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

M.Catherine Pietanza, Memorial Sloan-Kettering Cancer Center
Saiama N. Waqar, Washington University School of Medicine in St. Louis
Lee M. Krug, Memorial Sloan-Kettering Cancer Center
Afshin Dowlati, University Hospitals Case Medical Center
Christine L. Hann, Johns Hopkins University
Alberto Chiappori, Moffitt Cancer Center
Taofeek K Owonikoko, Emory University
Kaitlin M. Woo, Memorial Sloan-Kettering Cancer Center
Robert J. Cardnell, University of Texas MD Anderson Cancer Center
Junya Fujimoto, University of Texas MD Anderson Cancer Center

Only first 10 authors above; see publication for full author list.

Journal Title: Journal of Clinical Oncology
Volume: Volume 36, Number 23
Publisher: American Society of Clinical Oncology | 2018-08-10, Pages 2386-2394
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1200/JCO.2018.77.7672
Permanent URL: https://pid.emory.edu/ark:/25593/tbgdm

Final published version: http://dx.doi.org/10.1200/JCO.2018.77.7672

Copyright information:
© 2018 by American Society of Clinical Oncology
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed July 10, 2019 5:36 AM EDT
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.

J Clin Oncol 36:2386-2394. © 2018 by American Society of Clinical Oncology. Creative Commons Attribution Non-Commercial No Derivatives 4.0 License: https://creativecommons.org/licenses/by-nc-nd/4.0/

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.4-6 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.\(^7\),\(^18\),\(^19\) 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.

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.\(^7\) 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 TMZ were provided by the Cancer Therapy Evaluation Program at the National Cancer Institute. TMZ was obtained commercially.
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. 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. 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 chi² 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.

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).

#### 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 designations, 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>39 (81)</td>
<td>31 (64)</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.

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.
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 A4, online only). However, there was no significant difference on the basis of SLFN11 levels in either study arm (Appendix Fig A3, online only; TMZ/veliparib, \( P = .178 \)). 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, 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 \( (P = .614; \text{TMZ/placebo, } P = .783; \text{TMZ/veliparib, } P = .882) \). 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>Adverse Event</th>
<th>Grade 1/2</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMZ/Placebo</td>
<td>TMZ/veliparib</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase increase</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Dermatologic†</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20</td>
<td>43</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<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 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/m²/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 PARP response in SCLC models. Schlafen-11 (SLFN11) regulates response to DNA damage and replication stress, and was recently identified as a candidate predictive marker of sensitivity to DNA-damaging chemotherapies and PARPi in several cancers, including SCLC. Therefore, we amended our original planned biomarker analysis to investigate whether PARP-1 or SLFN11 expression levels predicted clinical benefit of TMZ/veliparib. 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 of 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 \( (5.7 \pm 3.6 \text{ months}; P = .009) \) and OS \( (12.2 \pm 7.5 \text{ months}; P = .014) \) 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 \( (P = .162 \text{ and .634, respectively}) \). 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, \( P = .614; \text{TMZ/placebo, } P = .178 \)). 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, which is associated with improved prognosis in patients with SCLC.
SLFN11 immunohistochemistry (IHC) predicts improved survival. (A) Example images of tumors with negative (neg) and positive (pos) SLFN11 by IHC (scale bar = 100 μM; 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 $\geq 1$) 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; (*) 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.

**Fig 4.**
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 from tumors of four 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).

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 study23) and a low dose of veliparib (per a phase II breast cancer study24). 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

<table>
<thead>
<tr>
<th>Patient Arm</th>
<th>Arm</th>
<th>Platform</th>
<th>Mutation</th>
<th>PFS/OS (mo)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vei105217</td>
<td>Veliparib</td>
<td>CMS400</td>
<td>ATM:c.8117_8118delG p.D2725G</td>
<td>9.0/16.0</td>
<td>PR</td>
</tr>
<tr>
<td>MDA-131753</td>
<td>Veliparib</td>
<td>CMS400</td>
<td>BRCA2:c.5171_5172delC p.1724T</td>
<td>6.0/10.8</td>
<td>PR</td>
</tr>
<tr>
<td>MDA-143253</td>
<td>Veliparib</td>
<td>CMS50</td>
<td>ATM:c.988C&gt;T p.S33F</td>
<td>4.2/4.2</td>
<td>SD</td>
</tr>
<tr>
<td>MDA-194938</td>
<td>Veliparib</td>
<td>CMS50</td>
<td>ATM:c.1229T&gt;C p.V410A</td>
<td>6.3/6.3</td>
<td>SD</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>
<td>SD</td>
</tr>
<tr>
<td>MSK-049</td>
<td>Control</td>
<td>IMPACT</td>
<td>ATM:c.1766delG p.G587fs</td>
<td>10.4/10.4</td>
<td>SD</td>
</tr>
<tr>
<td>MSK-035</td>
<td>Control</td>
<td>IMPACT</td>
<td>CHEK2:c.2269_2270insG</td>
<td>1.8/17.3</td>
<td>SD</td>
</tr>
</tbody>
</table>

