Randomized Phase II Trial of Cisplatin and Etoposide in Combination With Veliparib or Placebo for Extensive-Stage Small-Cell Lung Cancer: ECOG-ACRIN 2511 Study

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PURPOSE Veliparib, a poly (ADP ribose) polymerase inhibitor, potentiated standard chemotherapy against small-cell lung cancer (SCLC) in preclinical studies. We evaluated the combination of veliparib with cisplatin and etoposide (CE; CE+V) doublet in untreated, extensive-stage SCLC (ES-SCLC).

MATERIALS AND METHODS Patients with ES-SCLC, stratified by sex and serum lactate dehydrogenase levels, were randomly assigned to receive four 3-week cycles of CE (75 mg/m² intravenously on day 1 and 100 mg/m² on days 1 through 3) along with veliparib (100 mg orally twice per day on days 1 through 7) or placebo (CE+P). The primary end point was progression-free survival (PFS). Using an overall one-sided 0.10-level log-rank test, the study had 88% power to demonstrate a 37.5% reduction in the PFS hazard rate.

RESULTS A total of 128 eligible patients received treatment on protocol. The median age was 66 years, 52% of patients were men, and Eastern Cooperative Oncology Group performance status was 0 for 29% of patients and 1 for 71%. The respective median PFS for the CE+V arm versus the CE+P arm was 6.1 versus 5.5 months (unstratified hazard ratio [HR], 0.75 [one-sided $P = .06$]; stratified HR, 0.63 [one-sided $P = .01$]), favoring CE+V. The median overall survival was 10.3 versus 8.9 months (stratified HR, 0.83; 80% CI, 0.64 to 1.07; one-sided $P = .17$) for the CE+V and CE+P arms, respectively. The overall response rate was 71.9% versus 65.6% (two-sided $P = .57$) for CE+V and CE+P, respectively. There was a significant treatment-by-strata interaction in PFS: Male patients with high lactate dehydrogenase levels derived significant benefit (PFS HR, 0.34; 80% CI, 0.22 to 0.51) but there was no evidence of benefit among patients in other strata (PFS HR, 0.81; 80% CI, 0.60 to 1.09). The following grade ≥ 3 hematology toxicities were more frequent in the CE+V arm than the CE+P arm: CD4 lymphopenia (8% v 0%; $P = .06$) and neutropenia (49% v 32%; $P = .08$), but treatment delivery was comparable.

CONCLUSION The addition of veliparib to frontline chemotherapy showed signal of efficacy in patients with ES-SCLC and the study met its prespecified end point.

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BACKGROUND

Systemic chemotherapy with a platinum and etoposide combination remains the most commonly used frontline treatment of extensive-stage small-cell lung cancer (ES-SCLC).¹ Although this regimen induces objective tumor response in 50% to 70% of patients, the response is not durable, leading to a modest median overall survival (OS) of approximately 9 to 11 months and survival rate at 5 years < 5%.² Significant improvement in clinical outcome for patients with ES-SCLC has been very difficult to achieve over the past two decades.³⁻⁵ Although a high-intensity, multiagent chemotherapy regimen achieved an improved response rate, these strategies did not translate

into survival benefit, because of the heightened toxicities and treatment-related mortality. The addition of biologic agents with limited additive toxicity to standard platinum-based chemotherapy is an area of active investigation, but this strategy has yet to translate into improved efficacy and better outcome for patients, in part because there is no strong mechanistic rationale for the previously evaluated combinations of platinum doublet and targeted agents.⁶⁻⁹

Poly (ADP-ribose) polymerase (PARP) is a family of enzymes that catalyze the addition of ADP-ribose to a variety of cellular molecules, including DNA, histones, and nonhistone proteins.¹⁰ PARP is involved in DNA damage repair, primarily through the base excision

