2018

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VOLUME 36 · NUMBER 23 · AUGUST 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer

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Published at jco.org on June 15, 2018.

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Clinical trial information: NCT01638546.

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0732-183X/18/3623w-2386w/$20.00

ABSTRACT

Purpose

Both temozolomide (TMZ) and poly (ADP-ribose) polymerase (PARP) inhibitors are active in small-cell lung cancer (SCLC). This phase II, randomized, double-blind study evaluated whether addition of the PARP inhibitor veliparib to TMZ improves 4-month progression-free survival (PFS).

Patients and Methods

A total of 104 patients with recurrent SCLC were randomly assigned 1:1 to oral veliparib or placebo 40 mg twice daily, days 1 to 7, and oral TMZ 150 to 200 mg/m^2/day, days 1 to 5, of a 28-day cycle until disease progression, unacceptable toxicity, or withdrawal of consent. Response was determined by imaging at weeks 4 and 8, and every 8 weeks thereafter. Improvement in PFS at 4 months was the primary end point. Secondary objectives included overall response rate (ORR), overall survival (OS), and safety and tolerability of veliparib with TMZ. Exploratory objectives included PARP-1 and SLFN11 immunohistochemical expression, *MGMT* promoter methylation, and circulating tumor cell quantification.

Results

No significant difference in 4-month PFS was noted between TMZ/veliparib (36%) and TMZ/placebo (27%; $P = .19$); median OS was also not improved significantly with TMZ/veliparib (8.2 months; 95% CI, 6.4 to 12.2 months; *v* 7.0 months; 95% CI, 5.3 to 9.5 months; $P = .50$). However, ORR was significantly higher in patients receiving TMZ/veliparib compared with TMZ/placebo (39% *v* 14%; $P = .016$). Grade 3/4 thrombocytopenia and neutropenia more commonly occurred with TMZ/veliparib: 50% versus 9% and 31% versus 7%, respectively. Significantly prolonged PFS (5.7 *v* 3.6 months; $P = .009$) and OS (12.2 *v* 7.5 months; $P = .014$) were observed in patients with SLFN11-positive tumors treated with TMZ/veliparib.

Conclusion

Four-month PFS and median OS did not differ between the two arms, whereas a significant improvement in ORR was observed with TMZ/veliparib. SLFN11 expression was associated with improved PFS and OS in patients receiving TMZ/veliparib, suggesting a promising biomarker of PARP-inhibitor sensitivity in SCLC.

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2018.77.7672

Data Supplement
DOI: https://doi.org/10.1200/JCO.2018.77.7672

DOI: https://doi.org/10.1200/JCO.2018.77.7672

INTRODUCTION

Therapeutic options for patients with relapsed small-cell lung cancer (SCLC) have remained unchanged for three decades. The only Food and Drug Administration–approved agent for recurrent or progressive SCLC is topotecan, on the basis of three phase III trials,[1-3] which showed modest response rates of 24% in patients with platinum-sensitive disease and 2% to 6% in platinum-refractory SCLC.[3-6] Median time to progression with topotecan is short, between 13 and 16 weeks,[1,3] and there are no approved regimens after second-line treatment. More effective therapies in SCLC are critically needed.

SCLC is characterized by aberrant expression of several genes implicated in DNA damage repair. Proteomic profiling previously identified poly (ADP-ribose) polymerase (PARP)-1 as a candidate drug target.[7] Frequent epigenetic silencing of the *MGMT* gene, which encodes the DNA-repair protein O^6 methylguanine-DNA methyltransferase (MGMT), also has been demonstrated.[8-10] As such, DNA damage response pathways represent attractive targets in SCLC.[11]

Temozolomide (TMZ) is an oral alkylating agent that produces O^6-alkyl-guanine lesions on DNA, which are removed by MGMT. Left unrepaired, TMZ-induced lesions are cytotoxic and trigger apoptosis.[9,10] We previously showed single-agent activity of TMZ in patients with relapsed SCLC,[12] leading to its incorporation into treatment guidelines for this disease.[13] However, the benefit provided by single-agent TMZ typically is brief, with median progression-free survival (PFS) of 3.5 months.[12]

One well-defined mechanism of resistance to TMZ is through the PARP-dependent base excision repair pathway.[14-16] In several cancer types, the combination of veliparib (formerly ABT-888), an oral inhibitor of PARP-1 and PARP-2, and TMZ results in greater tumor growth delay or regression, relative to TMZ alone.[17] Furthermore, PARP inhibitors (PARPi) have single-agent activity in SCLC models and potentiate the effect of cytotoxic agents.[7,18,19] On the basis of this, PARPi trials have been initiated in SCLC.[20,21] In this multi-institutional, double-blind, placebo-controlled, randomized phase II study (ClinicalTrials.gov identifier: NCT01638546), we hypothesized that adding veliparib to TMZ may overcome resistance and improve outcomes in patients with relapsed SCLC and explored candidate predictive biomarkers, including *MGMT* promoter methylation.

PATIENTS AND METHODS

This study was reviewed and approved by the institutional review boards of each center (Appendix Table A1, online only). Written informed consent was provided by all patients. See the Data Supplement for the trial protocol.

Eligibility Criteria

Patients had SCLC that was sensitive or refractory to platinum-based chemotherapy (Fig 1). Sensitive disease was defined as progression or relapse ≥ 60 days after completion of first-line chemotherapy.[1] Refractory disease was defined as progression during initial therapy or within 60 days after completing first-line treatment. For the purposes of this study, patients receiving third-line therapy and those with refractory disease were all considered refractory. Patients were eligible if they were ≥ 18 years of age and had one or two prior chemotherapeutic regimens, Karnofsky performance status ≥ 70%, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1,[22] and adequate liver, kidney, and bone marrow function. Those with asymptomatic progression of disease in the brain were eligible. Patients were excluded if they had chemotherapy or radiation treatment within 21 days, leptomeningeal involvement, or a history of seizures.

Treatment

Veliparib and was provided by the Cancer Therapy Evaluation Program at the National Cancer Institute. TMZ was obtained commercially.

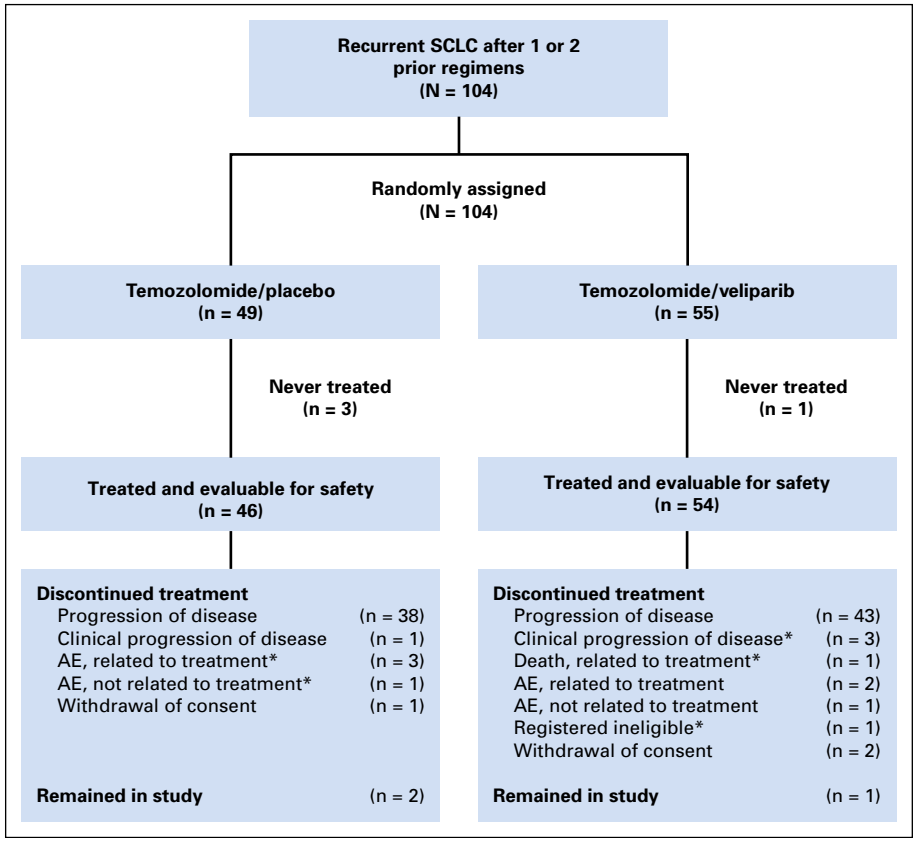

Fig 1. CONSORT diagram. A total of 104 patients were randomly assigned in a 1:1 fashion, stratified by sensitive disease or refractory disease and center. Four patients were not treated: three in the temozolomide (TMZ)/placebo arm (one each: withdrawal of consent, complications of disease, and concomitant therapy prohibitive to initiate study medication), and one in the TMZ/veliparib arm (complications of disease). Forty-six and 54 patients were evaluable for safety in the TMZ/placebo and TMZ/veliparib arms, respectively. In the TMZ/placebo arm, 44 patients were evaluable for response because two patients were removed for toxicity during the first cycle and before undergoing imaging, indicated by (*). In the TMZ/veliparib arm, five patients were removed from the study, indicated by (*), during the first cycle: registered ineligible (n = 1), clinical progression of disease (n = 3), and death due to treatment toxicity (n = 1). As such, 49 patients were evaluable for response. AE, adverse event; SCLC, small-cell lung cancer.

