Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study

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ABSTRACT

Purpose

Data suggest that DNA damage by poly (ADP-ribose) polymerase inhibition and/or reduced vascular endothelial growth factor signaling by vascular endothelial growth factor receptor inhibition may complement antitumor activity of immune checkpoint blockade. We hypothesize the programmed death-ligand 1 (PD-L1) inhibitor, durvalumab, olaparib, or cediranib combinations are tolerable and active in recurrent women's cancers.

Patients and Methods

This phase I study tested durvalumab doublets in parallel 3 + 3 dose escalations. Durvalumab was administered at 10 mg/kg every 2 weeks or 1,500 mg every 4 weeks with either olaparib tablets twice daily or cediranib on two schedules. The primary end point was the recommended phase II dose (RP2D). Response rate and pharmacokinetic analysis were secondary end points.

Results

Between June 2015 and May 2016, 26 women were enrolled. The RP2D was durvalumab 1,500 mg every 4 weeks with olaparib 300 mg twice a day, or cediranib 20 mg, 5 days on/2 days off. No dose-limiting toxicity was recorded with durvalumab plus olaparib. The cediranib intermittent schedule (n = 6) was examined because of recurrent grade 2 and non-dose-limiting toxicity grade 3 and 4 adverse events (AEs) on the daily schedule (n = 8). Treatment-emergent AEs included hypertension (two of eight), diarrhea (two of eight), pulmonary embolism (two of eight), pulmonary hypertension (one of eight), and lymphopenia (one of eight). Durvalumab plus intermittent cediranib grade 3 and 4 AEs were hypertension (one of six) and fatigue (one of six). Exposure to durvalumab increased cediranib area under the curve and maximum plasma concentration on the daily, but not intermittent, schedules. Two partial responses (≥ 15 months and ≥ 11 months) and eight stable diseases ≥ 4 months (median, 8 months [4 to 14.5 months]) were seen in patients who received durvalumab plus olaparib, yielding an 83% disease control rate. Six partial responses (≥ 5 to ≥ 8 months) and three stable diseases ≥ 4 months (4 to ≥ 8 months) were seen in 12 evaluable patients who received durvalumab plus cediranib, for a 50% response rate and a 75% disease control rate. Response to therapy was independent of PD-L1 expression.

Conclusion

To our knowledge, this is the first reported anti-PD-L1 plus olaparib or cediranib combination therapy. The RP2Ds of durvalumab plus olaparib and durvalumab plus intermittent cediranib are tolerable and active. Phase II studies with biomarker evaluation are ongoing.

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ASSOCIATED CONTENT

Appendix
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INTRODUCTION

Immune checkpoint inhibition, such as programmed death (PD)-1 and PD-ligand 1 (PD-L1)

pathway blockade, has led to important clinical advances in the treatment of solid tumors.¹ One of the major challenges of this approach is the limited single-agent activity in many cancers, leaving opportunity to test combination

strategies.¹ Active therapeutic targets in recurrent women's cancers include the DNA damage repair and vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathways.²

Preclinical studies showed DNA damage promotes neoantigen expression, and DNA-damaging agents result in systemic antitumor responses.³ Olaparib is an oral poly (ADP-ribose) polymerase-inhibitor (PARPi) that has significant clinical activity in *BRCA1* and *BRCA2* (*BRCA*) mutation-associated ovarian carcinoma; it also has activity in subsets of sporadic ovarian carcinoma and *BRCA*-mutated breast or prostate carcinoma.⁴ It is possible that increased DNA damage by PARPi would yield greater mutational burden and expand neoantigen expression, leading to greater immune recognition of the tumor. PARPi is also associated with immunomodulation. The PARPi talazoparib increases the number of peritoneal CD8⁺ T cells and natural killer cells and increases production of interferon (IFN)- γ and tumor necrosis factor- α in a *BRCA1*-mutated ovarian cancer xenograft model.⁵ Hence, addition of PARPi to immune checkpoint blockade could complement the clinical benefit of immune checkpoint inhibition.