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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repair mechanism, and its inhibition induces synthetic lethality in genetically vulnerable cancer cells, such as BRCA-deficient tumors with defective homologous recombination-repair capacity.¹¹ In addition, PARP inhibition also enhances anticancer agents that exert their cytotoxic effect through DNA damage induction.¹² PARP overexpression has been linked to drug resistance and the ability of tumor cells to withstand genotoxic stress. SCLC shows high PARP expression in comparison with normal lung epithelial cells and other histologic subtypes of lung cancer.¹³ Small-molecule PARP inhibitors such as veliparib and talazoparib potentiated standard chemotherapy agents and radiation against SCLC in in vitro and in vivo preclinical models.^{14,15} Furthermore, talazoparib showed a modest single-agent activity in relapsed SCLC in a phase I trial.¹⁶ We showed the combination of veliparib with platinum doublet of cisplatin and etoposide (CE) to be safe and tolerable in a phase I trial.¹⁷ The current phase II study was conducted, therefore, to evaluate the additive benefit of veliparib when combined with standard frontline chemotherapy regimen of CE in patients with previously untreated ES-SCLC.

MATERIALS AND METHODS

Objectives

The primary objective of this phase II trial was to determine whether the addition of veliparib to cisplatin and etoposide (CE+V) resulted in improved progression-free survival (PFS) over CE with placebo (CE+P) as frontline treatment of newly diagnosed ES-SCLC. Salient secondary objectives were to determine differences in overall survival (OS), overall response rate (ORR), and toxicity profile between the two arms of the study. The study was approved by the respective institutional review boards at all participating sites. Study participants provided a written informed consent before undergoing any study-related procedures. The study was registered at www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT01642251).

Patient Selection

Adult patients (> 18 years old) with newly diagnosed, treatment-naïve, pathologically confirmed ES-SCLC were eligible. Extensive stage was defined by the presence of extrathoracic metastatic disease, malignant pleural effusion, and bilateral or contralateral supraclavicular adenopathy. Patients were also required to have good Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and adequate end-organ function defined by prespecified laboratory parameters. Excluded from trial participation were patients with CNS metastases (screening brain magnetic resonance imaging or computed tomography scan of the head was required) regardless of radiation treatment and or symptom, inability to swallow pills, and uncontrolled intercurrent illness such as active infection, symptomatic congestive

heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, and known active HIV infection requiring treatment with antiretroviral therapy.

Study Design

The study was designed as a two-arm, randomized, double-blind, phase II clinical trial to compare patients treated with CE+P with patients treated with CE+V.

Treatment. Patients randomly assigned to the experimental arm received a fixed dose previously defined as the recommended phase II dose from the phase I component of this protocol.¹⁴ This consisted of cisplatin (75 mg/m²) intravenously on day 1, etoposide (100 mg/m²) intravenously on days 1 through 3, and veliparib (100 mg twice per day) orally on days 1 through 7 in a 21-day treatment cycle. The control arm received the same regimen with substitution of veliparib with placebo. Prophylactic growth factor support was allowed according to local practice standard. Participants and study personnel were blinded to the treatment assignment. A maximum of four cycles of treatment was allowed, with restaging scans after every two cycles, after which patients were monitored for disease progression every 3 months for 2 years or until disease progression, whichever was earlier.

Statistical considerations. The primary objective of the trial was to determine whether combination therapy including veliparib extends PFS for this patient population. The primary comparison included all eligible patients who started

FIG 1. CONSORT diagram of all patients enrolled in the study and their contribution to the primary end point of the study. (*) Reasons for ineligibility were unconfirmed diagnosis, abnormal laboratory values, and no measurable disease. Per protocol, four of the six ineligible patients excluded from efficacy assessment who received treatment were included in the toxicity data in Table 3. (†) Reasons for not starting assigned therapy included patient refusal or withdrawal of consent, medical reasons, adverse events, disease progression, treatment delay, and death. CE, cisplatin and etoposide; P, placebo; V, veliparib.