After randomization, treatment was started within 7 days. Patients received oral veliparib or placebo 40 mg twice daily on days 1 to 7 and oral TMZ 200 mg/m^2/day on days 1 to 5 of a 28-day cycle, on the basis of a phase II study of the combination and our prior experience.[23,24] See the Data Supplement for additional details.

Study Evaluation

Patients were assessed every 2 weeks during the first two cycles and every 4 weeks thereafter. At each visit, a history, physical examination, toxicity assessment, CBC, and comprehensive metabolic panel were performed. At cycle 3 and beyond, patients were required to have a CBC on day 15. Toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Tumor assessments are described in the Data Supplement.

Immunohistochemistry, Promoter Methylation, Mutational Analysis, and Circulating Tumor Cell Enumeration

Details are included in the Data Supplement.

Statistical Analysis

The primary end point was improvement in PFS at 4 months in patients receiving TMZ/veliparib compared with TMZ/placebo. Patients were stratified according to sensitive disease versus refractory disease and center. In the phase II study of TMZ in SCLC, which enrolled sensitive and refractory patients in a proportion of 4:1, PFS at 4 months was 18% for the combined groups.[12] On the basis of these findings, the expected PFS at 4 months in the control group was 15%. With 50 patients per arm, the study had 85% power to detect an improvement in 4-month PFS from 15% to 35% (one-sided type I error, 0.15). All randomly assigned patients were included in the intent-to-treat analysis. PFS was calculated as the proportion of patients alive and without disease progression at 4 months after randomization and compared across the two arms using a χ^2 test. A patient who discontinued therapy before 4 months but was alive without documented progression at 4 months was not considered a failure for this end point. See the Data Supplement for additional details regarding secondary and exploratory objectives.

RESULTS

Patient Characteristics

Between August 2012 and February 2015, 104 patients from seven centers in the United States were randomly assigned to receive veliparib or placebo with TMZ (Fig 1). Baseline characteristics were balanced between treatment arms (Table 1). All 104 randomly assigned patients were included in the intent-to-treat analysis for PFS and overall survival (OS). Those with diagnostic imaging at least once beyond baseline were evaluated for response (n = 93). Safety was assessed in patients who initiated one cycle of study treatment (n = 100; Fig 1).

Efficacy

At the final analysis, no significant difference in 4-month PFS was demonstrated between TMZ/veliparib (20 of 55; 36%) and TMZ/placebo (13 of 49; 27%; $P = .19$). Median PFS was 3.8 months and 2.0 months in the TMZ/veliparib and TMZ/placebo arms, respectively (log-rank $P = .39$; hazard ratio, 0.84; 95% CI, 0.56 to 1.25; Fig 2A; Appendix Table A2, online only). The median duration of response was 4.61 months (95% CI, 2.86 to 9.9 months) and 3.68 months (95% CI, 2.76 months to not achieved) in the TMZ/veliparib (n = 19) and TMZ/placebo (n = 6) arms, respectively (log rank $P = .507$). At the time of data cutoff, 19 patients (18%) remained alive (TMZ/veliparib, n = 9; TMZ/placebo, n = 10). Median OS was similar between TMZ/veliparib and TMZ/placebo: 8.2 months (95% CI, 6.4 to 12.2 months) versus 7.0 months (95% CI, 5.3 to 9.5 months; $P = .50$), respectively (Fig 2B; Appendix Table A2). One- and 2-year survival rates were 35% and 10% for TMZ/veliparib versus 30% and 11% for TMZ/placebo, respectively.

Table 1. Baseline Patient Characteristics

Characteristic	All Patients (N = 104)	Temozolomide/ Placebo (n = 49)	Temozolomide/ Veliparib (n = 55)
Sex: male/female (No.)	50/54	26/23	24/31
Median age, years (range)	62.5 (31-84)	62 (35 -84)	63 (31-80)
ECOG performance status, No. (%)			
0	29 (28)	13 (27)	16 (29)
1	75 (72)	36 (73)	39 (71)
Smoking history*			
Current/former, No. (%)	93 (89)	44 (90)	49 (89)
Pack-year history (range)	5-150	8-150	5-135
Never, No. (%)	4 (4)	1 (2)	3 (5)
Previous lines of therapy, No. (%)			
1	70 (67)	34 (69)	36 (65)
2	34 (33)	15 (31)	19 (35)
Cohort designation, No. (%)			
Sensitive	43 (41)	19 (39)	24 (44)
Refractory†	61 (59)	30 (61)	31 (64)
Median time from diagnosis to treatment, months (range)	10 (2.5-33)	10 (4.5-25)	10.5 (2.5-33)
New brain metastases, No. (%)‡	22 (21)	10 (20)	12 (22)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Not available (n = 7; in the placebo arm [n = 3], in the veliparib arm [n = 4]).
†Patients with refractory disease, as defined by relapse within 60 days of completing first-line chemotherapy or in need of third-line therapy.
‡Noted at the time of study entry, target or nontarget lesions.

In 93 evaluable patients (Appendix Table A2; Figs 3A and 3B; Appendix Fig A1, online only), a significantly higher objective response rate (ORR) was observed in patients receiving TMZ/veliparib (ORR, 39%; 95% CI, 25% to 54%) versus TMZ/placebo (ORR, 14%; 95% CI, 5% to 27%; $P = .016$). Two patients who received veliparib had a complete response, including one with sensitive disease who continued to receive treatment, with continued response for over 2 years.

A preplanned subgroup analysis found that responses were higher with TMZ/veliparib in both platinum-sensitive and platinum-refractory patients. In sensitive patients, the ORR for TMZ/veliparib was 41% (9 of 22) versus 11% (2 of 18) for TMZ/placebo ($P = .055$); in refractory patients, the ORR for TMZ/veliparib was 37% (10 of 27) versus 15% (4 of 26) for TMZ/placebo ($P = .22$). Furthermore, the improvement in ORR for TMZ/veliparib compared with TMZ/placebo was similar for second- and third-line patients. In patients with one previous line of therapy, the ORR for TMZ/veliparib was 39% (13 of 33) versus 16% (5 of 31) for TMZ/placebo ($P = .047$), whereas patients with two prior lines of therapy had an ORR with TMZ/veliparib of 38% (6 of 16) versus 8% (1 of 13) with TMZ/placebo ($P = .21$).