Angiogenesis inhibitors also are active in gynecologic cancers, with improved progression-free survival in both front-line and recurrent settings seen with the oral VEGFR1-3 tyrosine kinase inhibitor (TKI) cediranib² and the VEGF ligand-binding antibody bevacizumab.⁶ Angiogenesis pathways interact with both DNA repair mechanisms and immune activity. Tumor hypoxia induces downregulation of genes involved in DNA repair, such as *RAD51* and *BRCA1*, leading to further DNA damage, genomic instability, and cell death.⁷ In addition, PD-L1 expression is upregulated under hypoxic conditions in a panel of mouse and human cancer cell lines, through a hypoxia-inducible factor-dependent mechanism.⁸ VEGF suppresses lymphocyte trafficking across endothelia into neoplastic deposits and sites of inflammation to promote vessel growth.⁹ VEGF also reduces the antitumor immune response, including the inhibition of T cell responses and increase of regulatory T cell proliferation.¹⁰ These results suggest that VEGF/VEGFR inhibition may promote an antitumor immune response. Furthermore, recent data showed olaparib and cediranib together are clinically superior to olaparib alone in recurrent platinum-sensitive ovarian cancer.¹¹

High PD-L1 expression in human ovarian cancer is shown to correlate with a poor prognosis, and PD-L1 expression has been shown to be inversely related to intratumoral CD8⁺ T cells.¹² Recent phase I and II studies demonstrate limited monotherapy activity of PD-1/PD-L1 pathway inhibition in recurrent ovarian cancer, yielding 11% to 17% response rates,¹³ with a few durable complete responses in a subset of heavily pretreated patients.

Therefore, we hypothesized that increased DNA damage by PARPi and/or reduced VEGF signaling by the VEGFR inhibitor may complement the antitumor activity of immune checkpoint inhibition in recurrent women's cancers.

Durvalumab is a human immunoglobulin G1 κ monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 (B7.1).¹⁴ Its adverse effects include immune-related adverse events that are typically transient but can occasionally be severe.¹⁴ Because of potential overlapping toxicities such as diarrhea, we separately examined the recommended phase II dose (RP2D) and safety of the two immune checkpoint inhibitor combinations. We now report the phase I study results of RP2D, pharmacokinetics (PK), and antitumor activity of durvalumab plus olaparib and durvalumab plus cediranib.

PATIENTS AND METHODS

Study Design and Patients

Eligible patients had recurrent or metastatic (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) measurable solid malignancies without prior immune checkpoint inhibitor therapy, controlled hypertension with no more than three antihypertensives, and good end-organ function (Appendix, online only); germline *BRCA* mutation status was requested at entry. All patients provided written informed consent before enrollment. The trial was approved by the institutional review board of the Center for Cancer Research, National Cancer Institute (ClinicalTrials.gov identifier: NCT02484404).

Eligible patients received durvalumab plus olaparib or durvalumab plus cediranib in a 3 + 3 dose-escalation format as listed in Table 1. Cohorts enrolled patients simultaneously. Patients were evaluated for toxicity per Common Terminology Criteria for Adverse Events v4. Clinical response was assessed every two cycles by imaging using RECIST v1.1 criteria. Study treatment was discontinued for progression of disease, intercurrent illness, adverse events not recovering to $\leq$ grade 1 within 14 days, or patient withdrawal of consent.

Definitions of Dose-Limiting Toxicity and Maximum Tolerated Dose

The primary end point of this phase I study was to determine RP2Ds of durvalumab plus olaparib and durvalumab plus cediranib combinations, defined by the maximum tolerated dose (MTD) or the highest protocol-defined dose in the absence of dose-limiting toxicity (DLT). DLT was defined as grade 3 or 4 nonhematologic and grade 4 hematologic adverse events (AEs) related to study medications occurring during the first cycle (28 days). Exceptions are described in the Appendix. The MTD was defined as the highest dose level at which one or fewer of six patients experienced a DLT. If the observed AE was specifically attributed to only one of the drugs, that drug was held while the patient continued to receive

Table 1. Dose Levels

Dose Level	Durvalumab Plus Olaparib			Durvalumab Plus Cediranib		
	Olaparib Tablets	Durvalumab (MEDI4736), IV	No.	Cediranib Tablets	Durvalumab (MEDI4736), IV	No.*
DL1	200 mg twice daily	10 mg/kg every 2 weeks	3	20 mg once daily	10 mg/kg every 2 weeks	4
DL2	300 mg twice daily	10 mg/kg every 2 weeks	3	30 mg once daily	10 mg/kg every 2 weeks	4
DL3	300 mg twice daily	1,500 mg every 4 weeks	6	20 mg (5 days on/2 days off)	1,500 mg every 4 weeks	6

Abbreviations: DL, dose level; IV, intravenously.