TABLE 1. Patient Demographics and Disease Characteristics

Variable	CE+V (n = 64)	CE+P (n = 64)	Total (N = 128)
Sex			
Female	30 (47)	32 (50)	62 (48)
Male	34 (53)	32 (50)	66 (52)
Age, years			
Median (Q1,Q3)	66 (59,72)	64 (59,70)	66 (59,71)
ECOG performance status			
0	15 (23)	22 (34)	37 (29)
1	49 (77)	42 (66)	91 (71)
Baseline weight loss			
< 5%	45 (70)	45 (70)	90 (70)
≥ 5%	19 (30)	19 (30)	38 (30)
Race			
Black	2 (3)	2 (3)	4 (3)
White	61 (95)	57 (89)	118 (92)
Others	1 (2)	5 (8)	6 (5)
Abnormal creatinine level			
No	64 (100)	58 (91)	122 (95)
Yes	0 (100)	6 (9)	6 (5)
Abnormal LDH level			
No	20 (31)	21 (33)	41 (32)
Yes	44 (69)	43 (67)	87 (68)
Pathologic N stage			
N0	1 (5)	2 (11)	3 (8)
N1	0 (0)	4 (21)	4 (10)
N2	6 (29)	7 (37)	13 (32)
N3	10 (48)	1 (5)	11 (28)
NX	1 (5)	1 (5)	2 (5)
Unknown	3 (14)	4 (21)	7 (18)
Pleural effusion			
No	40 (62)	41 (64)	81 (63)
Yes	24 (38)	23 (36)	47 (37)
Brain metastasis			
No	64 (100)	64 (100)	128 (100)
Yes	0	0	0

NOTE. Data are given as No. (%).

Abbreviations: CE, cisplatin and etoposide; ECOG, Eastern Cooperative Oncology Group; P, placebo; Q, quartile; V, veliparib.

treatment with the assigned therapy, of whom 135 were to be accrued and randomly assigned equally, for a total accrual of 67 patients per arm. After adjusting for an ineligibility rate of 10%, the total required sample size for randomization was 150 patients. Randomization to treatment was determined using permuted blocks within strata with dynamic balancing on main Eastern Cooperative Oncology Group institutions plus affiliates. The randomization was stratified by sex (male v female) and lactate

dehydrogenase (LDH) level (ie, levels within normal limits v levels above the upper limit of normal on the basis of local testing).

Using an overall one-sided, 0.10-level log-rank test, this study had 88% power to detect a 37.5% reduction in the PFS hazard rate of 0.139 to 0.087, on the basis of the estimated accrual and follow-up period. Assuming exponential survival, this corresponded to a 60% improvement in the median PFS of 5 months for those receiving CE+P to 8 months for those receiving CE+V. The number of PFS events needed to achieve this power was 113 events under the alternative hypothesis. PFS was defined as the time from randomization to documented disease progression or death from any cause, whichever occurred first.

Patients who had not experienced an event of interest by the time of analysis were censored at the date they were last known to be alive and progression free. OS was defined as the time from randomization to death from any cause, and patients known to be alive at the time of final analysis were censored as of the last date of contact. The best objective response was classified according to the RECIST 1.1 criteria, whereas adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, criteria.

Time-to-event data (ie, PFS and OS) were estimated using the Kaplan-Meier method, and Cox proportional hazards models were used to estimate treatment hazard ratios. The prespecified primary comparison of PFS was a log-rank test stratified on the randomization stratification factors with a one-sided type I error rate of 10%. Other comparisons of groups were made using the log-rank test and Cox modeling. ORR and rates of toxicity were compared using Fisher's exact tests with a one-sided type I error rate of 10%. Multivariable logistic regression modeling was used to adjust for the effect of any covariables that were associated with these categorical outcomes. All *P* values are two-sided unless otherwise stated and no adjustments were made for multiple comparisons.

RESULTS

Accrual and Disposition of Patients

The study was activated on October 24, 2013, and enrolled 147 patients before termination on July 2, 2015. Figure 1 is a CONSORT diagram of patient disposition in the study. At the time of data analysis, 23 patients in the primary analysis population were alive. The median follow-up of patients still alive was 18.5 months (18.1 months in the CE+V arm and 21.5 months in the CE+P arm).

Patient Demographics and Disease Characteristics

Details of patient demographics and disease characteristics at the time of registration to this trial, by treatment arm are summarized in Table 1. Variables were well balanced by treatment arm with the exception of abnormal creatinine

level ($P = .01$) and pathologic N stage ($P = .01$). Stratification was accurate for sex in 100% of cases, whereas LDH status was concordant in 96.6% of cases.

Treatment Delivery

Most patients completed the planned four cycles of therapy in each arm (including = 53 [82.8%] in CE+V; $n = 49$ [76.6%] in CE+P). Appendix Table A1 (online only) displays the total number of cycles received and reason for treatment discontinuation for each arm of the study.