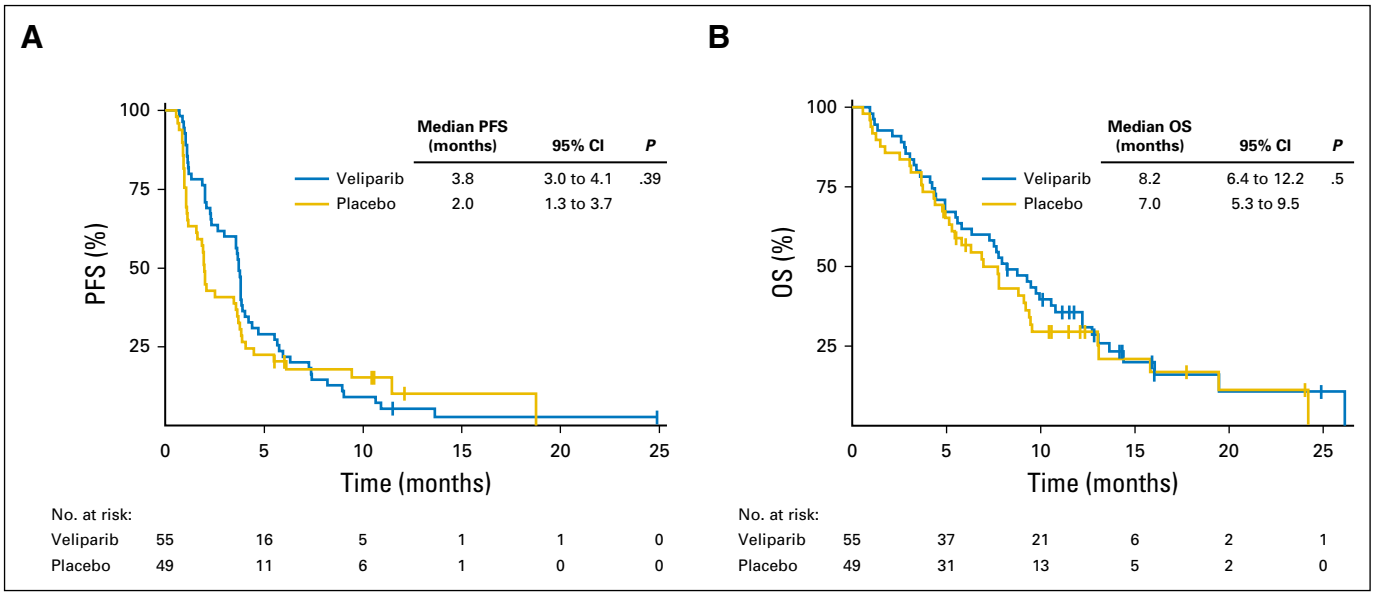

Fig 2. Kaplan Meier curves for outcomes. (A) Progression-free (PFS) and (B) overall survival (OS) for the 104 patients with sensitive or refractory small-cell lung cancer in need of second- or third line-therapy.

Treatment Exposure

One hundred of 104 patients enrolled and randomly assigned received at least one cycle of treatment. Twelve of the 54 treated patients (22%) in the TMZ/veliparib arm received five or more cycles of therapy (median, 3; range, 1 to 21), compared with six of the 46 patients who were treated (13%) in the TMZ/placebo arm (median, 2; range, 1 to 19). Reasons for discontinuation of study treatment were disease progression (81%), unacceptable toxicity related or unrelated to treatment (6%), intercurrent illness/symptomatic deterioration (4%), withdrawal of consent (3%), more than a 3-week delay in treatment administration due to thrombocytopenia (2%), and death (1%).

Toxicity

Table 2 lists the most common treatment-related toxicities. Hematologic toxicities were the most common adverse effects in both study arms. After the first 24 patients were accrued and evaluated for at least one cycle, it was noted that 14 incurred the following adverse events: grade 3/4 neutropenia (TMZ/veliparib, n = 7; TMZ/placebo, n = 2); grade 3/4 thrombocytopenia (TMZ/veliparib, n = 10; TMZ/placebo, n = 3); and grade 4 febrile neutropenia (TMZ/veliparib, n = 1; leading to sepsis and death). Four of these patients had their second cycle of treatment held and subsequently were found to have disease progression at week 8

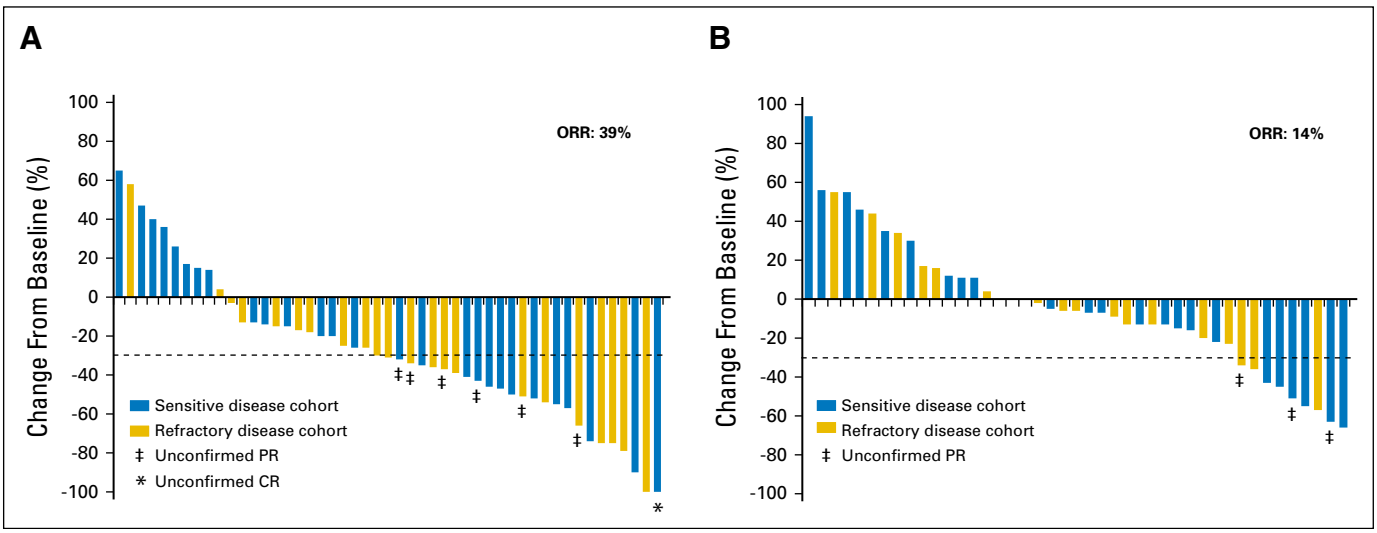

Fig 3. Tumor response. The best calculated percentage change in tumor size on the basis of measurable lesions for (A) 49 evaluable patients in the temozolomide (TMZ)/veliparib arm and (B) 44 evaluable patients in the TMZ/placebo arm. In the TMZ/veliparib arm, five patients were removed from the study during the first cycle and were not evaluable for response: registered ineligible (n = 1), clinical progression of disease (n = 3), and death due to treatment toxicity (n = 1). In the TMZ/placebo arm, two patients were removed for toxicity during the first cycle and before undergoing imaging; thus, they were not evaluable for response; one other patient's tumor measurements were not available, although the patient developed progression of disease on the basis of the appearance of new nontarget lesions. CR, complete response; ORR, .overall response rate; PR, partial response.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Patients

Adverse Event	Grade 1/2				Grade 3/4			
	Temozolomide/ Placebo		Temozolomide/ Veliparib		Temozolomide/ Placebo		Temozolomide/ Veliparib	
	No.	%	No.	%	No.	%	No.	%
Hematologic								
Anemia	19	41	23	43	1	2	6	11
Leukopenia	8	17	16	30	3	7	13	24
Lymphopenia	5	11	8	15	12	26	11*	20
Neutropenia	0	0	6	11	3	7	17	31
Febrile Neutropenia	0	0	0	0	0	0	2†	4
Thrombocytopenia	15	33	13	24	4	9	27	50‡
Nonhematologic								
Alkaline phosphatase increase	2	4	8	15	0	0	0	0
Anorexia	5	11	10	19	0	0	0	0
Constipation	11	24	9	17	0	0	1	2
Dermatologic§	3	7	6	11	0	0	0	0
Dizziness	1	2	6	11	0	0	0	0
Fatigue	20	43	24	44	2	4	2	4
Nausea	16	35	22	41	0	0	0	0
Vomiting	6	13	9	17	1	2	0	0

*One patient who received eight cycles of temozolomide/veliparib and experienced grade 4 lymphopenia was hospitalized repeatedly secondary to pneumonia in the setting of a known history of *Mycobacterium avium intracellulare* and *Nocardia* infections.
†Grade 3 and 4 febrile neutropenia were noted in two patients in the temozolomide/veliparib arm; one recovered, and one suffered shock with *Klebsiella pneumonia* septicemia and died during the study.
‡Although grade 3 and 4 thrombocytopenia was noted in 50% of patients in the temozolomide/veliparib arm, only one suffered a bleeding sequela (hemoptysis) and was found to have an endobronchial lesion on bronchoscopy.
§Dermatologic adverse events included dry skin, pruritus, and maculopapular rash.