*One patient who received DL1 withdrew consent during cycle one; one patient who received DL2 took cediranib 20 mg instead of 30 mg for a week during cycle one; one patient who received DL3 developed grade 4 hypertension, thus came off treatment during cycle one.

the drug not associated with the observed AE. Treatment-related serious AEs occurring within 90 days after the last dose of study drugs were reported.

Pharmacokinetic Studies

Plasma samples for olaparib and cediranib PK analysis were collected before drug initiation and in the presence of durvalumab (cycle one, day 15 or cycle two, day 1). Samples were stored at -80°C until measurement using separate validated assays with a lower limit of quantitation of 0.5 ng/mL for both olaparib¹⁵ and cediranib (Appendix).

Archival Tissue PD-L1 Expression and BRCA-HR Analysis

Prespecified exploratory end points included tumor PD-L1 expression. PD-L1 labeling of cancer cells and tumor-infiltrating lymphocytes (TILs) were evaluated in available archival tissue samples by immunohistochemistry (clone SP142; Spring Bioscience, Pleasanton, CA) paired with a rabbit IgG1 isotype control.¹⁶ Details are described in the Appendix. Mutations in homologous recombination (HR) DNA repair genes were identified by targeted sequencing of tumor DNA using BROCA-HR¹⁷ (Appendix). Fresh tissue was not obtained in this phase I study.

Pharmacodynamic Studies

We did a post hoc analysis of circulating plasma IFN- γ and interleukin (IL)-6,¹⁸ collected before study treatment and in the presence of durvalumab (cycle one, day 15 or cycle two, day 1; Appendix).

Statistical Analyses

All statistical tests for PK and correlative studies analysis used a two-sided significance level .05, adjusted for multiple comparisons. Paired *t* tests were performed in a parametric manner.

RESULTS

Patient Characteristics

Between June 29, 2015 and May 19, 2016, 26 women were enrolled, with one patient still receiving durvalumab plus olaparib at data cutoff (October 13, 2016), at > 15 months continuous treatment. Table 2 lists baseline patient characteristics. Ovarian carcinoma was the most common tumor type (19 of 26 [73%]).

Dose Optimization and Toxicities

We have identified the RP2Ds as olaparib tablets 300 mg twice daily plus durvalumab 1,500 mg intravenously every 4 weeks, and cediranib 20 mg 5 days on/2 days off with durvalumab 1,500 mg every 4 weeks. No DLT was observed with durvalumab plus olaparib treatment. The most common treatment-emergent AE (TEAE) with durvalumab plus olaparib was hematologic toxicity, which was observed in frequencies greater than reported for single-agent olaparib. In contrast, daily cediranib with durvalumab was not well tolerated, although it did not meet the formal mark of DLT during the first treatment cycle. Daily cediranib was discontinued or dose reduced because of recurrent grade 2 or non-DLT grade 3 or 4 AEs in seven of eight patients; two patients who received dose level one discontinued cediranib because of new pulmonary thromboembolism while enrolled in the study; one patient who received dose level one had the dose reduced during cycle two, with four patients who received dose level two having the dose reduced one level because of recurrent grade 2 abdominal pain, diarrhea,

Table 2. Baseline Characteristics

Characteristic	Durvalumab Plus Olaparib (n = 12)	Durvalumab Plus Cediranib (n = 14)
Age, years, median (range)	66.1 (39.1-70.3)	58.4 (44.4-73.8)
Tumor type		
Ovarian cancer, No. (%)	10 (83)	9 (64)
Platinum-sensitive/platinum-resistant disease	5/5	4/5
High-grade serous/clear cell histology	10/0	7/2
BRCA mutation status*		
Germline/wild type/unknown	0/11/1	2/6/1
Lines of prior therapy		
2-4	5	4
≥ 5	5	5
Prior PARPi	2	4
Prior bevacizumab	6	6
ECOG performance status, 0/1/2	3/6/1	2/12/0
Triple-negative breast cancer, No. (%)	2 (17)	
Lines of prior therapy	2, 7	
ECOG performance status, 0/1/2†	1/1/0	
Cervical cancer, squamous cell histology		2
Lines of prior therapy		1, 4 each
Prior PARPi		0
Prior bevacizumab		1
ECOG performance status, 0/1/2		0/2/0
Uterine cancer		3
Endometrial/leiomyosarcoma		2/1
Lines of prior therapy		1, 2, 3 each
Prior PARPi		0
Prior bevacizumab		0
ECOG performance status, 0/1/2		1/2/0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PARPi, poly (ADP-ribose) polymerase inhibition.

