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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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


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/m²/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; vs 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% vs 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 vs 3.6 months; \( P = .009 \)) and OS (12.2 vs 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.

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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, which showed modest response rates of 24% in patients with platinum-sensitive disease and 2% to 6% in platinum-refractory SCLC. Median time to progression with topotecan is short, between 13 and 16 weeks, 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. Frequent epigenetic silencing of the MGMT gene, which encodes the DNA-repair protein O6-methylguanine-DNA methyltransferase (MGMT), also has been demonstrated. As such, DNA damage response pathways represent attractive targets in SCLC.

Temozolomide (TMZ) is an oral alkylating agent that produces O6-alkyl-guanine lesions on DNA, which are repaired by MGMT. Left unrepaired, TMZ-induced lesions are cytotoxic and trigger apoptosis. We previously showed single-agent activity of TMZ in patients with relapsed SCLC, leading to its incorporation into treatment guidelines for this disease. However, the benefit provided by single-agent TMZ typically is brief, with median progression-free survival (PFS) of 3.5 months.

One well-defined mechanism of resistance to TMZ is through the PARP-dependent base excision repair pathway. 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. Furthermore, PARP inhibitors (PARPi) have single-agent activity in SCLC models and potentiate the effect of cytotoxic agents. On the basis of this, PARPi trials have been initiated in SCLC. 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.

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

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**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/m²/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.25,24 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.15 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 1 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 χ² 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 3.6 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 = .50). 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.

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).

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Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 104)</th>
<th>Temozolomide/Placebo (n = 49)</th>
<th>Temozolomide/Veliparib (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male/female (No.)</td>
<td>50/54</td>
<td>26/23</td>
<td>24/31</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>62.5 (31-84)</td>
<td>62 (35-84)</td>
<td>63 (31-80)</td>
</tr>
<tr>
<td>ECOG performance status, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29 (28)</td>
<td>13 (27)</td>
<td>16 (29)</td>
</tr>
<tr>
<td>1</td>
<td>75 (72)</td>
<td>36 (73)</td>
<td>39 (71)</td>
</tr>
<tr>
<td>Smoking history*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former, No. (%)</td>
<td>93 (89)</td>
<td>44 (90)</td>
<td>49 (89)</td>
</tr>
<tr>
<td>Never, No. (%)</td>
<td>4 (4)</td>
<td>1 (2)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Previous lines of therapy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>70 (67)</td>
<td>34 (69)</td>
<td>36 (65)</td>
</tr>
<tr>
<td>2</td>
<td>34 (33)</td>
<td>15 (31)</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Cohort designation, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive</td>
<td>43 (41)</td>
<td>19 (39)</td>
<td>24 (44)</td>
</tr>
<tr>
<td>Refractory†</td>
<td>61 (59)</td>
<td>30 (61)</td>
<td>31 (56)</td>
</tr>
<tr>
<td>Median time from diagnosis to treatment, months (range)</td>
<td>10 (2.5-33)</td>
<td>10 (4.5-25)</td>
<td>10.5 (2.5-33)</td>
</tr>
<tr>
<td>New brain metastases, No. (%)‡</td>
<td>22 (21)</td>
<td>10 (20)</td>
<td>12 (22)</td>
</tr>
</tbody>
</table>

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.
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.
Therefore, we amended our original planned biomarker analysis to investigate whether PARP-1 or SLFN11 expression was associated with improved PFS or OS (Appendix Fig A3, online only). The interaction 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 was also 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, which is associated with improved prognosis in patients with SCLC.

**MGMT Promoter Methylation as a Biomarker**

Analysis of MGMT promoter methylation 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).

### Table 2. Treatment-Emergent Adverse Events Occurring in \( \geq 10\% \) of Patients

<table>
<thead>
<tr>
<th></th>
<th>Adverse Event</th>
<th>Grade 1/2</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Temozolomide/Placebo</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td>Alkaline phosphatase increase</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Dermatologic†</td>
<td>Dermatologic§</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>20</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>6</td>
<td>13</td>
</tr>
</tbody>
</table>

*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 prolonged thrombocytopenia leading to treatment termination for an additional two patients, one in each arm.

‡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.
Veliparib and Temozolomide in Second-Line Treatment of SCLC

**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 μM, 400x 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 $\geq 1$) 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; (*) MDM2 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.
Interestingly, two of the four partial responses with mutations (with TMZ/placebo. In the TMZ/veliparib arm, the four patients had a median OS of 10.4 months, compared with 6.2 months for all patients treated with TMZ/placebo. Additionally, the sequencing data observed in the TMZ/veliparib arm had DNA repair gene mutations (Fig 4E).

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 Repair 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.37

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).

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.25,24,40,41 Here, in contrast, we used a recommended monotherapy treatment dose and schedule of TMZ (prior phase II study22) and a low dose of veliparib (per a phase II breast cancer study23). 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 were more frequent in our clinical trial than within the prior breast cancer study.45-47 Of note, we did not see more hematologic toxicity compared with our prior study22 in patients receiving both TMZ and veliparib versus TMZ/placebo. Additional data are needed to inform the optimal nontoxic dose for patients receiving both agents.

