Published OnlineFirst January 14, 2015; DOI: 10.1158/1078-0432.CCR-14-2565

Cancer Therapy: Clinical

Clinical Cancer Research

Randomized Trial of Oral Cyclophosphamide and Veliparib in High-Grade Serous Ovarian, Primary Peritoneal, or Fallopian Tube Cancers, or *BRCA*-Mutant Ovarian Cancer

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Abstract

Purpose: Veliparib, a PARP inhibitor, demonstrated clinical activity in combination with oral cyclophosphamide in patients with *BRCA*-mutant solid tumors in a phase I trial. To define the relative contribution of PARP inhibition to the observed clinical activity, we conducted a randomized phase II trial to determine the response rate of veliparib in combination with cyclophosphamide compared with cyclophosphamide alone in patients with pretreated *BRCA*-mutant ovarian cancer or in patients with pretreated primary peritoneal, fallopian tube, or high-grade serous ovarian cancers (HGSOC).

Experimental Design: Adult patients were randomized to receive cyclophosphamide alone (50 mg orally once daily) or with veliparib (60 mg orally once daily) in 21-day cycles. Crossover to the combination was allowed at disease progression.

Results: Seventy-five patients were enrolled and 72 were evaluable for response; 38 received cyclophosphamide alone and 37 the combination as their initial treatment regimen. Treatment was well tolerated. One complete response was observed in each arm, with three partial responses (PR) in the combination arm and six PRs in the cyclophosphamide alone arm. Genetic sequence and expression analyses were performed for 211 genes involved in DNA repair; none of the detected genetic alterations were significantly associated with treatment benefit.

Conclusion: This is the first trial that evaluated single-agent, low-dose cyclophosphamide in HGSOC, peritoneal, fallopian tube, and *BRCA*-mutant ovarian cancers. It was well tolerated and clinical activity was observed; the addition of veliparib at 60 mg daily did not improve either the response rate or the median progression-free survival. *Clin Cancer Res; 21(7); 1574–82. ©2015 AACR.*

Introduction

PARP 1 and 2 enzymes regulate DNA damage repair and maintain genomic stability in cells. Inhibition of DNA repair by small-molecule PARP inhibitors potentiates DNA damage caused by cytotoxic chemotherapies, including cyclophosphamide (1–3). Inhibition of PARP activity in the presence of deleterious mutations in the *BRCA* gene, which is involved in the homologous recombination pathway of DNA damage repair, can result in tumor cell death through the process of synthetic lethality (4, 5). Clinical activity is observed with PARP inhibitors alone and in combination with cytotoxic chemotherapy in patients with breast or ovarian cancers carrying germline *BRCA* mutations (*BRCA*-mutant; refs. 6–8). Clinical responses have also been observed with PARP inhibitors in patients with high-grade serous ovarian cancer (HGSOC), a disease known to have a high incidence of DNA repair defects even in patients who do not carry germline *BRCA* mutations (9).

Low daily doses of oral cyclophosphamide (Cytoxan; Bristol-Myers Squibb Company) in combination with other agents have demonstrated clinical activity in lymphomas and multiple solid tumors (10–13). Our phase I study of oral cyclophosphamide in combination with veliparib was well tolerated and demonstrated activity in patients with *BRCA*-mutant tumors: 6 of 13 patients experienced a partial response (PR), and 3 additional patients had prolonged disease stabilization (14). Based on this promising activity, we conducted a multicenter, randomized phase II trial to

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-14-2565

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Translational Relevance

Administration of PARP inhibitors has been shown to result in antitumor responses as single agents in *BRCA*-mutant tumor models and in combination with DNA-damaging therapies. Veliparib, a small-molecule PARP inhibitor, demonstrated clinical activity in combination with oral cyclophosphamide in patients with *BRCA*-mutant solid tumors in a phase I trial. To define the relative contribution of PARP inhibition to the observed clinical activity, we conducted a multicenter, randomized phase II study of low-dose, oral cyclophosphamide, alone and in combination with veliparib, in patients with *BRCA*-mutant ovarian cancer or in patients with pretreated primary peritoneal, fallopian tube, or high-grade serous ovarian cancers. Clinical responses were observed; however, there was no difference in the response rate between the arms. Genetic sequence and expression analyses were performed for 211 genes involved in DNA damage repair; mutations were detected but did not correlate with clinical benefit on study.

compare the response rate (complete plus partial responses; CR+PR) of veliparib in combination with oral cyclophosphamide with that of oral cyclophosphamide alone in patients with pretreated *BRCA*-mutant ovarian cancer or in patients with pretreated HGSOC, primary peritoneal, or fallopian tube cancers. This trial was designed to estimate the relative contribution of PARP inhibition to the activity of this combination in patients with known *BRCA* mutations or in tumors known to have a high incidence of DNA repair defects (9). Secondary objectives were to evaluate archival tissue and blood samples for mutations in genes involved in DNA damage repair and determine poly(ADP-ribose) (PAR) levels in peripheral blood mononuclear cells (PBMC) and levels of phosphorylated histone H2AX (γH2AX), a marker of DNA damage response, in circulating tumor cells (CTC) before and during treatment (15, 16). Archival patient tumor samples were sequenced for 211 genes involved in DNA damage repair thought to possibly affect the therapeutic potential of both cyclophosphamide and PARP inhibitors. We also performed gene expression profiling to examine whether the expression of specific DNA repair genes might correlate with PARP mRNA levels, *BRCA* mutation status, or response to therapy.

