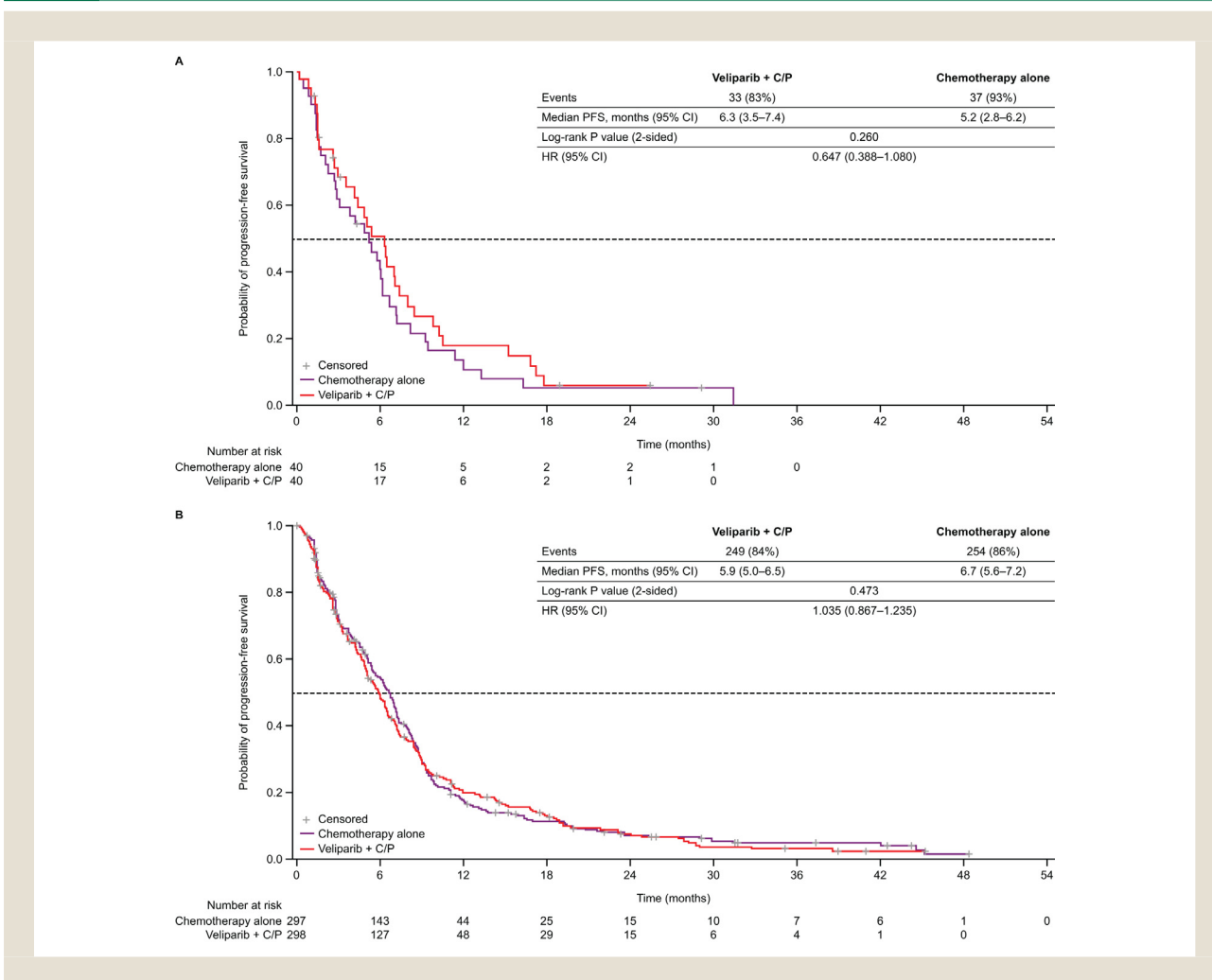
9.2 months in the chemotherapy-alone arm (HR: 0.644 [95% CI: 0.396–1.048], stratified log-rank 2-sided  $P = .113$ ) (*Figure 2A*).