(TMZ/veliparib, n = 3; TMZ/placebo, n = 1). Therefore, the protocol was amended in October 2013 to reduce the starting dose of TMZ to 150 mg/m^2/day to avoid myelosuppression and dose delays. At the lower dose of TMZ, only three patients treated with TMZ/veliparib and one treated with TMZ/placebo experienced multiple dosing delays. Prolonged thrombocytopenia led to treatment termination for an additional two patients, one in each arm.

PARP-1 and SLFN11 Immunohistochemistry as Biomarkers

Unlike other cancer types, mutations in DNA repair genes (eg, *BRCA1/2*) are uncommon and do not predict PARPi response in SCLC models.[25] Schlafen-11 (SLFN11) regulates response to DNA damage and replication stress,[26] and was recently identified as a candidate predictive marker of sensitivity to DNA-damaging chemotherapies[27] and PARPi in several cancers, including SCLC.[18,25,28] Therefore, we amended our original planned biomarker analysis to investigate whether PARP-1 or SLFN11 expression levels predicted clinical benefit of TMZ/veliparib.[18,25,28,29] Unstained tumor sections from original diagnostic biopsies were available from 58 patients (56%), of whom 48 and 47 had adequate tumor content for PARP-1 and SLFN11 analysis, respectively. PARP-1 expression was detected in 87% of tumors (H-score range, 0 to 219; median, 78). However, there was no association between PARP-1 expression and clinical outcomes (Appendix Fig A2, online only).

For SLFN11 biomarker analysis, we used an H-score cutoff ≥ 1 to define SLFN11-positive (n = 23) versus SLFN11-negative tumors (H-score < 1; n =25; Fig 4A). SLFN11-positive tumors were equally distributed between the treatment arms (TMZ/veliparib, n = 12; TMZ/placebo, n = 11). Clinical stage at initial diagnosis, platinum-sensitivity, and smoking history were not significantly different between the SLFN11-positive and SLFN11-negative groups.

Patients with SLFN11-positive tumors treated with TMZ/veliparib had significantly prolonged PFS (5.7 *v* 3.6 months; $P = .009$) and OS (12.2 *v* 7.5 months; $P = .014$) from time of randomization (Fig 4B). In contrast, no differences in PFS or OS were observed in those patients treated with TMZ/placebo on the basis of SLFN11 expression ($P = .162$ and .634, respectively). The interaction P value was .0092 (by Cox proportional hazards regression model), demonstrating an improved PFS in patients with SLFN11-positive disease receiving TMZ/veliparib. ORR was not significantly different on the basis of SLFN11 levels in either study arm (Appendix Fig A3, online only; TMZ/veliparib, $P = .614$; TMZ/placebo, $P = .178$). Interestingly, there also was a trend toward improved OS (from initial diagnosis) in patients with SLFN11-positive tumors (Fig 4C; $P = .058$) in the overall patient population. This may be due to SLFN11 also predicting sensitivity to platinum chemotherapy and topoisomerase inhibitors,[25] which is associated with improved prognosis in patients with SCLC.

MGMT Promoter Methylation as a Biomarker

Analysis of *MGMT* promoter methylation[30-32] was limited by the availability of adequate tissue, because sufficient DNA was present in only 32 tumor samples (TMZ/veliparib, n = 17; TMZ/placebo, n = 15). The *MGMT* promoter was methylated in 31% of the tumor samples tested (seven of 32) and was not associated with response to treatment among all patients treated ($P = .657$), or within either treatment arm (TMZ/veliparib, $P = .283$; TMZ/placebo, $P = .882$). *MGMT* promoter methylation also was not associated with improved PFS or OS (Appendix Fig A4, online only).

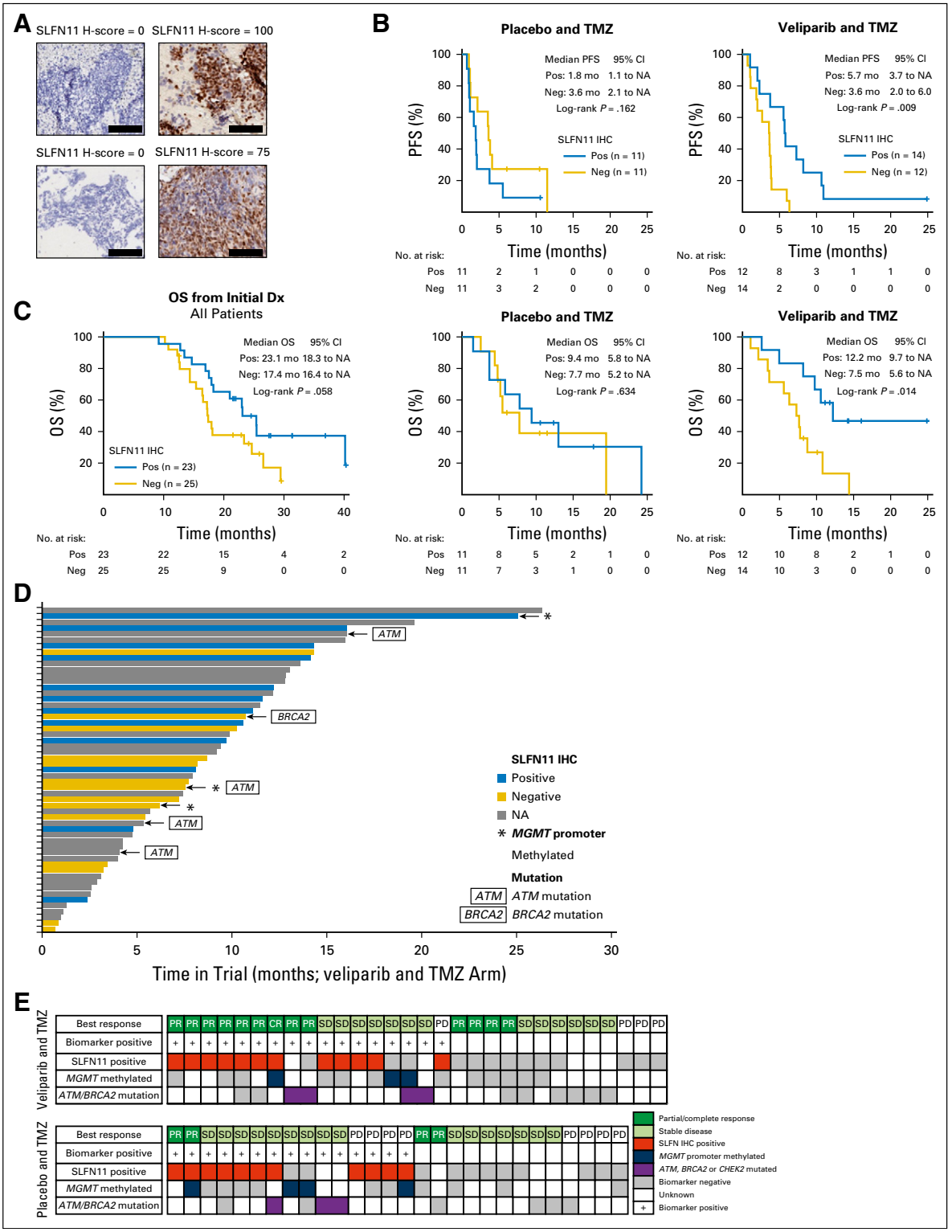

Fig 4. SLFN11 immunohistochemistry (IHC) predicts improved survival. (A) Example images of tumors with negative (neg) and positive (pos) SLFN11 by IHC (scale bar = 100 uM, 400× magnification). (B) Overall survival (OS) and progression-free survival (PFS) from date of randomization was improved in patients with SLFN11-positive disease in the temozolomide (TMZ)/veliparib treatment arm (PFS overall interaction log-rank $P = .046$; OS overall interaction log-rank $P = .095$). (C) OS from time of diagnosis trends toward increased survival in patients with SLFN11 positive (IHC score ≥ 1) disease. (D) Swim-plot of months on trial in the TMZ/veliparib treatment arm color coded by potential biomarker of response (time calculated from start of treatment to date of last follow-up). Blue indicates SLFN11 positive; (*)*MGMT* promoter methylation. (E) Summary of biomarker status (SLFN11; *MGMT* methylation; *ATM*, *BRCA2*, or *CHEK2* mutation for patients with response data). Gray indicates biomarker assayed and not detected; white indicates no data. Best response to treatment in each treatment arm. *ATM*, *ATM* mutation; *BRCA2*, *BRCA2* mutation; CR, complete response; Dx, diagnosis; mo, months; NA, not achieved; PD, progression of disease; PR, partial response; SD, stable disease.