Materials and Methods

Eligibility criteria

Patients 18 years of age or older with histologically documented *BRCA* mutation–positive ovarian cancer [documented deleterious *BRCA1/2* mutation or a BRCAPRO score (17) of ≥30%] were eligible to participate. Patients with primary peritoneal cancer, fallopian tube cancer, or HGSOC were also eligible to participate, regardless of *BRCA* mutation status. All patients were required to have received at least one line of standard therapy and have measurable disease. A Karnofsky performance status ≥70% and adequate liver, kidney, and marrow function defined as an absolute neutrophil count ≥1,500/μL, platelets ≥100,000/μL, total bilirubin ≤1.5× the upper limit of normal (ULN), aspartate aminotransferase and/or alanine aminotransferase <2.5× ULN, creatinine <1.5× ULN were also required. Prior exposure to PARP inhibitors or cyclophosphamide was allowed unless previously administered in combination.

Previous anticancer therapy or surgery must have been completed at least 4 weeks before enrollment. Patients with treated brain metastases stable for greater than 4 weeks off steroids were eligible. This trial was conducted under an NCI-sponsored IND with institutional review board approval at each participating site. Protocol design and conduct followed all applicable regulations, guidance, and local policies [ClinicalTrials.gov Identifier: NCT01306032].

Trial design

This was an open-label, multicenter, randomized phase II study of the combination of veliparib and oral cyclophosphamide compared with oral cyclophosphamide alone in patients with pretreated primary peritoneal cancer, fallopian tube cancer, HGSOC, or *BRCA*-mutant ovarian cancer. Veliparib (ABT-888) was supplied by the Division of Cancer Treatment and Diagnosis, NCI, under a Collaborative Research and Development Agreement with AbbVie. Cyclophosphamide was obtained from commercial sources.

Oral cyclophosphamide was administered at 50 mg once daily, alone or with oral veliparib at 60 mg once daily throughout a 21-day cycle, the same combination regimen studied in our prior phase I trial (14). Patients were required to maintain a diary documenting when drugs were taken and any associated side effects. There were no restrictions on food consumption. Adverse events were graded according to NCI Common Toxicity Criteria version 4.0. Doses of both drugs were reduced for grade ≥2 nonhematologic and grade 4 hematologic toxicities. Nonhematologic toxicities were required to have resolved to ≤grade 1, and hematologic toxicities to ≤grade 2 (except lymphopenia) before continuing treatment. Radiographic evaluation was performed at baseline and every three cycles to assess tumor response based on the RECIST version 1.1 (18).

The trial was randomized and used a phase 2.5 design, intending to enroll 65 patients per arm to have 80% power to permit a 0.10 alpha level one-sided test to compare clinical responses of 35% for the combination therapy to 15% for single-agent cyclophosphamide (19). In addition, there was 80% power to perform a 0.10 alpha level one-sided test to compare 6-month progression-free survival (PFS) probabilities between the arms. The study had a provision for an early stopping rule: if approximately 50% of the intended patients (approximately 32–33 per arm) had responses evaluated and the response rate on the combination arm was less than that of single-agent cyclophosphamide, then accrual would end whenever this was determined. Patient data were analyzed with and without being stratified by known *BRCA* mutation status.

Correlative studies

Formalin-fixed paraffin-embedded (FFPE)–archived tumor tissue samples were collected, and the tumor content was assessed from an hematoxylin and eosin (H&E)–stained 4-μm section of the specimen. If tumor content was found to be less than 70% of the total cellular content in the section, a manual macrodissection of the remaining tissue was performed to enrich for tumor cells (Fig. 1). DNA and RNA were extracted using Qiagen AllPrep DNA/RNA FFPE Kits. For the whole-

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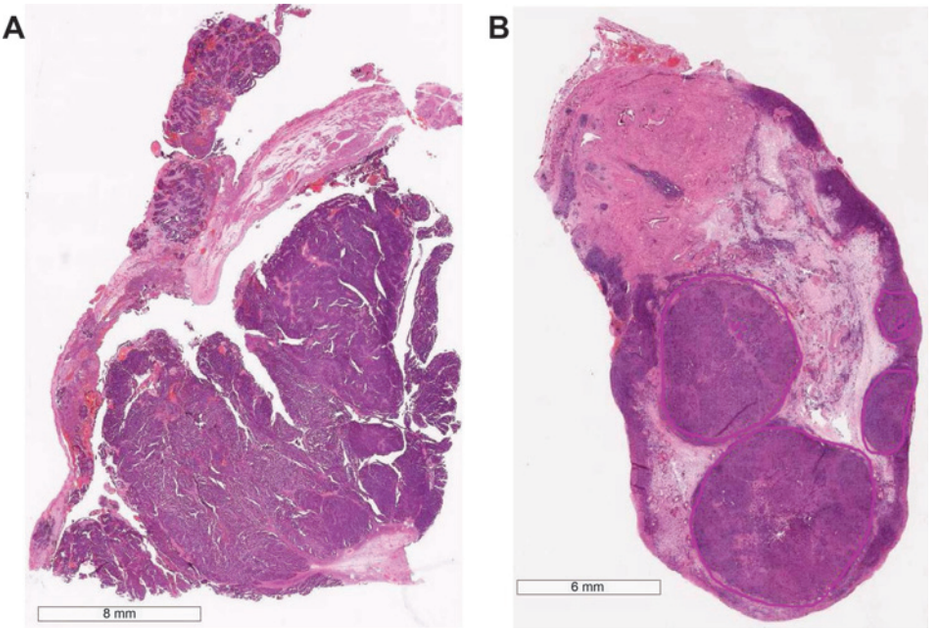