Because the primary endpoint was not met, analyses of secondary efficacy endpoints were carried out in a descriptive manner. The trend for OS benefit observed in the LP52+ patients was not observed in the overall population; median OS was 12.1 months in both arms (HR: 0.986 [95% CI: 0.827–1.176]; nominal 2-sided  $P = .846$ ) (*Figure 2B*). Similarly, there was no trend toward an OS benefit in LP52– patients, or those with unknown or missing LP52 status (*Supplementary Figure 2*). Median OS was 12.1 months in both arms for LP52– patients (HR: 0.922 [95% CI: 0.623–1.366]; nominal 2-sided  $P = .996$ ). For those with unknown or missing LP52 status, OS was 12.3 months and 13.0 months in the veliparib + carboplatin/paclitaxel and chemotherapy-alone arms, respectively (HR: 1.086 [95% CI: 0.873–1.350]; nominal 2-sided  $P = .364$ ).

PFS directionally favored veliparib + carboplatin/paclitaxel versus chemotherapy alone in the LP52+ population, with medians

# Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice

**Figure 3** Kaplan–Meier curves for PFS in the (A) LP52+ population and (B) Overall Population. Abbreviations: C/P = carboplatin/paclitaxel; CI = confidence interval; HR = hazard ratio; LP52 = Lung Panel 52; OS = overall survival; PFS = progression-free survival.



of 6.3 and 5.2 months, respectively (HR: 0.647 [95% CI: 0.388–1.080]; nominal 2-sided  $P = .260$ ; *Figure 3A*). In the overall population, PFS did not improve at 5.9 months and 6.7 months in the veliparib + carboplatin/paclitaxel versus chemotherapy-alone arms, respectively (HR: 1.035 [95% CI: 0.867–1.235]; nominal 2-sided  $P = .473$ ) (*Figure 3B*). Median PFS was 5.6 months in the veliparib + carboplatin/paclitaxel arm, versus 7.2 months in the chemotherapy-alone arm for LP52– patients (HR: 1.066; 95% CI: 0.687–1.654) and 6.0 months versus 6.9 months amongst those with unknown or missing LP52 status (HR: 1.136; 95% CI: 0.914–1.413) (data not shown).

Among the LP52+ patients, ORR was 23% in the veliparib + carboplatin/paclitaxel arm and 30% in the chemotherapy-alone arm (*Table 2*). All responses were partial. Stable disease as best response was achieved by 43% of patients in the veliparib + carboplatin/paclitaxel arm and 38% in the chemotherapy-alone arm. In the overall population, ORR was achieved by 26% of patients in the veliparib + carboplatin/paclitaxel

arm and 29% of patients in the chemotherapy-alone arm. Two patients in each arm achieved complete response. Similar proportions of patients achieved stable disease as best response (43% in the veliparib + carboplatin/paclitaxel arm and 40% in the chemotherapy-alone arm).

No clinically meaningful differences were observed between treatment arms for DoR. For patients who achieved an objective response within the overall population ( $n = 164$ ), median DoR was 7.3 months in the veliparib + carboplatin/paclitaxel arm, and 6.6 months in the chemotherapy-alone arm. Among responders in the LP52+ population ( $n = 21$ ), median DoR was 9.0 months in the veliparib + carboplatin/paclitaxel arm, and 6.1 months in the chemotherapy-alone arm.

Approximately half of all patients received posttreatment anti-cancer therapy, which was comparable between treatment arms (*Supplementary Table 2*).



**Table 2** ORR in LP52+ and Overall Populations

	LP52+ population		Overall population	
	Veliparib + carboplatin/paclitaxel n = 40	Chemotherapy alone n = 40	Veliparib + carboplatin/paclitaxel n = 298	Chemotherapy alone n = 297
Objective response, n (%)				
CR	0	0	2 (1)	2 (1)
PR	9 (23)	12 (30)	76 (26)	84 (28)
ORR (CR+PR)	9 (23)	12 (30)	78 (26)	86 (29)
Odds ratio (95% CI)	0.66 (0.23-1.90)		0.86 (0.59-1.24)	
P value	.445		.409	
Best response, n (%)				
CR	0	0	2 (1)	4 (1)
PR	13 (33)	14 (35)	103 (35)	113 (38)
SD	17 (43)	15 (38)	127 (43)	119 (40)
PD	7 (18)	4 (10)	34 (11)	34 (11)
Incomplete data	3 (8)	7 (18)	32 (11)	27 (9)

Abbreviations: CI = confidence interval; CR = complete response; LP52 = Lung Panel 52; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

### Safety

Patients in the veliparib + carboplatin/paclitaxel arm received a median of 5 cycles of veliparib, with a mean of 32 dosed days (out of a maximum of 42). Chemotherapy exposure was comparable between the veliparib + carboplatin/paclitaxel arm (median of 5 cycles each for carboplatin/paclitaxel) and the chemotherapy-alone arm (median of 5 cycles). Relative dose intensity was  $\geq 94\%$  for all study drugs in the overall population.