Table 3. Mutations in DNA Genes Among Patients With Available Next-Generation Sequencing

Patient	Arm	Platform	Mutation	PFS/OS (mo)	Response
MDA-131753	Veliparib	CMS400	*ATM*:c.8174A>G p.D2725G	9.0/16.0	PR
MSK-031	Veliparib	IMPACT	*BRCA2*:c5171T>C p.I1724T	6.0/10.8	PR
MDA-144253	Veliparib	CMS50	*ATM*:c.998C>T p.S333F	4.2/4.2	SD
MDA-149438	Veliparib	CMS50	*ATM*:c.1229T>C p.V410A	6.3/6.3	SD
MSK-021	Control	IMPACT	*ATM*:c.5738T>C p.V1913A	4.5/9.2	SD
MSK-049	Control	IMPACT	*ATM*:c.1760delG p.G587fs	10.4/10.4	SD
MSK-035	Control	IMPACT	*CHEK2*:c226G>T p.E76*	1.8/17.3	SD

Abbreviations: CMS50 and CMS400, amplicon-based panel of 50 and 400 cancer-related genes, respectively; IMPACT, Integrated Mutation Profiling of Actionable Cancer Targets; MDA, MD Anderson Cancer Center; mo, months; MSK, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Circulating Tumor Cells

Baseline circulating tumor cells (CTCs) were evaluated on 94 patients at baseline and ranged from 0 to 262 per 7.5mL. In univariable analysis, elevated baseline CTCs ≥ 5, which had been validated in other tumor types,[33-35] seemed to be associated with worse OS: median OS, 5.6 versus 9.7 months; ($P < .001$; Appendix Fig A5A, online only). CTCs after one cycle of treatment were evaluated in 64 patients. A persistently elevated CTC number ≥ 5 at cycle 2, day 1, also was associated with worse OS in univariable analysis: median OS, 7.2 versus 8.8 months ($P = .012$; Appendix Fig A5B).

Analysis of Mutations in DNA Damage Response Genes

Targeted sequencing was performed on tumors from few patients (n = 22) at their respective treating institutions and revealed mutations in the following DNA repair genes previously implicated in PARPi response in other disease types: *ATM* (n = 5), *BRCA2* (n = 1), and *CHEK2* (n = 1; Table 3).[36] Although none of these seven mutations previously have been described as deleterious to gene/protein function, two (*CHEK2* p.E76* and *ATM* p.G587fs) may confer functional homologous repair deficiency.

Three patients with DNA repair gene mutations (*ATM,* n = 2; *CHEK2,* n = 1) received TMZ/placebo and had a median OS of 10.4 months, compared with 6.2 months for all patients treated with TMZ/placebo. In the TMZ/veliparib arm, the four patients with mutations (*ATM,* n = 3; *BRCA2,* n = 1) had a median OS of 8.6 months, compared with 8.1 months for others in this cohort (Fig 4D). Interestingly, two of the four partial responses with sequencing data observed in the TMZ/veliparib arm had DNA repair gene mutations (Fig 4E).

DISCUSSION

This randomized phase II study assessed the efficacy of veliparib, a PARPi, with TMZ compared with TMZ monotherapy in patients with relapsed SCLC. Although 4-month PFS did not differ significantly between veliparib- and placebo-treated patients, we observed significant improvement in ORR with the addition of veliparib. Furthermore, we demonstrated for the first time in a clinical trial that SLFN11—a promising biomarker of PARPi sensitivity—may identify patients who benefit from PARPi therapy.

In our prior phase II study of single-agent TMZ, 4-month PFS was 18%,[12] which we hoped to improve significantly by adding veliparib. However, we found no significant difference in 4-month PFS between patients in the TMZ/veliparib arm (36%) and those in the TMZ/placebo arm (27%; $P = .19$). Although median PFS and OS in patients receiving TMZ/veliparib were improved numerically by 1.8 months and 1.2 months, respectively, neither reached statistical significance. However, the substantially higher ORR and depth of response observed in patients receiving TMZ/veliparib (ORR, 39%; 95% CI, 25% to 54%) versus TMZ/placebo (ORR, 14%; 95% CI, 5% to 27%; $P = .016$) was statistically significant and is encouraging.

Several reasons may account for the high response rates found with the combination not translating into an improvement in PFS or OS. These include more frequent myelosuppression, treatment delays, dose reductions in patients receiving TMZ/veliparib, and a higher-than-expected number of platinum-resistant patients enrolled in the trial. Whereas we anticipated that approximately 20% of the study population would have platinum-refractory disease, in actuality, this highly resistant patient population represented the majority of study participants (59%), although well balanced between the two arms. A recent retrospective study challenged the premise that platinum sensitivity is associated with outcomes,[37] yet data consistently have shown that those with platinum-resistant disease treated with cytotoxic agents have worse PFS and OS, which may have affected the observed study outcomes.[38,39]

Preclinical data show that the dose levels chosen for the two agents in combination is important, with recent data suggesting that optimal synergy may result from near-maximal dosing of a PARPi, with substantially submaximal dose exposure of TMZ.[23,24,40,41] Here, in contrast, we used a recommended monotherapy treatment dose and schedule of TMZ (per prior SCLC study[24]) and a low dose of veliparib (per a phase II breast cancer study[23]). This may have compromised the effectiveness of the combination, especially because veliparib is relatively less potent compared with other PARPi that produce greater PARP-DNA trapping, a secondary mechanism by which these agents function.[42-44] Furthermore, hematologic toxicities were greater with TMZ/veliparib versus TMZ/placebo, including grade 3/4 thrombocytopenia, neutropenia, and anemia, which often were incidental laboratory findings and not clinically significant. Cytopenias with TMZ/veliparib were often observed early, leading to treatment delays and, potentially, loss of response. After such

toxicities occurred in 14 of the first 24 patients, the protocol was amended to start at a lower dose of TMZ. After this change, fewer patients required treatment delays.

In breast, ovarian, and prostate cancers, mutations in *BRCA1/2*, *ATM*, and other homologous repair genes predict PARPi response.[36,45-47] However, in preclinical models of SCLC, neither mutations in DNA repair genes nor homologous repair deficiency scores predict PARPi sensitivity.[18,25] In this trial, we tested, for the first time, SLFN11 expression by immunohistochemistry as a predictive biomarker of clinical response to PARPi therapy on the basis of preclinical data from SCLC and other cancers.[18,25,27-29] In addition to SLFN11, biomarker analysis included PARP-1 expression[7,25] and *MGMT* promoter hypermethylation,[12,30-32] although these were not associated with differences in response or survival.

In contrast, patients with SLFN11-positive tumors (H-score ≥ 1) who received TMZ/veliparib had significantly better PFS and OS than those treated with TMZ/placebo. This finding is consistent with several recent preclinical studies in SCLC[18,25,28,29] and other cancer types,[29] which have shown greater activity of multiple PARPi, including veliparib in models expressing relatively high levels of SLFN11. However, our groups recently have also found that SLFN11 decreases in many models after exposure to chemotherapy,[18,25,48] suggesting that a repeat biopsy to assess SLFN11 levels at the time of study entry may be important to optimize its predictive power, as opposed to using pretreatment samples from diagnosis.

To our knowledge, this is the first demonstration of SFLN11 as a predictive biomarker in a randomized, double-blind clinical trial. SLFN11 warrants further investigation in other trials of PARPi combinations for SCLC. Should this result be substantiated, high SLFN11 expression could represent a biomarker in select patients with SCLC for treatment with PARPi.