Figure 1.
Archival tumor tissue was assessed for tumor content, necrosis, and inflammation before sequencing. A, the sample shown from patient 1039 was 90% tumor and did not require macrodissection. B, the tissue from patient 1044 was 30% tumor, and macrodissection was carried out to enrich to >70% tumor in the circled areas.

exome capture sequence analysis, a total of 500 ng fragmented DNA for each sample was used to make a sequencing library by hybridization with Agilent SureSelectXT Human All Exon 50Mb capture baits, followed with sequencing on the Illumina HiSeq 2000 platform. Gene expression profiling was performed on the Affymetrix U133plus2 GeneChip (methods available in the Supplementary Data). Mutation and gene expression data were analyzed to identify any subset of patients benefiting from veliparib treatment using the cross-validated adaptive signature design approach (20). The same data were also interrogated with a multivariate penalized Cox proportional hazards model to investigate if any of the genes were associated with the hazard of disease progression in either the cyclophosphamide only or combination cohorts.

Whole blood for PBMC and CTC isolation and analysis was collected from patients enrolled at the NCI only. Specimens for CTC analysis were collected into 7.5-mL CellSave tubes (Veridex) at baseline (before administration of study drugs), 24 hours after dosing on cycle 1, day 1, before drug on cycle 2 day 1, and just before each restaging (every 3 cycles); levels of γH2AX were determined as previously described (16). Blood for PBMCs was collected into 8-mL Cell Prep tubes (Becton Dickinson) on cycle 1 day 1 at baseline and at 4 and 24 hours after drug, on cycle 2 day 1 before dosing and 4 hours after drug, and just before each restaging; PAR, a product of PARP, was measured as previously described (21). PBMC and CTC sampling were repeated after patient crossover.

Results

Demographics

Seventy-five patients were enrolled (Table 1); treatment was discontinued for 1 patient due to adverse events, 1 patient withdrew from the study, and 1 patient died before the end of the first cycle, leaving 72 patients evaluable for response (Table 1). Of these, 37 received cyclophosphamide alone and 35 the combination as their initial treatment regimen. Patients were heavily pretreated, all having received prior platinum and taxanes with the exception of patient #1071 who did not receive taxanes. Two patients had received prior PARP inhibitor therapy (niraparib, olaparib, veliparib), and 3 patients had received prior cyclophosphamide. No patient was eligible based on a BRCAPRO score alone.

Toxicity

Grade 2/3 leucopenia and lymphopenia were the most common adverse events experienced by patients receiving cyclophosphamide alone or in combination (Table 2); grade 4 lymphopenia and grade 4 thrombocytopenia were reported in two separate patients receiving the combination, necessitating dose reduction. There was a trend toward increased myelosuppression with the combination compared with single-agent cyclophosphamide; however, both treatment regimens were well tolerated and the toxicities were easily managed.

Table 1. Patient characteristics

Characteristics	Number of patients
Number of patients enrolled/evaluable	75/72
Median age, y (range)	58 (37–79)
Karnofsky performance status	
100	23
90	33
80	17
70	2
Diagnosis	
BRCA-mutant ovarian cancer	26
HGSOC	39
Fallopian tube cancer	6
Primary peritoneal cancer	4
BRCA status	
Mutant	31
Wild-type	1
Unknown	43
Median number of prior therapies (range)	4 (1–9)

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Table 2. Adverse events by patient. Worst grade (≥2), that is at least possibly related to study drugs, is shown for each patient ($N = 75$ patients)

Adverse event	C alone ($N = 38$)		V+C at crossover ($N = 29$)			V+C combination ($N = 37$)		
	Gr 2	Gr 3	Gr 2	Gr 3	Gr 4	Gr 2	Gr 3	Gr 4
Gastrointestinal								
Abdominal pain	1	—	—	—	—	1	—	—
ALT increased	—	—	1	—	—	—	—	—
Anorexia	2	—	—	—	—	1	—	—
Bloating	—	—	—	—	—	1	—	—
Diarrhea	1	—	—	—	—	1	—	—
Nausea	1	—	2	—	—	1	—	—
Vomiting	—	—	1	—	—	1	—	—
Oral mucositis	1	—	—	—	—	—	—	—
Hematologic								
Anemia	2	—	9	—	—	7	2	—
Leucopenia	6	—	6	2	—	10	2	—
Lymphopenia	13	3	9	8	1	11	13	—
Neutropenia	1	—	3	1	—	7	2	—
Thrombocytopenia	—	—	2	—	—	1	1	1
Electrolyte								
Dehydration	—	—	—	—	—	—	1	—
Hypochloremia	—	—	—	—	—	1	—	—
Hypophosphatemia	1	—	—	—	—	—	—	—
Hyponatremia	—	—	—	—	—	—	1	1
Infection								
Pelvic infection	1	—	—	—	—	—	—	—
Tooth infection	—	—	—	—	—	1	—	—
Urinary tract infection	—	—	1	—	—	—	—	—
Other								
Fatigue	3	—	5	—	—	4	—	—
Generalized muscle weakness	—	—	1	—	—	—	—	—
Hematuria	1	—	—	—	—	—	—	—
Hot flashes	1	—	—	—	—	—	—	—
Hypoalbuminemia	—	—	—	—	—	1	—	—
Psychiatric disorders, other (tearfulness)	—	—	1	—	—	—	—	—

Abbreviations: ALT, alanine aminotransferase; C, cyclophosphamide; Gr, grade; V, veliparib.