The majority of patients experienced at least one AE (98% in the veliparib + carboplatin/paclitaxel arm and 96% in the chemotherapy-alone arm), the most common being alopecia (47%), peripheral sensory neuropathy (45%), and anemia (41%) in the veliparib + carboplatin/paclitaxel arm, and nausea (47%), anemia (42%), and neutropenia (33%) in the chemotherapy-alone arm (Table 3). AEs occurring more frequently with veliparib + carboplatin/paclitaxel and with a  $\geq 10\%$  difference between the randomized treatment arms included alopecia (47% and 12%, respectively) and peripheral sensory neuropathy (45% and 15%), both of which are toxicities associated with paclitaxel (received by all patients in veliparib arm and  $< 25\%$  of patients in the chemotherapy-alone arm). AEs occurring within the chemotherapy-alone arm reflected the distinct safety profiles of each regimen (Supplementary Table 3).

In the veliparib + carboplatin/paclitaxel treatment arm, AEs leading to discontinuation of veliparib, carboplatin or paclitaxel occurred in 27% of patients, with the most common being peripheral sensory neuropathy (5%), malignant neoplasm progression (4%), and anemia (3%). Within the chemotherapy-alone arm, AEs leading to discontinuation were experienced by 25% of patients overall, and this was broadly comparable across regimens. In the veliparib + carboplatin/paclitaxel arm, AEs that led to delay or reduction of veliparib occurred in 25% of patients, and AEs leading to delay or reduction of carboplatin/paclitaxel dosing occurred in 37%/42% of patients. In the chemotherapy-alone arm, 45% of patients experienced an AE that led to delay or reduction of dose; the

most frequently reported of these were hematologic across regimens, and treatment arms.

AEs considered veliparib, carboplatin, or paclitaxel-related were experienced by 59%, 89%, and 91% of patients in the veliparib + carboplatin/paclitaxel arm, respectively. Within the chemotherapy-alone arm, AEs considered chemotherapy-related were experienced by 89% of patients overall (77%/81%, 90%/87%, and 91%/91% in those who received carboplatin/paclitaxel, cisplatin/pemetrexed, and carboplatin/pemetrexed, respectively).

Grade 3 or 4 AEs were experienced by 68% of patients in the veliparib + carboplatin/paclitaxel arm and 57% of patients in the chemotherapy-alone arm, the majority of which were hematologic (Table 3). Only neutropenia occurred at  $\geq 10\%$  difference between treatment arms. Serious AEs were experienced by 41% of patients in the veliparib + carboplatin/paclitaxel arm and 34% in the chemotherapy-alone arm (Supplementary Table 4). The most frequent of these that were considered study-drug related in the veliparib + carboplatin/paclitaxel arm were febrile neutropenia, anemia, neutropenia, vomiting, and pneumonia, while the most frequent considered related to doublet chemotherapy in the chemotherapy-alone arm was anemia. AE-related deaths occurred in 8% of patients in both treatment arms. Two deaths (0.7%) were assessed as having a reasonable possibility of being related to veliparib.

### Discussion

The study did not meet its primary endpoint, with no significant OS improvement observed with veliparib + carboplatin/paclitaxel versus chemotherapy alone in LP52+ patients. The original primary endpoint in the current smoker population was amended in light of emerging data from LP52+ populations in other studies,<sup>28</sup> which occurred following randomization and treatment in this study. The change in endpoint resulted in a smaller primary analysis population (40 patients in each arm) which should be considered when inter-

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**Table 3** TEAEs Occurring in  $\geq 10\%$  of Patients and Grade 3/4 TEAEs Occurring in  $\geq 5\%$  of Patients, in Any Treatment Arm