In conclusion, despite not achieving the primary end point of an improvement in 4-month PFS, we did observe significantly higher ORR in patients with relapsed SCLC treated with TMZ/veliparib, supporting additional studies of this regimen. Hematologic toxicities were noted with the combination of veliparib and TMZ, most of which did not lead to untoward clinical events and were less frequent after adjusting the starting dose of TMZ. Importantly, we demonstrated that high SLFN11 expression, a promising candidate biomarker of PARPi sensitivity, predicts longer survival in patients treated with TMZ/veliparib, substantiating our preclinical findings. Careful patient selection, application of SLFN11 as a biomarker, and optimization of the dosing schedule have the potential to further improve outcomes of the combination of PARPi and TMZ in SCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by the Cancer Therapy Evaluation Program at the National Cancer Institute (NCI; Grant No. UM1CA186691); National Institutes of Health (NIH)/NCI Grants No. CCSG P30-CA008748 and NIH/NCI CCSG P30-CA016672; University of Texas-Southwestern and MD Anderson Cancer Center Lung SPORE (Grant No. 5 P50 CA070907); through generous philanthropic contributions to The University of Texas MD Anderson Lung Cancer Moon Shot Program (J.W., J.V.H., L.A.B.); MD Anderson Cancer Center Physician Scientist Award (L.A.B.); The LUNGevity Foundation (L.A.B.); Lee Clark Fellowship of The University of Texas MD Anderson Cancer Center, supported by the Jeane F. Shelby Scholarship Fund (L.A.B.); NIH/NCI award No. 1-R01-CA207295 (L.A.B.); an NCI Cancer Clinical Investigator Team Leadership Award (No. P30-CA016672; L.A.B.); The Rexanna Foundation (J.V.H, L.A.B.); The Sidney Kimmel Foundation for Cancer Research (L.A.B.); and The Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy (L.A.B.).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell Lung Cancer

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Patents, Royalties, Other Intellectual Property: Overcoming acquired resistance to chemotherapy treatments through suppression of STAT3 (Inst), selective chemotherapy treatments and diagnostic methods related thereto (Inst)

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Acknowledgment

We thank Andy Ni, Amy Quinterio, Isabella Bergagnini, Gianna McArthur, Patrick Nolan, Lakeisha Lubin, Sarah Riva, and Hazem Karabeber for the collection and organization of data.

Appendix

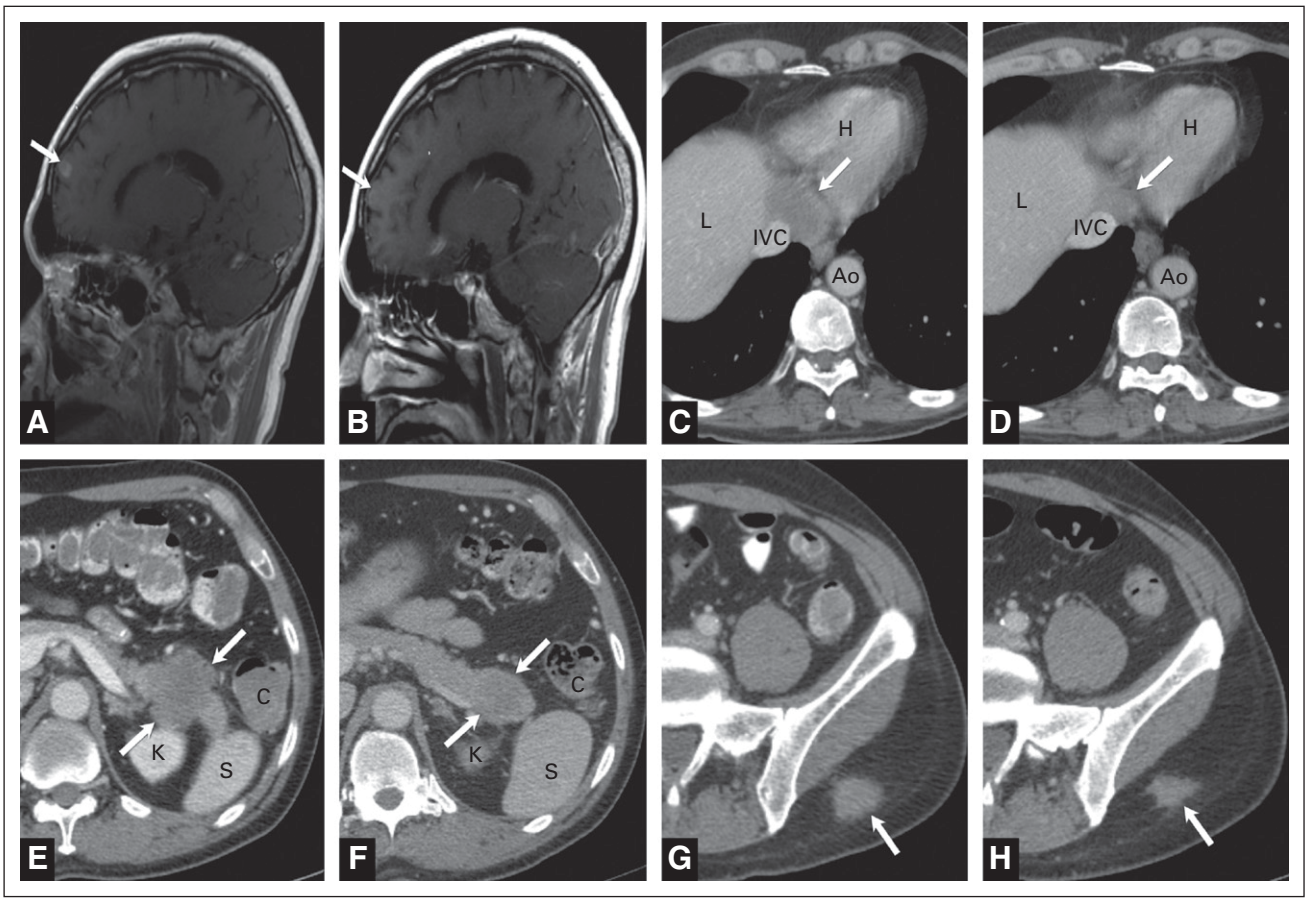

Fig A1. Tumor response in a patient treated with veliparib and temozolomide. A 57-year-old man with small-cell lung cancer metastatic to the brain, pancreatic tail, juxtaphrenic nerve, and subcutaneous tissue treated with the temozolomide (TMZ)/veliparib arm. (A) Sagittal T1-weighted magnetic resonance imaging scan with contrast shows a 1-cm metastasis (arrow) in the right frontal lobe at the time of enrollment in the study. (B) Sagittal T1-weighted magnetic resonance imaging scan with contrast demonstrates complete resolution of the brain lesion (arrow shows previous location) after therapy with TMZ/veliparib. (C) Axial computed tomography scan (CT) with contrast in narrow windows illustrates a 5-cm juxtaphrenic nodal mass (arrow) at the time that therapy was commenced. (D) Axial CT with contrast after therapy with TMZ/veliparib shows significant decrease in the lesion (arrow) compatible with response to therapy. (E) Axial abdominal CT with contrast shows a 5-cm heterogeneously enhancing lesion in the pancreatic tail (arrows). (F) Axial abdominal CT with contrast after therapy with TMZ/veliparib shows interval decrease in the pancreatic lesion to 3.5 cm. (G) Axial CT with contrast in narrow windows shows a 2.5-cm soft tissue implant (arrow) in the subcutaneous fat overlying the left gluteal muscles. Axial CT with contrast after treatment with the combination of veliparib and TMZ demonstrates a decrease in the size of the lesion (arrow). Importantly, there was significant pain associated with the lesion, which improved with temozolomide/veliparib therapy. Ao, aorta; C, colon; IVC, inferior vena cava; H, heart; K, kidney; L, liver; S, spleen.