Efficacy

The addition of veliparib to cyclophosphamide did not improve the response rate over cyclophosphamide alone, and patient accrual ended early per the stopping rule defined in the protocol. Out of 70 total patients with responses reported, 1 patient in each arm (#1095 and #1088) had a CR. PR was seen in 6 patients in the cyclophosphamide-only arm [7/36 (19.4%) responses overall; 95% confidence interval (CI), 8.2%–36.0%], 3 patients in the combination arm [4/34 (11.8%) responses overall; 95% CI, 3.3%–27.5%], and 1 patient who crossed over to the combination arm after progressing on the cyclophosphamide-only arm. Four of the patients who responded on the cyclophosphamide-only arm had *BRCA*-mutant ovarian cancer (including the patient who had a CR), two had HGSOC, and one had fallopian tube cancer. Two of the patients who responded on the combination arm had HGSOC (including the patient who had a CR), one had *BRCA*-mutant ovarian cancer, and one had fallopian tube cancer.

In addition, 6 patients in the cyclophosphamide-only arm and 5 patients on the combination arm had stable disease (SD) for six or more cycles of treatment, as did 4 of the 29 patients who crossed over to the combination treatment. One patient on the cyclophosphamide-only arm (#1056) had prolonged disease stabilization, receiving more than 32 cycles of treatment. Exome analysis of the tumor samples from this patient revealed mutation in *BRCA2*. Two patients had prolonged clinical benefit on the combination treatment, one with fallopian tube cancer (#1093; *BRCA* status unknown) and one with *BRCA1*-mutant ovarian cancer (#1087) who initially progressed on the cyclophosphamide arm and subsequently crossed over. Both were continuing on treatment at the time of data analysis, each having received over 38 cycles (more than 2 years) of treatment. The numbers of cycles of initial and crossover treatment per patient are shown in Fig. 2A–C. There was no improvement in PFS with the addition of veliparib to cyclophosphamide (median 2.3 and 2.1 months for cyclophosphamide-alone and combination treatment, respectively; Fig. 2D; $P = 0.68$ by two-tailed log-rank test), nor did stratification by *BRCA* status (either reported or determined from sequencing archival tumor samples) reveal a subset with improved PFS (Supplementary Fig. S1).

Correlative studies

PAR levels were determined in PBMC samples collected before and after coadministration of veliparib from 10 patients on the combination arm and 11 patients who had crossed over to the combination arm. Four hours after treatment, PAR levels were reduced by at least 48% compared with baseline in all samples (mean, 85%; SD, 13%) and were rebounding in most patients by 24 hours after treatment (Supplementary Fig. S2). Sufficient CTC counts (≥6 CTCs) were isolated in samples from 10 (5 from each treatment arm) of 23 patients analyzed; counts ranged from 6 to 24 per 7.5 mL whole blood (data not shown). An increase in γH2AX-positive CTCs was observed in the only patient for whom quantitative analysis could be performed (data not shown).

A panel of 211 genes selected for their involvement in DNA repair (Supplementary Table S1) were interrogated by whole-exome capture sequencing and gene expression profiling in tumor