*All patients with triple-negative breast cancer were *BRCA* wild type. One patient with triple-negative breast cancer and one patient with ovarian cancer who received durvalumab plus olaparib had somatic *BRCA* mutation by commercial testing, but her germline *BRCA* mutation testing was negative.

†0, 1, 2 for 3 patients/6 patients/1 patient for durvalumab plus olaparib, and 2 patients/12 patients/0 patients for durvalumab plus cediranib.

and fatigue during later cycles (cycles two, three, and five). Two patients were removed from treatment because of TEAE consisting of grade 3 colitis (cycle six) and grade 3 pulmonary hypertension (cycle five). Patients were treated with systemic corticosteroids with no symptom improvement. The patient with pulmonary hypertension also had a thromboembolism and expired approximately 1 month after discontinuation of treatment; autopsy findings revealed disease progression, including pericardial effusion and infiltration of lung, thyroid, lymph nodes, and other organs. A protocol amendment added a new dose level with cediranib 20 mg 5 days on/2 days off. One patient on the intermittent schedule had DLT of grade 4 hypertension on cycle one, and five other patients tolerated the treatment across all administered cycles. All patients had at least one any-grade TEAE, as summarized in Table 3.

Clinical Activity

The objective response rate of durvalumab plus olaparib was 17% (two of 12). However, a majority of patients had some benefit shown by the disease control rate (complete response plus partial response [PR] plus stable disease [SD] ≥ 4 months) of 83% (10 of 12). All but one patient had negative comprehensive germline

Table 3. Durvalumab Plus Olaparib and Durvalumab Plus Cediranib Treatment-Related Adverse Events by Maximum Grade per Patient

Treatment-Related Adverse Events	Durvalumab Plus Olaparib (n = 12)				Durvalumab Plus Once-Daily Cediranib (n = 8)				Durvalumab Plus Intermittent Cediranib (n = 6)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Lymphopenia	0	6	3	0	2	2	1	1	0	0	0	0
Anemia*	2	2	1	0	1	2	2	0	0	0	0	0
Thrombocytopenia	3	0	0	0	6	0	0	0	1	0	0	0
Neutropenia	1	0	0	0	0	0	0	0	0	0	0	0
Nausea	4	3	0	0	0	1	1	0	0	0	0	0
Abdominal pain	4	1	0	0	1	2	0	0	0	0	0	0
Diarrhea	2	2	0	0	2	2	3	0	3	0	0	0
GERD	4	0	0	0	0	0	0	0	0	0	0	0
Anorexia	3	0	0	0	1	1	0	0	0	0	0	0
Vomiting	2	0	0	0	1	1	0	0	1	0	0	0
Constipation	1	0	0	0	0	0	0	0	0	0	0	0
Oral mucositis	1	0	0	0	3	2	0	0	0	0	0	0
Dysgeusia	1	0	0	0	0	0	0	0	0	0	0	0
Colitis	0	0	0	0	0	0	1	0	0	0	0	0
Hypothyroidism	0	1	0	0	0	2	0	0	0	0	0	0
Hyperthyroidism	0	0	0	0	2	0	0	0	0	1	0	0
Blood creatinine increased	3	0	0	0	0	0	0	0	0	0	0	0
Alkaline phosphatase increased	1	0	0	0	2	0	0	0	0	0	0	0
AST increased	0	0	0	0	2	0	0	0	1	0	0	0
ALT increased	0	0	0	0	0	0	0	0	1	0	0	0
Fatigue	7	2	0	0	3	2	1	0	2	1	1	0
Headache	4	0	0	0	1	1	1	0	0	0	0	0
Skin rash	2	0	0	0	3	0	0	0	1	0	0	0
Pruritus	2	0	0	0	0	0	0	0	1	0	0	0
Hoarseness	1	0	0	0	0	0	0	0	1	0	0	0
Weight loss	0	0	0	0	1	2	0	0	0	0	0	0
Hypertension	0	0	0	0	0	4	3	0	0	4	0	1
Pulmonary thromboembolism†	0	0	0	0	0	0	1	1	0	0	0	0
Dyspnea on exertion	0	0	0	0	1	1	0	0	1	0	0	0
Pulmonary hypertension†	0	0	0	0	0	0	1	0	0	0	0	0