In summary, we continue to learn about the potential of PARPi in SCLC, and our analysis suggests that we may need to look beyond the PARP pathway to other potential mechanisms and therapeutic combinations.48-50 These results also support continued investigation of other PARPi, includingibrutinib, along with durvalumab, and the investigation of other mechanisms to improve outcomes for patients with relapsed SCLC.

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

<table>
<thead>
<tr>
<th>Patient Arm</th>
<th>Platform</th>
<th>Mutation</th>
<th>PFS/OS (mo)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA-131753</td>
<td>Veliparib</td>
<td>CMS400</td>
<td>ATM:c.8174A&gt;G, p.D2725G</td>
<td>9.0/16.0</td>
</tr>
<tr>
<td>MSK-031</td>
<td>Veliparib</td>
<td>IMPACT</td>
<td>BRCA2:c.5171T&gt;C, p.I1724T</td>
<td>6.0/10.8</td>
</tr>
<tr>
<td>MDA-144253</td>
<td>Veliparib</td>
<td>CMS50</td>
<td>ATM:c.988C&gt;T, p.S333F</td>
<td>4.2/4.2</td>
</tr>
<tr>
<td>MDA-149438</td>
<td>Veliparib</td>
<td>CMS50</td>
<td>ATM:c.1229T&gt;C, p.V410A</td>
<td>6.3/6.3</td>
</tr>
<tr>
<td>MSK-021</td>
<td>Control</td>
<td>IMPACT</td>
<td>ATM:c.5738T&gt;C, p.V1913A</td>
<td>4.5/9.2</td>
</tr>
<tr>
<td>MSK-049</td>
<td>Control</td>
<td>IMPACT</td>
<td>ATM:c.1760delC, p.G587fs</td>
<td>10.4/10.4</td>
</tr>
<tr>
<td>MSK-035</td>
<td>Control</td>
<td>IMPACT</td>
<td>CHEK2:c.2268G&gt;T, p.E76*</td>
<td>1.8/17.3</td>
</tr>
</tbody>
</table>

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.

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.

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.25,24,40,41 Here, in contrast, we used a recommended monotherapy treatment dose and schedule of TMZ (prior phase II breast cancer study22) and a low dose of veliparib (per a phase II breast cancer study23). 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 were more frequent in our clinical trial than within the prior breast cancer study.45-47 Of note, we did not see more hematologic toxicity compared with our prior study22 in patients receiving both TMZ and veliparib versus TMZ/placebo. Additional data are needed to inform the optimal nontoxic dose for patients receiving both agents.

In summary, we continue to learn about the potential of PARPi in SCLC, and our analysis suggests that we may need to look beyond the PARP pathway to other potential mechanisms and therapeutic combinations.48-50 These results also support continued investigation of other PARPi, includingibrutinib, along with durvalumab, and the investigation of other mechanisms to improve outcomes for patients with relapsed SCLC.
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. However, in preclinical models of SCLC, neither mutations in DNA repair genes nor homologous repair deficiency scores predict PARPi sensitivity. 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. In addition to SLFN11, biomarker analysis included PARP-1 expression and MGMT promoter hypermethylation, 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 and other cancer types, 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, 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 SLFN11 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 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. Hemato logic 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.

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Veliparib and Temozolomide in Second-Line Treatment of SCLC

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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Appendix
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.
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

<table>
<thead>
<tr>
<th>Sites</th>
<th>Patients Enrolled and Treated, No.</th>
</tr>
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<tbody>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>49</td>
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<tr>
<td>MD Anderson Cancer Center</td>
<td>19</td>
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<tr>
<td>Washington University School of Medicine in St. Louis</td>
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<td>University Hospitals Cleveland Medical Center</td>
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<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
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<tr>
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Table A2. Summary of Efficacy Parameters Categorized by Treatment Received

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Arm (n = 49)*</th>
<th>Veliparib Arm (n = 55)*</th>
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<tr>
<td></td>
<td>No.</td>
<td>%</td>
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<tr>
<td>ORR, ( P = .016 )</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>CR†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>SD</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>PD</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>PFS at 4 months, ( P = .39 ) (%)</td>
<td>27</td>
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<tr>
<td>Median PFS, (months), ( P = .39 )</td>
<td>2.0</td>
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<tr>
<td>95% CI</td>
<td>1.6 to 3.7</td>
<td>3.0 to 4.1</td>
</tr>
<tr>
<td>Median OS (months), ( P = .59 )</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>5.3 to 9.5</td>
<td>6.4 to 12.2</td>
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<tr>
<th>Cohort designation (%)</th>
<th>Placebo Arm</th>
<th>Veliparib Arm</th>
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<tbody>
<tr>
<td>Sensitive disease</td>
<td>11</td>
<td>41</td>
</tr>
<tr>
<td>ORR, ( P = .055 )</td>
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<td></td>
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<tr>
<td>Refractory disease</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>ORR, ( P = .22 )</td>
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<tr>
<td>Previous lines of therapy received (%)</td>
<td>16</td>
<td>39</td>
</tr>
<tr>
<td>One, ( P = .047 )</td>
<td>8</td>
<td></td>
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<tr>
<td>Two, ( P = .21 )</td>
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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.