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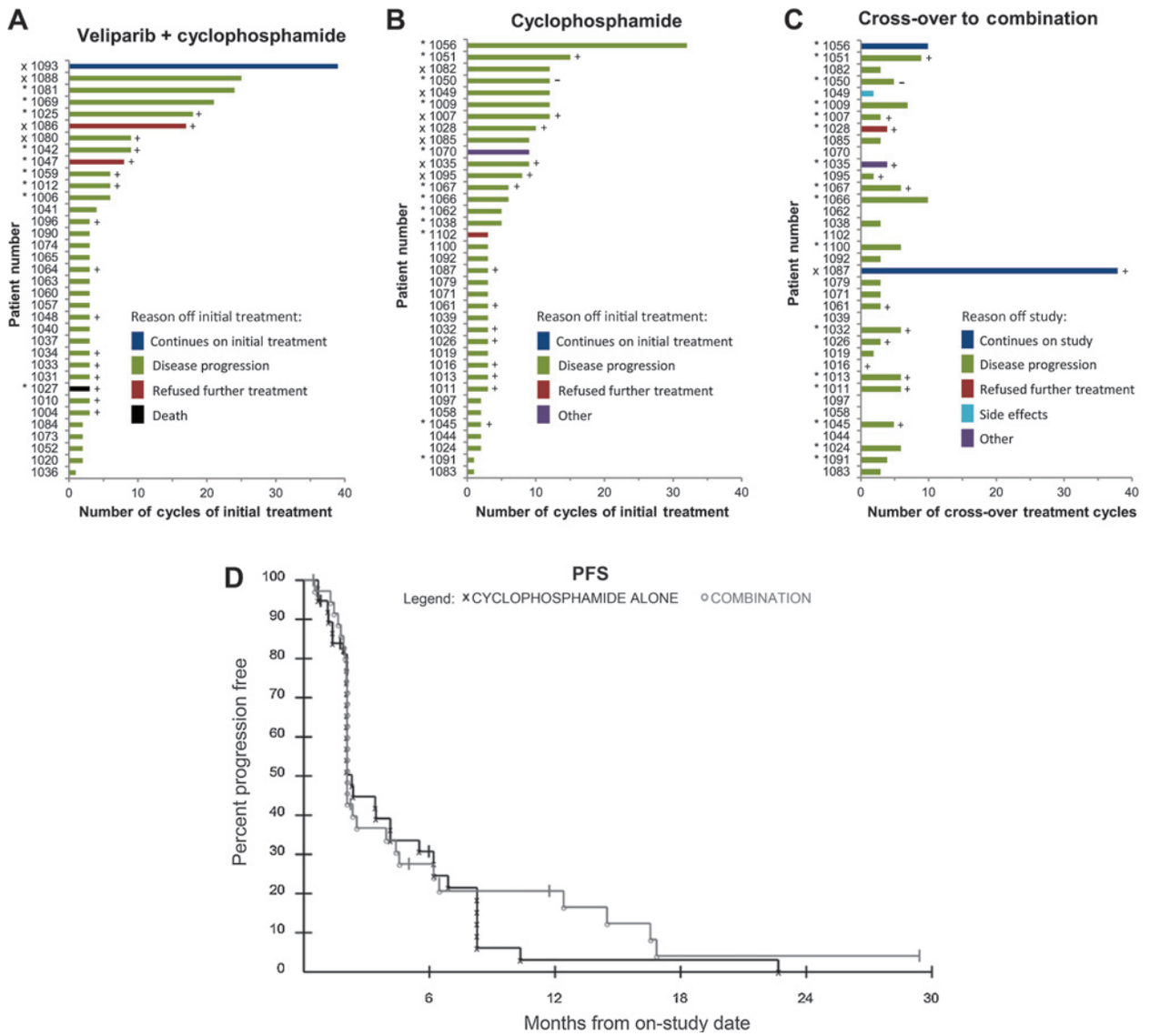

Figure 2.
Treatment cycles for the 72 evaluable patients. Each patient's best response during each treatment is listed to the left of the patient number: complete or partial response (×) or stable disease (*). A, thirty-five patients received the combination of veliparib plus cyclophosphamide as their initial treatment, of whom 16 reported deleterious *BRCA* mutations (+). B, thirty-seven patients initially received cyclophosphamide alone, of whom 14 reported deleterious *BRCA* mutations (+) and 1 reported wild-type *BRCA* status (−). C, twenty-nine patients crossed over to the combination treatment after disease progression on cyclophosphamide-only treatment. D, no difference in PFS ($P = 0.68$) was observed between patients treated with cyclophosphamide alone (median PFS of 2.3 months) or in combination with veliparib (median PFS of 2.1 months).

tissue from 55 patients (27 treated with cyclophosphamide alone and 28 with the combination). All 55 patients had deleterious mutations (i.e., nonsynonymous mutations at coding regions) in at least 4 (and up to 70) of the genes evaluated, with an average of 9.3 mutations per patient (Table 3). The most common mutations observed, by far, were in *TP53*, followed by *BRCA1*; our patients displayed proportionally higher frequencies of mutations in DNA repair genes such as *BRCA1*, *BRCA2*, and *APC* than are commonly found in ovarian serous carcinoma (Table 4). We observed no significant difference in either the total number of genes mutated or the mutational frequency of any particular gene between those patients who did or did not respond to treatment. Gene expression profiling over the 211 DNA repair genes was suggestive of two different populations within the 55 patients, but these populations did not align with *BRCA* mutational status, patient response, or any other characteristic that we could demonstrate (Supplementary Fig. S3 and Supplementary Excel file).

We used the cross-validated adaptive signature design approach (20) to analyze whether the mutation status or expression levels of the genes in our DNA repair panel could be used to identify a subset of patients who benefited from PARP inhibitor treatment. Although 22 genes with a *P* value less than 0.05 were identified (Supplementary Table S2), none of the genetic

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Table 3. DNA repair gene mutations observed, listed by patient