NOTE. Data show number. A patient could be counted under more than one preferred term. No one who received durvalumab plus olaparib had dose reduction. One patient who received DL1 of durvalumab plus daily cediranib withdrew her consent on cycle one, day 15 and did not report any adverse events. One patient who received durvalumab plus daily cediranib DL1 had dose reduction to daily cediranib 15 mg on cycle two; all four patients who received durvalumab plus daily cediranib DL2 had dose reduction to daily cediranib 20 mg due to recurrent grade 2 abdominal pain, diarrhea, fatigue on cycle two (two patients), cycle three (one patient), and cycle five (one patient).

Abbreviations: DL, dose level; GERD, gastroesophageal reflux disease.

*Two patients who received durvalumab plus daily cediranib received packed RBC transfusion on cycle one (DL1) and cycle five (DL2).

†Daily cediranib was discontinued in two patients receiving DL1 because of pulmonary thromboembolism on cycle three and cycle five. One with pulmonary thromboembolism developed pulmonary hypertension during cycle five. One patient discontinued daily cediranib and durvalumab because of grade 3 colitis during cycle six.

BRCA mutation testing; that patient with unknown germline BRCA mutation status had 3 months of SD. Twelve of 14 patients on durvalumab plus cediranib were assessed for tumor response; two were not evaluable because of drug toxicity or withdrawal of consent during cycle one, without demonstrated progression. Six of 12 patients attained a PR (≥ 5 to ≥ 8 months, 50% ORR); three of those received dose level three, suggesting response was not attenuated with the intermittent cediranib schedule. Changes from baseline in tumor size and duration of response in the combined dose cohorts are shown in Figure 1. CA125 changes from baseline in women with ovarian cancer are shown in Appendix Figure A1 (online only); by protocol, CA125 changes were not used for clinical decisions.

PK Studies

The PK profiles of olaparib and cediranib are shown in Figure 2. Dose-normalized olaparib area under the curve (AUC; adjusted for first dose and steady state) increased with durvalumab

exposure, although the mean values (unpaired analysis) were not statistically different ($P = .09$; Fig 2A). There were no significant differences in any PK parameters for olaparib alone before durvalumab versus olaparib after durvalumab (Appendix Fig A2, online only), and overall results were similar to comparable olaparib tablet PK.¹⁹ First-dose cediranib PK was consistent with literature²⁰; however, cediranib dose-normalized AUC (AUC/D) and maximum plasma concentration (C_{max}) were increased by exposure to durvalumab only when cediranib was administered daily (Figs 2B and 2C). Greater AUC/D was observed in the two patients who developed pulmonary hypertension ($n = 1$) and colitis ($n = 1$). The patient with pulmonary hypertension had marked increase in C_{max}/D (ng/mL/mg) and AUC for the dosing interval, 12 hr for olaparib, 24 hr for cediranib (AUC τ /D; hr*ng/mL/mg) from 3.81 to 14.8 and 38.6 to 106, respectively. The patient who developed colitis also had increase in C_{max}/D and AUC τ /D of 1.79 to 5.99 and 33 to 103, respectively. A possible cause for this increased exposure was a decreased clearance at steady state ($P = .010$; Fig 2D). The intermittent cediranib schedule was associated with sufficient washout to avoid significant PK changes

Fig 1. (A) Duration in the study, and (B, C) best response. Color code defines dose level of treatment with arbitrary patient number assignment. Blue, gold, and gray horizontal bars represent dose levels (DL) 1 to 3, respectively. Patients are denoted as follows: patients with ovarian cancer (gold squares), and two with triple-negative breast cancer in durvalumab plus olaparib (D + O) arm and two cervical and three endometrial cancers in durvalumab plus cediranib (D + C) arm are unmarked. The blue dot indicates patients with partial response. The red arrows indicate those who received drug at data lock. The gray diamond indicates patients who received poly (ADP-ribose) polymerase inhibitor (PARPi) before study enrollment. Homologous recombination deficiency (HRD) status is marked as a triangle (red, RAD51C methylation; blue, BRCA1 methylation; pink, BRCA2 somatic mutation; gold, BRCA1 somatic mutation). One patient receiving D + O had clinical progression before the first restaging scans. One of 12 evaluable patients receiving D + C had clinical progression before the first restaging scans. R, platinum-resistant recurrent ovarian cancer; S, platinum-sensitive recurrent ovarian cancer.

for cediranib in the presence of durvalumab, as evidenced by constant plasma exposure, and clearance (Figs 2E and 2F; Appendix Fig A2).