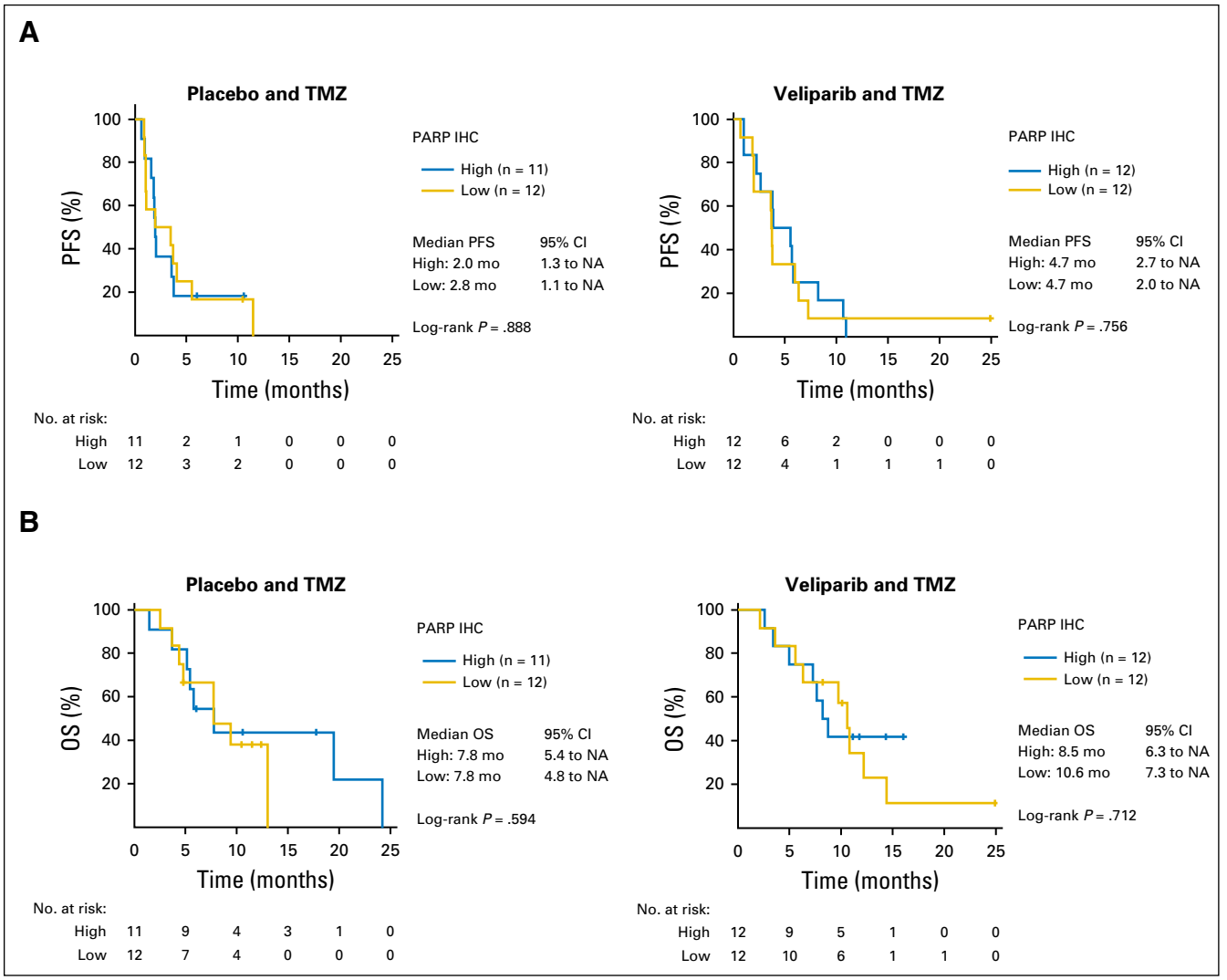

Fig A2. Poly (ADP-ribose) polymerase (PARP)-1 expression does not predict improved survival. (A) Progression-free survival (PFS) and (B) overall survival (OS) from date of randomization was not improved in patients whose tumors expressed PARP-1 by immunohistochemistry in the temozolomide (TMZ)/veliparib arm compared with the TMZ/placebo arm. IHC, immunohistochemistry; mo, months; NA, not achieved.

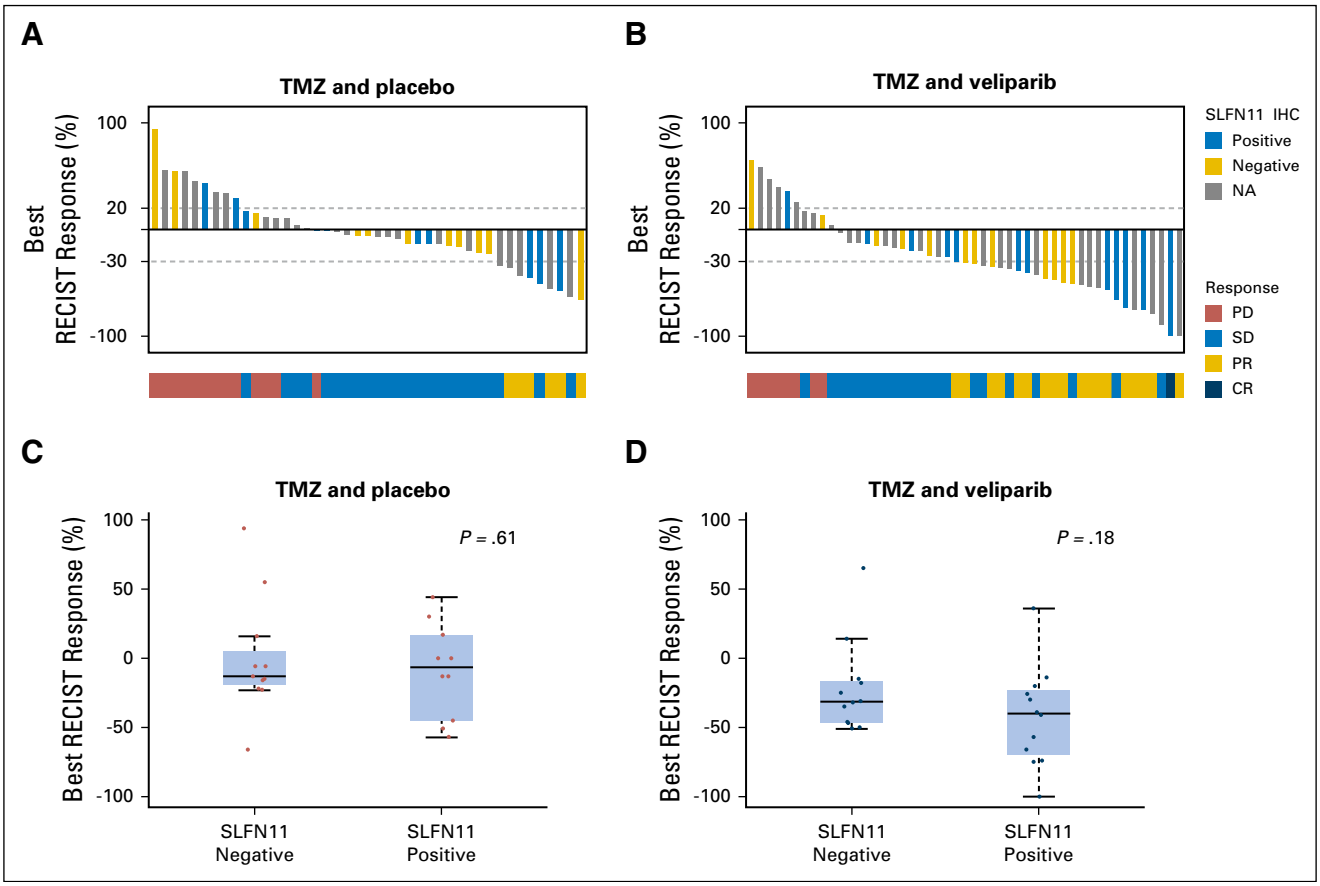

Fig A3. SLFN11 expression does not predict improved response to treatment. Waterfall plots of best Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 response (%) in each treatment arm color coded by SLFN-11 immunohistochemistry (IHC) status (positive, negative, or unknown): (A) temozolomide (TMZ)/placebo and (B) TMZ/veliparib. Boxplot of RECIST 1.1 responses in each treatment arm by SLFN-11 IHC: (C) TMZ/placebo and (D) TMZ/veliparib; trend toward deeper responses among patients with SLFN11-positive disease receiving veliparib and TMZ combination. CR, complete response; NA, not available; PD, progression of disease; PR, partial response; SD, stable disease.