Patient ID	Total variant count	Genes mutated from the panel of 211 DNA repair genes
1004	8	*APLF, POLH, REV3L, ATM, TP53, BRCA1, POLI, UBE2A*
1006	8	*RIF1, TREX1, HELQ, WRN, APEX1, TP53, RECQL5, POLD1*
1007	9	*FANCL, HLTF, DDB2, BLM, TP53, BRCA1, BRCA1, BRCA1, LIG1*
1010	14	*EXO1, GEN1, ERCC8, TDP2, HUS1, NBN, MMS19, FANCF, BIVM—ERCC5, ERCC5, BUB1B, NTHL1, TP53, BRCA1, ENDOV*
1011	13	*MSH4, RIF1, ATRIP, MSH3, RAD50, TDP2, KNTC1, FAN1, SLX4, TP53, RAD51D, BRCA1, CHEK2*
1012	10	*TREX1, ATR, MDC1, POLE, TP53BP1, PIF1, TP53, TP53, BRCA1, POLD1*
1013	10	*RIF1, RFC4, POLN, RECQL4, UNG, BRCA2, LIG4, TP53, RBBP8, CD3EAP*
1016	10	*GEN1, PARP3, ATR, POLM, CSB—PGBD3, PGBD3, POLE, BRCA2, TP53, TP53, LIG3*
1024	6	*PMS1, APC, PRKDC, RECQL4, ERCC6, DCLRE1A*
1025	9	*RIF1, PRKDC, RAD54B, BRCA2, MLH3, TP53, PER1, BRCA1, RBBP8*
1026	11	*MSH4, RFC1, MSH3, MDC1, TOP1MT, RAD51B, FANCI, TP53, TOP2A, BRCA1, TOP3B*
1028	11	*RAD18, POLQ, POLQ, MSH5, REV3L, POLE2, RAD51B, TP53, BRCA1, ERCC2, TREX2*
1031	8	*MUTYH, GEN1, FANCD2, POLN, MSH3, NABP2, POLE, TP53*
1032	8	*MBD4, POLN, RECQL4, MLH3, TP53BP1, BRCA1, BRCA1, BRCA1*
1033	8	*MSH6, APC, TDG, BRCA2, BRCA2, TP53, XRCC1, CHEK2*
1034	14	*MUTYH, RAD54L, EXO1, HLTF, RECQL4, DNA2, FEN1, TDG, FANCM, TP53, BRCA1, RBBP8, TOP1, TREX2*
1035	7	*EXO1, OGG1, MRE11A, TP53, BRCA1, BRCA1, SPO11*
1036	9	*RIF1, APC, WEE1, WEE1, POLE, BRCA2, NEIL1, TP53, PNKP*
1037	5	*MSH4, RECQL4, WEE1, TP53, RECQL5*
1038	12	*TP73, APC, MDC1, REV3L, REV3L, XRCC2, ATM, PARP2, MLH3, BLM, TP53, BRCA1*
1039	4	*PARP3, RAD51B, TP53, POLI*
1042	7	*MAD2L1, APC, SHPRH, RECQL, NTHL1, TP53, BRCA1*
1044	7	*EXO1, RIF1, RIF1, ATR, HLTF, POLM, TP53*
1045	5	*MMS19, BRCA2, MLH3, BRCA1, CHEK2*
1047	7	*BRCA2, BLM, ZNF276, FANCA, TP53, BRCA1, CCNE1*
1049	4	*DNA2, FANCM, TP53, RAD23A*
1050	11	*TOP2B, BAP1, MBD4, RAD54B, FSBP, MMS19, PARP4, APEX1, TP53BP1, TP53, CHAF1A*
1051	8	*HELQ, ATM, ATM, KNTC1, FANCM, SLX4, POLI, CD3EAP*
1052	7	*TP73, FANCL, RFC1, APC, KNTC1, FANCM, TP53*
1053[a]	6	*POLE, TP53, LIG3, BRCA1, RAD23A, CCNE1*
1056	6	*MLH1, MSH3, APC, BRCA2, BIVM-ERCC5, ERCC5, TP53*
1057	5	*WRN, FANCA, TP53, RECQL5, XAB2*
1058	8	*HLTF, XRCC4, PRKDC, POLE, FAN1, TP53, POLI, TREX2*
1059	5	*FANCC, PALB2, TP53, BRCA1, BRCA1*
1060	8	*MBD4, MBD4, PALB2, TP53, TP53, RAD23A, SPO11, RPA4*
1061	5	*ATM, ATM, BRCA2, TP53, TOP3A*
1062	11	*GEN1, ERCC8, NEIL2, NBN, TOP1MT, ERCC6, PARP4, RAD51B, PIF1, NEIL1, BRCA1*
1063	10	*EXO1, PARP3, UVSSA, POLK, PRKDC, RAD23B, FEN1, EME2, TOP3B, RPA4*
1064	10	*ATRIP, POLQ, MSH3, FANCM, TP53, PER1, PER1, PER1, BRCA1, XAB2*
1065	5	*MSH3, TP53, TP53, TP53, POLD1*
1069	5	*EXO1, ATR, TP53, BRCA1, PNKP*
1070	7	*MSH6, POLQ, FSBP, RECQL4, RAD51, TP53, LIG1*
1073	10	*ERCC3, HLTF, PRKDC, PRKDC, PRKDC, FANCA, TP53, POLI, RAD23A, POLD1*
1074	7	*NEIL2, FANCG, ALKBH3, UNG, POLG, POLG, TP53*
1079	6	*RAD1, POLE, NEIL1, TP53, PER1, POLI*
1081	7	*UVSSA, MDC1, PRPF19, ATM, ERCC4, TP53, LIG1*
1082	12	*RIF1, RIF1, ATR, POLN, RAD1, GTF2H5, TDG, TP53BP1, TP53, PER1, TOP3A, RBBP8*
1086	8	*RIF1, POLN, XRCC4, POLH, RECQL4, BRCA1, ENDOV, XRCC1*
1087	7	*FEN1, ATM, FANCI, PALB2, BRCA1, XAB2, RAD23A*
1088	9	*ATRIP, POLQ, XRCC2, CSB—PGBD3, ERCC6, BRCA2, MLH3, TP53, RBBP8, LIG1*
1090	5	*HELQ, POLE, ERCC4, ERCC4, RECQL5*
1091	6	*POLQ, TDP2, RAD9A, POLE, TP53, TP53*
1096	6	*POLQ, HELQ, DCLRE1C, BLM, TP53, BRCA1*
1097	9	*FANCL, OGG1, XPC, DCLRE1C, MPG, TP53, TOP3A, TOP3A, CETN2*
1098[a]	70	*C1orf86, MUTYH, RAD54L, EXO1, GEN1, BUB1, PMS1, ATRIP, TREX1, BAP1, POLQ, ATR, UVSSA, MDC1, MDC1, GTF2H4, MSH5, MSH5, MSH5, PMS2, RFC2, WRN, POLB, PRKDC, PRKDC, FSBP, TOP1MT, RECQL4, FANCG, DCLRE1A, GTF2H1, DDB1, MUS81, MUS81, MUS81, RAD9A, POLE, POLE, POLE, POLE, POLE, POLE, FANCM, TDP1, FAN1, NEIL1, BLM, NTHL1, NTHL1, SLX4, SLX4, PALB2, FANCA, TP53, TP53, TP53, TOP3A, RAD51D, BRCA1, BRCA1, BRCA1, BRIP1, RECQL5, RECQL5, CHAF1A, CD3EAP, ERCC1, ERCC1, LIG1, POLD1*