Efficacy

PFS. The primary efficacy analysis was conducted using data from the 128 eligible and treated patients. At the time of analysis, 118 patients had experienced a PFS event ($n = 58$ in the CE+V arm; $n = 60$ in the CE+P arm). The estimated median PFS was 6.1 months (95% CI, 5.9 to 6.7 months) for the CE+V arm and 5.5 months (95% CI, 5.0 to 6.1 months) for the CE+P arm (Fig 2); the unstratified hazard ratio (HR) was 0.75 (80% CI, 0.59 to 0.95; one-sided $P = .06$). The observed stratified PFS HR was 0.63 (one-sided $P = .01$).

Because the stratified and unstratified point estimates differed, we also estimated PFS within each of the four strata that were used for randomization. The within-strata analysis was an unplanned analysis but was conducted because the assumption of a proportional hazards within strata was violated, therefore making the stratified HR

difficult to interpret. Also, the significant difference between the stratified and unstratified PFS HRs led us to explore the treatment effect within strata. Kaplan-Meier estimates of that analysis are displayed in Figure 3 and revealed that the effect of veliparib was different across patient strata, with treatment effect only observed among the patient subset of men with abnormally high LDH levels.

We next fitted a multivariable Cox model to see if adjusting for other known prognostic factors and variables imbalanced by randomization had any impact on the PFS results. Variables explored for the multivariable model included abnormal creatinine level, pathologic N stage, performance status, abnormal ALT level, abnormal AST level, abnormal protein level, and creatinine clearance (24 hours), as well as an indicator for whether a patient was included in the stratum of male patients with abnormal LDH levels. The results of the final model (Table A2, online only) suggest a significant treatment interaction with the male/abnormal LDH stratum (estimated adjusted PFS treatment HR, 0.34; 80% CI, 0.22 to 0.51; one-sided $P < .001$), but no significant treatment effect of veliparib in the other strata (adjusted PFS HR, 0.81; 80% CI, 0.60 to 1.09; one-sided $P = .18$). This significant interaction indicates a violation of the proportional hazards within strata assumption, which renders the overall stratified HR uninterpretable.

OS. At the time of analysis, there were 105 deaths in the primary efficacy population ($n = 51$ patients in the CE+V

FIG 2. Kaplan-Meier plots for (A) PFS and (B) OS in eligible patients. The estimated median PFS was 6.1 months (95% CI, 5.9 to 6.7 months) for the CE+V arm and 5.5 months (95% CI, 5.0 to 6.1 months) for the CE+P arm (unstratified hazard ratio [HR], 0.75 [one-sided $P = .06$]; stratified PFS HR, 0.63 [one-sided $P = .01$]). The estimated median OS was 10.3 months (95% CI, 8.9 to 12.0 months) and 8.9 months (95% CI, 8.3 to 11.3 months) for arms CE+V and CE+P, respectively. The stratified OS HR comparing the CE+V and CE+P arms was 0.83 (80% CI, 0.64 to 1.07; one-sided $P = .17$). CE, cisplatin and etoposide; OS, overall survival; P, placebo; PFS, progression-free survival; V, veliparib.

FIG 3. Kaplan-Meier plots for PFS in the four stratification groups of the study. Multivariable Cox analysis showed significant benefit of veliparib added to CE in the stratum of men with abnormal LDH levels ($n = 46$; adjusted hazard ratio [HR], 0.34; 80% CI, 0.22 to 0.51; one-sided $P < .001$). There was no significant treatment effect of veliparib in the other strata (adjusted PFS HR, 0.81; 80% CI, 0.60 to 1.09; one-sided $P = .18$): male patients with normal LDH levels ($n = 20$), female patients with normal LDH levels ($n = 18$), and female patients with abnormal LDH levels ($n = 44$). CE, cisplatin and etoposide; LDH, lactate dehydrogenase; P, placebo; PFS, progression-free survival; V, veliparib.

arm; $n = 54$ patients in the CE+P arm), with an estimated median OS of 10.3 months (95% CI, 8.9 to 12.0 months) and 8.9 months (95% CI, 8.3 to 11.3 months), respectively (Fig 2). The median follow-up of all patients who remain alive is 18.5 months, as of this writing. The estimated

stratified OS HR for the comparison of the CE+V arm with the CE+P arm was 0.83 (80% CI, 0.64 to 1.07; one-sided $P = .17$). There was no significant difference in OS by strata, contrary to the trend observed in the PFS analysis.