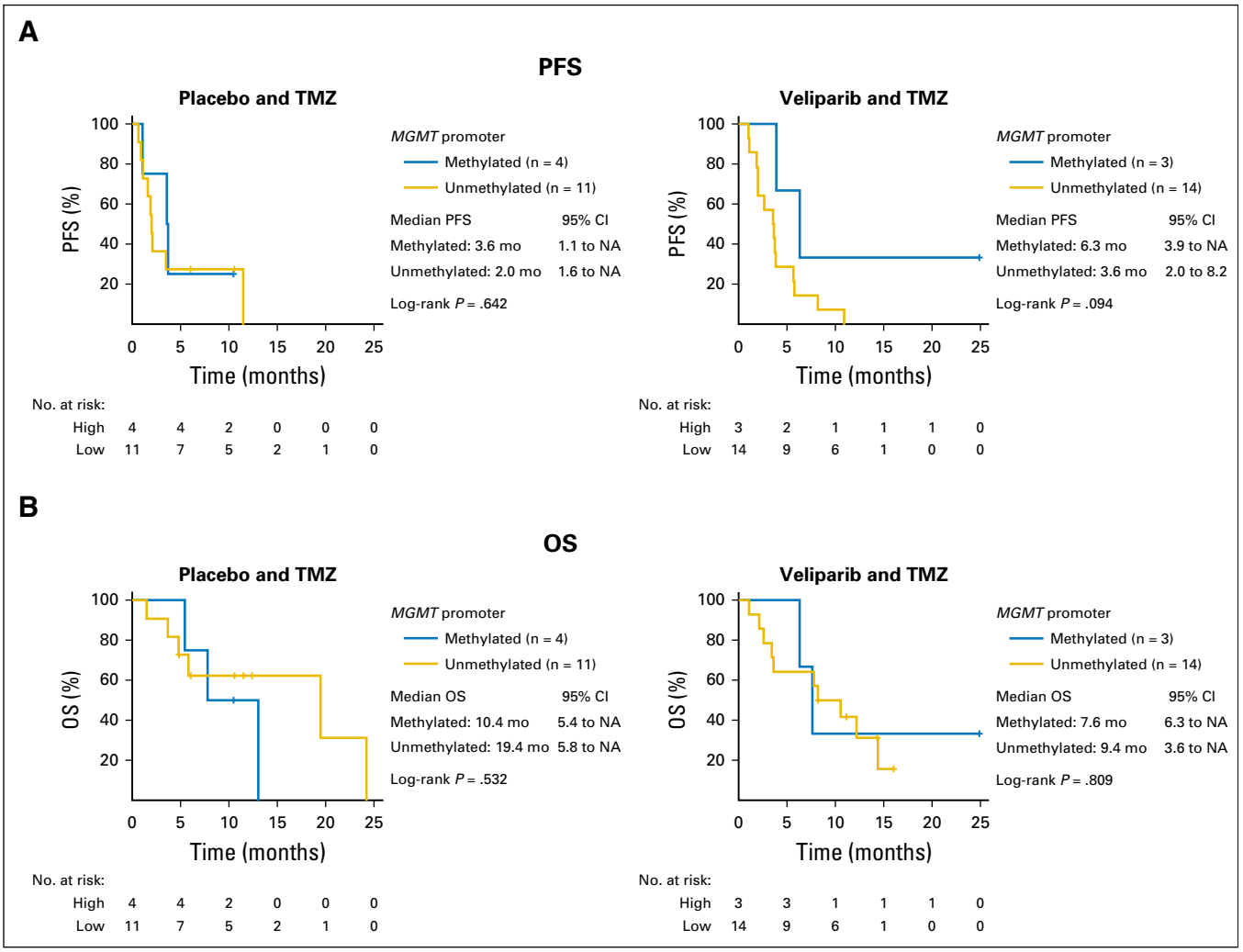

Fig A4. *MGMT* promoter methylation did not predict improved survival. (A) Progression-free survival (PFS) and (B) overall survival (OS) from the date of randomization in patients with known *MGMT* promoter methylation status. mo, months; NA, not achieved; TMZ, temozolomide.

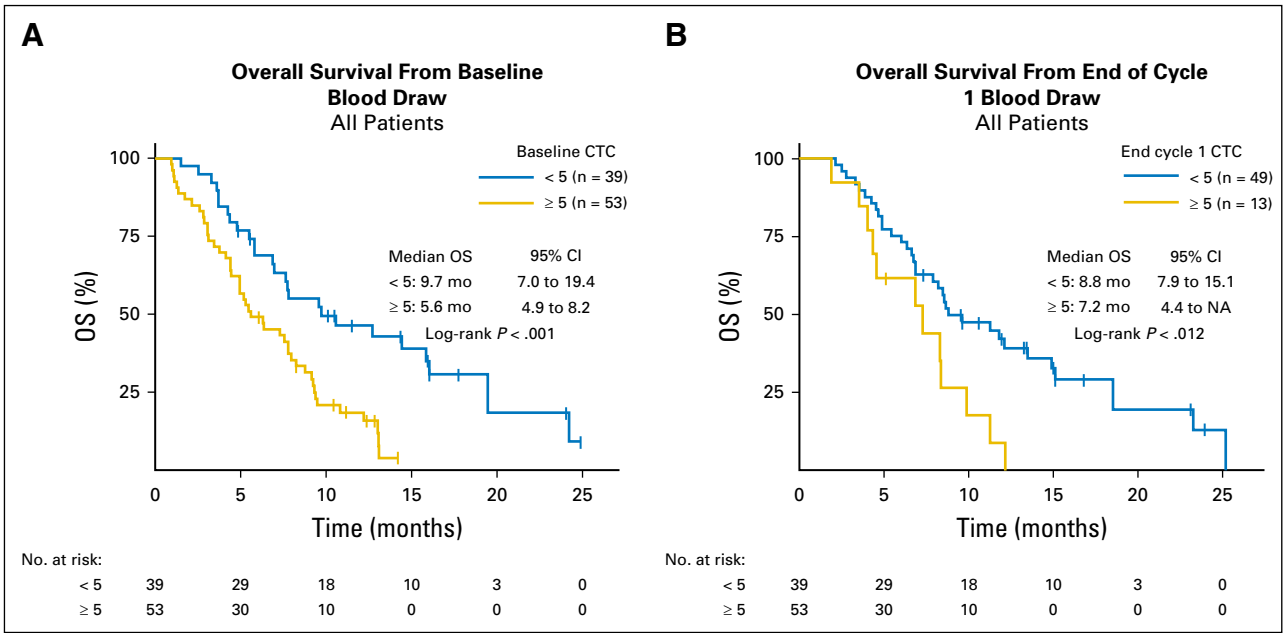

Fig A5. Low circulating tumor cell (CTC) numbers were associated with improved outcomes. CTCs < 5 in 7.5 mL were associated with improved survival. (A) At baseline and (B) at the end of cycle 1, CTCs < 5 in 7.5 mL were associated with improved survival. mo, months; OS, overall survival.

Table A1. Accrual by Site

Sites	Patients Enrolled and Treated, No.
Memorial Sloan Kettering Cancer Center	49
MD Anderson Cancer Center	19
Washington University School of Medicine in St. Louis	12
University Hospitals Cleveland Medical Center	11
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	9
H. Lee Moffit Cancer Center and Research Institute, Inc.	3
Emory University Winship Cancer Institute	1

Table A2. Summary of Efficacy Parameters Categorized by Treatment Received

Parameter	Placebo Arm (n = 49)*		Veliparib Arm (n = 55)*	
	No.	%	No.	%
ORR, $P = .016$	6	14	19	39
CR†	0	0	1	2
PR	6	14	18	37
SD	24	55	22	45
PD	14	32	81	6
PFS at 4 months, $P = .39$ (%)	27		36	
Median PFS, (months), $P = .39$	2.0		3.8	
95% CI	1.6 to 3.7		3.0 to 4.1	
Median OS (months), $P = .59$	7.0		8.2	
95% CI	5.3 to 9.5		6.4 to12.2	
Cohort designation (%)				
Sensitive disease				
ORR, $P = .055$	11		41	
Refractory disease				
ORR, $P = .22$	15		37	
Previous lines of therapy received (%)				
One, $P = .047$	16		39	
Two, $P = .21$	8		38	

Abbreviations: CR, complete response; ORR, overall response rate; OS, overall survival; PD, progression of disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

*All 49 and 54 patients randomly assigned to the placebo arm and veliparib arm, respectively, were included in the analysis for PFS and OS, whereas those who underwent diagnostic imaging at least once beyond baseline were evaluable for response (placebo group, n = 44; veliparib group, n = 49). Responses were all confirmed.

†The patient with the confirmed CR continued to receive treatment for > 21 cycles. There was an additional patient with an unconfirmed CR who withdrew consent after cycle 1.