Abbreviations: CMS50 and CMS400, amplicon-based panel of 60 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.

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.
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 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.

REFERENCES


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: M. Catherine Pietanza, Lee M. Krug, Alice Chen, John V. Heymach, Mark G. Kris, Charles M. Rudin, Lauren Averett Byers
Financial support: John V. Heymach, Mark G. Kris, Lauren Averett Byers
Administrative support: M. Catherine Pietanza, Afshin Dowlati, John V. Heymach, Lauren Averett Byers
Provision of study materials or patients: M. Catherine Pietanza, Lee M. Krug, Afshin Dowlati, John V. Heymach, Lauren Averett Byers
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors


Affiliations

M. Catherine Pietanza, Lee M. Krug, Mark G. Kris, and Charles M. Rudin, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College; Kaitlin M. Woo, Yevenigeya Bensman, Brenda Hurtado, and Martin Fleisher, Memorial Sloan Kettering Cancer Center, New York, NY; Saima N. Waqar, Washington University School of Medicine in St. Louis, St Louis, MO; Afshin Dowlati, Case Western Reserve University and University Hospitals Seidman Cancer Center, Cleveland, OH; Christine L. Hann, Johns Hopkins University, Baltimore; Alice Chen, National Institutes of Health, Bethesda, MD; Alberto Chiappori, H. Lee Moffitt Cancer Center, Tampa, FL; Taofeek K. Ovonikoko, Emory University, Atlanta, GA; and Robert J. Cardnell, Junya Fujimoto, Lihong Long, Lixia Diao, Jing Wang, Patricia de Groot, Erik P. Sulman, Ignacio I. Wistuba, John V. Heymach, and Lauren Averett Byers, The University of Texas MD Anderson Cancer Center, Houston, TX.

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 SPOR (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 Jeanie 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., 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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

M. Catherine Pietanza
Employment: Merck
Stock or Other Ownership: Merck

Saiama N. Waqar
Research Funding: Spectrum Pharmaceuticals (Inst), Eli Lilly (Inst), Pfizer (Inst), Genentech/Roche (Inst), Daiichi Sankyo (Inst), Newlink Genetics (Inst), EMD Serono (Inst), Puma Biotechnology (Inst), Novartis (Inst), Xcovery (Inst), Synermore biologics (Inst), Celgene (Inst), Vertex (Inst), Bristol-Myers Squibb (Inst), Stemcentrix (Inst), Hengrui Therapeutics (Inst), Checkpoint Therapeutics (Inst), Ignyta (Inst), AstraZeneca (Inst)

Lee M. Krug
Employment: Bristol-Myers Squibb
Stock or Other Ownership: Bristol-Myers Squibb

Afshin Dowlati
Consulting or Advisory Role: AbbVie, ARIAD
Research Funding: Endocyte, Merck Serono, Helix, Loxo Oncology, AstraZeneca, Mirati Therapeutics, AbbVie Stemcentrix, Vertex

Christine L. Hann
Consulting or Advisory Role: AbbVie, Genentech/Roche, Bristol-Myers Squibb
Research Funding: GlaxoSmithKline (Inst), AbbVie (Inst), Bristol-Myers Squibb (Inst), Merrimack

Alberto Chiappori
Honoria: Genentech, Celgene, Takeda, Novartis, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Merck, AbbVie, AstraZeneca
Consulting or Advisory Role: Genentech, Bristol-Myers Squibb, Novartis, AbbVie, AstraZeneca
Speakers’ Bureau: Boehringer Ingelheim, Merck, Genentech, Takeda, Celgene, Novartis, Pfizer
Research Funding: Novartis, Bristol-Myers Squibb