TABLE 2. Response Assessment by RECIST 1.1

Best Response	CE+V (n = 64)	CE+P (n = 64)	Total (N = 128)
Complete	0	1	1
Partial	46	41	87
Stable disease	8	8	16
Progressive disease	6	6	12
ORR	46	42	88
Not evaluable*	4	8	12

Abbreviations: CE, cisplatin and etoposide; ORR, overall response rate; P, placebo; V, veliparib.

*Early death (n = 2); inadequate assessments (n = 9); withdrawal of consent (n = 1)

Objective Response

The protocol required all patients to have measurable disease as defined by RECIST, version 1.1. At the time of this analysis, there were 46 partial responses in the CE+V arm, compared with one complete response and 41 partial responses in the CE+P arm. The ORR was not significantly different (71.9% for the CE+V arm v 65.6%; one-sided Fisher $P = .29$). A detailed breakdown of RECIST response by treatment arm is presented in Table 2.

Adverse Events

Treatment-related grade ≥ 3 adverse events occurring in $\geq 5\%$ of patients who received treatment regardless of eligibility (n = 66 patients in each arm) are listed in Table 3. The toxicities seem balanced across treatment arms with the exception of higher rates in the CE+V arm of grade 3 CD4 lymphopenia (8% v 0% in CE+P arm; $P = .06$) and grade 3/4 neutropenia (49% v 32% in CE+P arm; $P = 0.08$). There was a single case of grade 5 febrile neutropenia, which was recorded in the CE+P arm.

TABLE 3. Most Frequent Adverse Events Occurring in $\geq 5\%$ of Patients

Toxicity	CE+V (n = 66)			CE+P (n = 66)		
	Grade, %			Grade, %		
	3	4	5	3	4	5
Anemia	17	2	0	12	0	0
Febrile neutropenia	5	0	0	3	0	2
Fatigue	3	0	0	5	0	0
Lymphopenia*	8	0	0	0	0	0
Neutropenia*	20	29	0	14	18	0
Leukopenia	8	11	0	12	2	0
Dehydration	5	2	0	3	0	0
Hyperglycemia	5	0	0	0	0	0
Hyponatremia	12	0	0	2	5	0
Acute kidney injury	5	0	0	2	2	0

* $P < .1$.

DISCUSSION

This randomized, phase II study of platinum-based chemotherapy in combination with the PARP inhibitor veliparib or with placebo demonstrated a 36% reduction in the risk of disease progression in patients who received the PARP inhibitor over patients treated with placebo. This did not translate into reduction in overall mortality for patients treated with veliparib. However, the improvement in the point estimate of PFS was quite modest at 6.1 months compared with 5.5 months. One obvious explanation for this divergence between the magnitude of risk reduction measured as HR and the median PFS is the possible imbalance in treatment effect across the four strata of patients in the study. There is no biologically rational explanation for the strong effect seen in the subset of male patients with elevated LDH levels. However, this subset is also the largest of the four strata, with approximately 60 patients. Therefore, we hypothesize that this cohort probably contained a sufficient proportion of patients with SCLC who harbored some biologic vulnerability to this therapeutic strategy.

Although there is currently no established predictive biomarker for PARP inhibitor efficacy in SCLC, several promising biomarkers, such as SLFN-11 expression and loss of heterozygosity in homologous recombination deficiency genes, have been identified using preclinical modeling and post hoc analysis of tumor samples collected as part of human subject studies.¹⁸⁻²¹ On the basis of preclinical data suggesting a correlation between DNA-PKcs expression and veliparib activity when combined with cisplatin in SCLC cell lines,¹⁴ we assessed DNA-PKcs expression, as a predictive biomarker, in archival tissues samples from patients enrolled in the study. We did not find any significant association of DNA-PKcs expression with clinical efficacy of veliparib.²² Additional correlative studies looking at SLFN11 and loss of heterozygosity in homologous recombination deficiency genes as markers of DNA repair and PARP inhibitor sensitivity are ongoing.