	Veliparib + carboplatin /paclitaxel N = 293		Chemotherapy alone N = 288	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE	286 (98)	198 (68)	277 (96)	163 (57)
Alopecia	137 (47)	1 (< 1)	34 (12)	0
Peripheral sensory neuropathy	132 (45)	14 (5)	42 (15)	3 (1)
Anemia	119 (41)	49 (17)	122 (42)	47 (16)
Neutropenia	110 (38)	85 (29)	94 (33)	53 (18)
Nausea	89 (30)	5 (2)	134 (47)	7 (2)
Fatigue	80 (27)	5 (2)	91 (32)	10 (3)
Thrombocytopenia	78 (27)	20 (7)	60 (21)	26 (9)
Constipation	71 (24)	3 (1)	93 (32)	0
Decreased appetite	65 (22)	6 (2)	81 (28)	9 (3)
Diarrhea	53 (18)	6 (2)	49 (17)	4 (1)
Dyspnea	50 (17)	8 (3)	32 (11)	9 (3)
Leukopenia	45 (15)	20 (7)	40 (14)	13 (5)
Vomiting	45 (15)	3 (1)	78 (27)	7 (2)
Arthralgia	40 (14)	5 (2)	26 (9)	2 (1)
Myalgia	38 (13)	3 (1)	17 (6)	1 (< 1)
Insomnia	37 (13)	0	30 (10)	1 (< 1)
Asthenia	30 (10)	3 (1)	32 (11)	5 (2)
Cough	27 (9)	1 (< 1)	29 (10)	0
Pneumonia	25 (9)	18 (6)	13 (5)	7 (2)
Dysgeusia	19 (6)	0	29 (10)	0
Stomatitis	19 (6)	1 (< 1)	30 (10)	3 (1)
Febrile neutropenia	15 (5)	15 (5)	7 (2)	7 (2)
Pulmonary embolism	8 (3)	7 (2)	13 (5)	13 (5)

Abbreviation: TEAE = treatment emergent adverse event.

preparing these data. With a valid sample availability rate of just 35% and 80 LP52+ patients across the treatment arms, statistical power was limited.

There was a trend for OS and PFS benefit with veliparib + carboplatin/paclitaxel compared with chemotherapy alone in the LP52+ population, with an early, and consistent separation of survival curves. In the overall population, these efficacy outcomes were similar between treatment arms, and no clinically meaningful differences were observed for ORR, DoR, and changes from baseline in QoL and ECOG PS.

Exposure to chemotherapy was similar between treatment arms, and across the regimens administered in the chemotherapy-alone arm, with relative dose intensity  $\geq 94\%$  for all study drugs in the overall population. Of note, planned exposure to veliparib was lower than in other studies where veliparib was administered continuously or as monotherapy.<sup>10,30,31</sup>

Veliparib demonstrated an acceptable safety profile, with no new safety signals for the study combination. The higher frequency of alopecia and peripheral neuropathy reported in the veliparib arm may be a consequence of the higher proportion of patients who received paclitaxel (100% of patients in the veliparib + carboplatin/paclitaxel arm versus 24% in the chemotherapy arms, respec-

tively); this is reflected in the broadly comparable rates of these AEs in the veliparib + carboplatin/paclitaxel and carboplatin/paclitaxel arms. Hence, these data should be interpreted with caution.

Our results are consistent with those from a recent study that evaluated veliparib + carboplatin/paclitaxel versus placebo + carboplatin/paclitaxel as first-line treatment for patients with advanced squamous NSCLC, where no significant benefit was noted among efficacy parameters in the overall population. However, among the 360 patients evaluated for LP52, a trend for improved OS was observed in the veliparib + carboplatin/paclitaxel arm with  $\sim 34\%$  decreased risk of death versus placebo in patients who were LP52+.<sup>28</sup> The current study provides promising evidence for the potential of LP52 as a biomarker which may identify those patients more likely to benefit from addition of veliparib to carboplatin/paclitaxel. In addition, the median OS for LP52+ and LP52- subgroups within the chemotherapy-alone arm (9.2 months and 12.1 months, respectively) of this study suggests LP52 positivity may be an indicator of poor prognosis, consistent with data from the LSP signature.<sup>25</sup> In development of the HTGseq-based IUO assay using procured lung cancer tissue samples of known histology, the concordance rate between RNAseq and HTGseq in the adenocarcinoma samples was 75%, which may limit the conclusions in this

population; however, interestingly, the concordance rate was over 85% in the squamous, suggesting that this subgroup of patients may be more reliably classified as LP52+ or LP52-.