NOTE: Gray shading indicates combination treatment; white indicates cyclophosphamide-alone initial treatment.
[a]Patient was not evaluable for response due to insufficient time on study, but was included in the genetic and expression analyses.

alterations were significantly associated with veliparib treatment benefit when adjusted for multiplicity to control for the false discovery rate. The selected variables were therefore not sufficient to build a reliable predictor to select patients who would benefit from PARP inhibitor therapy.

Discussion

The combination of PARP inhibitors with cytotoxic chemotherapy has been poorly tolerated with enhanced myelosuppression limiting the doses of chemotherapy that can be safely

Published OnlineFirst January 14, 2015; DOI: 10.1158/1078-0432.CCR-14-2565

Table 4. Top mutated DNA repair genes in study patients, listed by frequency, and the frequency with which they occur in the COSMIC database (v68) of ovarian serous carcinoma (38)

Gene	Frequency in the ABT+CP cohort	Frequency in the CP cohort	COSMIC frequency
TP53	89.3%	75.0%	73.0%
BRCA1	46.4%	39.3%	5.0%
POLE	25.0%	14.3%	0.0%
BRCA2	17.9%	17.9%	3.0%
RIF1	17.9%	10.7%	0.0%
POLQ	3.6%	21.4%	0.0%
RECQL4	14.3%	14.3%	0.0%
EXO1	10.7%	14.3%	0.0%
RECQL5	7.1%	14.3%	0.0%
APC	10.7%	14.3%	2.0%
PRKDC	10.7%	10.7%	0.0%
ATM	10.7%	10.7%	0.0%
POLI	17.9%	3.6%	0.0%
MSH3	10.7%	10.7%	0.0%
ATR	7.1%	14.3%	0.0%
POLD1	7.1%	14.3%	0.0%
FANCM	7.1%	14.3%	0.0%

Abbreviations: ABT, veliparib; CP, cyclophosphamide.

administered (22). The combination of oral cyclophosphamide with veliparib, however, was well tolerated and could be safely administered on a chronic schedule providing uninterrupted PARP inhibition to the majority of patients (14); therefore, we decided to address the question of the relative contribution of PARP inhibition to the clinical activity of the combination by comparing veliparib with oral cyclophosphamide to oral cyclophosphamide alone in ovarian tumors carrying *BRCA* mutations or in gynecologic cancers known to have a high incidence of DNA repair defects (9). Even though oral cyclophosphamide has demonstrated activity in combination chemotherapy regimens in a variety of tumor types, this is the first trial to document the response rate, using current staging and response criteria, of oral cyclophosphamide alone in this patient population. Previously, the only report of single-agent cyclophosphamide activity in ovarian cancer was from a study conducted in 1965 in 17 patients (11 postoperative patients who had undergone incomplete resections and 6 patients with disease recurrence) that reported responses by physical examination and time to clinical progression or overall survival (23). As demonstrated in the current trial, oral cyclophosphamide is a well-tolerated oral regimen associated with responses and prolonged disease stabilization in this pretreated population.

Solid tumors carrying DNA repair defects, such as breast and ovarian tumors carrying *BRCA* mutations, demonstrate increased sensitivity to PARP inhibitors or DNA-damaging chemotherapies. In this trial, 9 of the 11 patients who responded to either cyclophosphamide alone or the combination had either HGSOC or known *BRCA*-mutant ovarian cancer. In previous work by investigators from the Cancer Genome Atlas, analysis of HGSOC identified defects in the homologous recombination DNA repair pathway in 51% of 316 patient samples analyzed (9). This finding could account for the responses observed in our patients. However, we did not demonstrate an increase in the response rate to oral cyclophosphamide with the addition of veliparib as the initial therapy in this trial, or with the addition of veliparib at the time of disease progression for patients initially treated with oral cyclophosphamide alone. The relative sensitivity of tumor cells carrying various defects in the homologous recombination pathway to PARP inhibition is not well characterized, and therefore it is not known whether including patients likely to carry other defects in the homologous recombination pathway (HGSOC) as well as patients carrying known deleterious mutations in *BRCA1* or *BRCA2* in a relatively small sample set may have affected the overall outcome of the trial. We did analyze the PFS of patients treated with the combination, stratifying by *BRCA*-mutant status. *BRCA* status from tumor exome analysis exhibited a slight trend toward an effect in patients who received the combination treatment ($P = 0.22$), indicating that it might potentially play a role in prognosis.