There is valid concern that the combination of a PARP inhibitor and other inhibitors of DNA repair along with cytotoxic chemotherapy will result in intolerable toxicities. Indeed, the frequency of hematologic toxicities was higher in patients treated with veliparib, but this did not affect delivery of standard chemotherapy as planned. This result confirms the observation made in the lead-in phase I component of the E2511 trial, in which we observed that the combination of veliparib, cisplatin, and etoposide led to an increased rate of hematologic toxicity without affecting chemotherapy delivery.¹⁷ That the study enrolled a treatment-naïve patient population could have contributed to the overall tolerability of this regimen. There are emerging data from preclinical experiments that the effect of PARP inhibitors on DNA damage repair is not only a result of the inhibition of the catalytic activity of PARP enzyme but also as a result of the PARP-trapping effects of these agents.

Agents with higher PARP-trapping activity, such as rucaparib and talazoparib, also showed greater cytotoxicity in preclinical models and have single-agent efficacy in patients.²²⁻²⁵ Interestingly, the strong PARP trappers also induce greater severity of hematologic toxicity in patients and are more difficult to combine with effective dose and schedules of cytotoxic chemotherapy regimens.^{16,26,27} Although veliparib is a weaker PARP trapper, it has also shown single-agent activity in gynecologic malignancies.^{28,29} Moreover, its tolerable toxicity profile makes it well suited to combine with cytotoxic chemotherapy agents such as platinum and etoposide doublets, whose hematologic toxicity is a major concern.

Results of PARP inhibitor trials in SCLC reported to date have been mixed. Single-agent olaparib was tested as maintenance therapy after completion of frontline chemotherapy in the Surveillance or Metastasis-Directed

Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) trial but did not show any clinical benefit in comparison with placebo.³⁰ The combination of olaparib and temozolomide, however, showed promising activity in relapsed SCLC, whereas the combination of veliparib and temozolomide showed efficacy only in subset of patients with relapsed SCLC who had with SLFN11 expression.^{31,32}

Although the initial result of our study is promising, additional confirmation in a larger definitive study is warranted, given the mixed results reported by other studies of PARP inhibitors in this patient population. There is an ongoing phase II study, M14-361 (Clinicaltrials.gov identifier: NCT02289690) that uses a carboplatin-based chemotherapy doublet backbone in combination with veliparib. A larger definitive study to evaluate the value of this therapeutic strategy would be justified if the M14-361 study shows a similar signal of efficacy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.18.00264>.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Randomized Phase II Trial of Cisplatin and Etoposide in Combination with Veliparib or Placebo for Extensive-Stage Small-Cell Lung Cancer: ECOG-ACRIN 2511 Study**

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APPENDIX

TABLE A1. Treatment Delivery and Discontinuation

Treatment	Reason Treatment Discontinued	C1	C2	C3	C4	Total
CE+V	Completed per protocol	0	0	0	53	53
	Progressive disease	0	2	1	0	3
	Adverse events	3	1	1	0	5
	Death on study	1	0	0	0	1
	Withdrawal or refusal	0	0	1	0	1
	Other complications	0	0	1	0	1
	Total	4	3	4	53	64
CE+P	Completed per protocol	0	0	0	49	49
	Progressive disease	0	2	1	0	3
	Adverse events	0	2	2	0	4
	Death on study	1	2	0	0	3
	Withdrawal or refusal	3	0	0	0	3
	Other complications	0	1	0	1	2
	Total	4	7	3	50	64

Abbreviations: C, cycle; CE, cisplatin and etoposide; P, placebo; V, veliparib.

TABLE A2. Final Multivariable Cox Model

Variable	Coef	Exp (coef)	SE (coef)	z	P
Veliparib	−0.215	0.806	0.237	−0.908	.3600
Male/abnormal LDH stratum	0.796	2.216	0.292	2.728	.0064
PS 1	0.459	1.583	0.223	2.059	.0390
Abnormal protein level	0.760	2.139	0.288	2.640	.0083
CE+V arm: male/abnormal LDH stratum ixn	−0.876	0.416	0.400	−2.192	.0280

Abbreviations: Coef, coefficient; Exp, exponential; ixn, interaction; LDH, lactate dehydrogenase; PS, performance status; SE, standard error.