Consistent with the findings in squamous NSCLC,<sup>28</sup> LP52+ tumors in the current trial samples were identified to have high stem score (*Supplementary Figure 3A*) and high p53 inactivation score (*Supplementary Figure 3B*). This phenomenon was also observed in 2 independent squamous NSCLC cohorts: The Cancer Genome Atlas program and a cohort of procured tissues to HTG classifier development (data not shown). 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.<sup>32</sup> PARP1/2 enzymes play a role in maintaining the self-renewal potency of embryonic cells.<sup>33,34</sup> LP52+ tumors may be more aggressive in nature. The antitumor activity observed with veliparib in the LP52+ group may be due to selective targeting of the cancer stem component, which is enriched in this group.

At the time this study was initiated, platinum-based doublet chemotherapy was the standard first-line treatment for non-squamous NSCLC without a targetable *EGFR* or *ALK* mutation.<sup>29,35</sup> Since then, the treatment paradigm has evolved and diversified with the approval of immunotherapies and additional targeted therapies.<sup>4</sup> Several studies have supported the immunomodulating effects of PARP inhibition, which can potentially enhance the clinical response to immunotherapies.<sup>36-38</sup> Based on this rationale, several ongoing clinical trials are assessing the efficacy, and safety of PARP inhibition combined with immunotherapy in lung cancer. The phase III KEYLYNK-006 and KEYLYNK-008 trials are evaluating pembrolizumab plus platinum-based regimen followed by pembrolizumab and maintenance olaparib in non-squamous NSCLC and squamous NSCLC, respectively.<sup>39,40</sup> The KEYLYNK-012 trial is another ongoing phase III trial, which assesses the superiority of pembrolizumab with concurrent chemoradiation therapy followed by pembrolizumab with or without olaparib versus concurrent chemoradiation followed by durvalumab in patients with stage III NSCLC.<sup>41</sup> The current therapeutic landscape is heavily in flux and these ongoing trials will further elucidate the potential benefit of PARP inhibition in NSCLC patients in different settings. Furthermore, the optimal positioning of therapies, both currently available and in development, for patients with non-squamous NSCLC without actionable alterations may be facilitated by the identification of robust biomarkers.

## Conclusions

No significant benefit was observed with the addition of veliparib to carboplatin/paclitaxel compared with chemotherapy alone for the treatment of patients with advanced or metastatic non-squamous NSCLC, both in the overall population and the LP52+ population. However, an early and consistent trend for improved OS and PFS was noted in the LP52+ population, supporting previous data and suggesting that this genetic signature may identify a population of patients more likely to benefit from veliparib. Additional research is required to further explore this in a larger, biomarker-selected population.

## Clinical Practice Points

- Platinum-based chemotherapy is one of the front-line therapies for patients with advanced non-small cell lung cancer (NSCLC) without actionable oncogene mutations. However, clinical outcomes are poor and there is an unmet clinical need to improve treatment options for these patients
- Biomarker studies are being developed to identify candidate prognostic biomarkers and to direct targeted therapies. We previously developed Lung Panel 52 (LP52), derived from the 52 classification genes of the lung subtyping panel, and showed the predictive value of LP52 in identifying patients with poor prognosis and improved response to PARP inhibitor treatment in exploratory analyses of phase II and phase III trials
- In this study, patients with advanced NSCLC, including those who are LP52+, were randomized to receive veliparib combined with carboplatin/paclitaxel or chemotherapy alone. While in the overall population the progression free survival and overall survival were similar between treatment arms, the LP52+ population showed a positive trend for these outcomes when receiving veliparib plus carboplatin/paclitaxel compared with chemotherapy alone
- This study showed evidence for the potential of LP52 as a predictive biomarker. LP52+ gene expression signature may help to identify a subgroup of patients with poor prognosis and to predict those more likely to benefit from the addition of PARP inhibition to chemotherapy

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## Data Sharing Statement

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 (eg, 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>.

## Author Contributions

*R. Govindan*: Conceptualization; Methodology; Formal analysis; Investigation; Resources; Writing - review & editing; Supervision; *M. Lind*: Investigation; Resources; Writing - review & editing;

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## Supplementary materials

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