The lack of increased response rate with the addition of veliparib to cyclophosphamide could also be due to the dose of veliparib employed in our study, which was below the 250 to 400 mg twice-a-day doses used in recent trials such as the Gynecologic Oncology Group (GOG) trial of single-agent veliparib and others (24–28). The safety of higher doses of single-agent veliparib used in the GOG trial and other studies had not been established when the current trial was initiated. Higher doses of veliparib in combination with cyclophosphamide may have resulted in more responses; however, the doses of study drugs used in this trial were established as the MTD in our prior phase I trial (14), had been shown to inhibit PAR levels in tumors, and allowed safe, uninterrupted dosing over the entire period of trial participation for patients receiving veliparib. We observed inhibition of PAR levels in PBMCs after veliparib in this trial; however, there was some recovery of PAR levels by 24 hours, favoring twice-a-day administration for veliparib to have continuous suppression of PARP activity.

It is not yet known what relative or absolute level of PAR inhibition is necessary for clinical efficacy; 90% inhibition has been measured in previous clinical trials (29). Because of the difficulties inherent in collecting research biopsies in patients with ovarian and peritoneal cancers, we measured PAR levels in PBMCs as a potential surrogate for tumor tissue in patients receiving combination treatment. We did demonstrate a decrease in PBMC PAR levels by an average of 85% 4 hours after the first administration of veliparib; however, given the modest response rates observed we could not correlate PAR inhibition to clinical benefit. PARP inhibitors can function both by inhibiting the catalytic activity of PARP, resulting in persistent, unrepaired DNA single strand breaks, and by trapping PARP–DNA complexes, interfering with DNA replication (30–32). Although a potent catalytic inhibitor of PARP (33), in cell lines, veliparib causes less PARP trapping

than some other PARP inhibitors at catalytically inactivating concentrations (32). The relative contribution of PARP–DNA trapping to the clinical activity of PARP inhibitors in combination with cytotoxic chemotherapy is not known. In addition, the role of PARP in modulating the activity of low-dose cyclophosphamide is postulated but not proven in the clinic.

Platinum sensitivity appears to be one of the determinants of response to PARP inhibitor therapy (34–36). In our trial, all patients had received prior platinum; however, we did not collect consistent data to determine the fraction of patients who had platinum-sensitive disease and how that correlated with clinical benefit on either arm. In view of our randomized trial design, we presume but cannot prove that the arms were evenly balanced with regard to the number of patients with platinum-sensitive versus -resistant disease.

We also performed an exploratory analysis of the mutation status and expression levels of 211 selected genes involved in DNA damage response. Widespread defects in pathways such as homologous recombination, nonhomologous end joining, mismatch repair, Fanconi anemia, and DNA replication were observed; however, the presence of these DNA repair defects did not predict for response to either cyclophosphamide or the combination of veliparib and cyclophosphamide, nor was the known *BRCA* status of the patients informative in determining the likelihood of patient response. The clinical significance of the genetic aberrations we observed and the optimal agent(s) and dosages for treatment based on those observations need to be further defined for the aberrations in the context of the disease histology.

Various mechanisms have been proposed for the antitumor activity of oral cyclophosphamide, including inhibition of cd4(+)25+ T regulatory cell function (37). However, the underlying mechanism(s) that account for the observed antitumor activity of low-dose oral cyclophosphamide in patients are not known. Even though the addition of a PARP inhibitor did not improve the response rate, this trial establishes the activity of low-dose cyclophosphamide, an oral, well-tolerated treatment, in patients with HGSOC, primary peritoneal and fallopian tube cancers, and *BRCA*-mutant ovarian cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acknowledgments

The authors thank Drs. Andrea Regier Voth and Yvonne Evrard (Leidos Biomedical Research, Inc.) for editorial assistance in the preparation of this article.

Grant Support

This project has been funded in part with federal funds from the NCI, NIH, under contract numbers HHSN261200800001E and N01-CM-2011-00032, N01-CM-2011-00038, N01-CM-2011-00071, N01-CM-2011-00099, and N01-CM-2011-00100, and by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

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Received October 3, 2014; revised January 7, 2015; accepted January 7, 2015; published OnlineFirst January 14, 2015.

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Published OnlineFirst January 14, 2015; DOI: 10.1158/1078-0432.CCR-14-2565

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Published OnlineFirst January 14, 2015; DOI: 10.1158/1078-0432.CCR-14-2565

Clinical Cancer Research

Randomized Trial of Oral Cyclophosphamide and Veliparib in High-Grade Serous Ovarian, Primary Peritoneal, or Fallopian Tube Cancers, or *BRCA*-Mutant Ovarian Cancer

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Clin Cancer Res 2015;21:1574-1582. Published OnlineFirst January 14, 2015.