Taofeek K. Owonikoko
Consulting or Advisory Role: Celgene, Eli Lilly, Sandoz, AbbVie, Eisai, G1 Therapeutics, Takeda, Seattle Genetics, Bristol-Myers Squibb, MedImmune
Research Funding: Novartis (Inst), Astellas Pharma (Inst), Celgene (Inst), Bayer (Inst), Stemcentrix (Inst), Regeneron (Inst), AstraZeneca/MedImmune (Inst), AbbVie (Inst), G1 Therapeutics (Inst), Bristol-Myers Squibb

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)

Kaitlin M. Woo
No relationship to disclose

Robert J. Cardnell
No relationship to disclose

Junya Fujimoto
Research Funding: Astellas Pharma

Lihong Long
No relationship to disclose

Lixia Diao
No relationship to disclose

Jing Wang
No relationship to disclose

Yevgeniva Bensman
No relationship to disclose

Brenda Hurtado
No relationship to disclose

Patricia de Groot
No relationship to disclose

Erik P. Sulman
Honoria: Merck Sharp & Dohme, Novocure
Consulting or Advisory Role: Merck Sharp & Dohme, Novocure
Research Funding: AbbVie (Inst), Novocure (Inst)
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Novocure

Ignacio I. Wistuba
Consulting or Advisory Role: Genentech/Roche, Eli Lilly, Bristol-Myers Squibb, HTG Molecular Diagnostics, Asuragen, Pfizer, AstraZeneca/MedImmune, GlaxoSmithKline, Bayer
Speakers’ Bureau: Pfizer, Boehringer Ingelheim, MSD Oncology, Bristol-Myers Squibb, Genentech/Roche, AstraZeneca/MedImmune
Research Funding: Genentech, Merck, HTG Molecular Diagnostics, Silicon Biosystems, Adaptimmune, EMD Serono, Pfizer, MedImmune, Amgen, Takeda, Kars Therapeutics, Adaptive Biotechnologies

Alice Chen
No relationship to disclose

Martin Fleisher
No relationship to disclose

John V. Heymach
Consulting or Advisory Role: AstraZeneca, AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Medivation, ARIAD, AstraZeneca, Synta, Oncomed, Novartis, Genentech, Calithera Biosciences
Research Funding: AstraZeneca (Inst)

Mark G. Kris
Consulting or Advisory Role: AstraZeneca

Charles M. Rudin
Consulting or Advisory Role: Bristol-Myers Squibb, AbbVie, Seattle Genetics, Harpoon Therapeutics, Genentech/Roche, AstraZeneca

Lauren Averett Byers
Consulting or Advisory Role: AbbVie, AstraZeneca
Research Funding: AbbVie, AstraZeneca, Tolero Pharmaceuticals
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.
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.
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 A4.**
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>
</thead>
<tbody>
<tr>
<td>Memorial Sloan Kettering Cancer Center</td>
<td>49</td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td>19</td>
</tr>
<tr>
<td>Washington University School of Medicine in St. Louis</td>
<td>12</td>
</tr>
<tr>
<td>University Hospitals Cleveland Medical Center</td>
<td>11</td>
</tr>
<tr>
<td>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins</td>
<td>9</td>
</tr>
<tr>
<td>H. Lee Moffitt Cancer Center and Research Institute, Inc.</td>
<td>3</td>
</tr>
<tr>
<td>Emory University Winship Cancer Institute</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig A5. Low circulating tumor cell (CTC) numbers were associated with improved outcomes. CTCs < 5 in 7.5 mL were associated with improved survival.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Arm (n = 49)*</th>
<th>Veliparib Arm (n = 55)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>ORR, <em>P</em> = .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, <em>P</em> = .39 (%)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Median PFS, (months), <em>P</em> = .39</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>1.6 to 3.7</td>
<td></td>
</tr>
<tr>
<td>Median OS (months), <em>P</em> = .59</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>5.3 to 9.5</td>
<td></td>
</tr>
<tr>
<td>Cohort designation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, <em>P</em> = .055</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Refractory disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, <em>P</em> = .22</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Previous lines of therapy received (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One, <em>P</em> = .047</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Two, <em>P</em> = .21</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

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.