Archival Tissue TIL Infiltration and PD-L1 Expression

An exploratory analysis of the relationship of TIL infiltration and PD-L1 membrane labeling with clinical activity was performed on 21 evaluable patients/samples (Appendix Tables A1 and A2, online only). All evaluable tumors displayed some degree of TILs and PD-L1-positive TILs. Tumors with more dense TIL infiltrate contained higher numbers of PD-L1-positive TILs ($P = .009$). There was no difference in the distribution of TILs, the degree of PD-L1-positive TILs, or carcinoma cell PD-L1 labeling between the two treatment arms. There was no statistical association between degree of TILs, presence of PD-L1-positive TILs, and PD-L1 expression status of the carcinoma and response to therapy in either treatment arm. However, a trend toward association of

response with degree of PD-L1-positive TIL was observed. A brisk (3+) PD-L1-positive TIL infiltrate was seen in the primary carcinomas of the three patients who attained a PR, compared with 33% of primary tumors in patients with best response of SD or PD ($n = 4$; $P = .077$). The three patient carcinomas with 3+ TIL infiltrate in the primary tumor also had a longer duration of response compared with patients with tumors having focal-moderate TILs ($n = 12$; median, 14.5 v 6.8 months; $P = .02$). Patients with PD-L1-positive and PD-L1-negative carcinoma cell expression (Fig 3) were equally likely to respond to therapy.

Homologous Recombination Deficiency Phenotype by BROCA-HR

Post hoc exploratory analysis of the BROCA-HR panel was performed to correlate a potential homologous recombination deficiency (HRD) phenotype (Appendix) with clinical response to

Fig 1. (Continued).

the durvalumab plus olaparib (Appendix Table A3, online only). Somatic *BRCA* mutations in two patients with SD previously documented by commercial testing were confirmed by BROCA-HR. There was no clear association between clinical response and HRD phenotype.

Pharmacodynamic Studies

We also assessed the changes of circulating plasma of IFN- γ and IL-6 before and after combination therapies. The median values of circulating plasma of IFN- γ and IL-6 were not statistically different (Appendix Fig A3, online only).

DISCUSSION

To our knowledge, this is the first reported combination therapy of immune checkpoint blockade plus olaparib or cediranib. This study established the RP2Ds of both durvalumab combinations and demonstrated preliminary evidence of durable activity of both combinations in heavily pretreated patients. The majority of AEs, primarily hematologic toxicities for the olaparib combination, were manageable with supportive care, and no new AEs were

noted. Surprisingly, we found more severe cardiovascular AEs with the daily cediranib combination than expected. Our PK results showed that durvalumab exposure increased cediranib exposure and peak concentration, which was mitigated by washout in the intermittent schedule. We observed that this intermittent cediranib schedule resulted in improved tolerability and maintained clinical benefit observed in the daily schedule.

There are limited data on antitumor activity and safety of PD-1/PD-L1 blockade combinations. PARPi monotherapy has limited activity in cancers without *BRCA* mutations, and response to PARPi in patients with ovarian cancer has been associated with platinum sensitivity.^{2,11} Three of four women with *BRCA* wild-type platinum-resistant ovarian carcinoma had durable responses of ≥ 9 months to durvalumab plus olaparib (Appendix Table A3). No new HR DNA repair mutations or *BRCA1* promoter methylation was found to explain the responses. One tumor had *RAD51C* promoter methylation, which has recently been associated with response to the PARPi rucaparib.¹⁷ None of the women receiving durvalumab plus olaparib ≥ 9 months had germline or somatic mutations in *BRCA* or other HR genes. This study is currently being expanded to a phase II study for patients with recurrent ovarian or triple-negative breast cancer. Further investigation on the role of mutational burden and associated neoantigen

Fig 2. Pharmacokinetic (PK) effects of durvalumab on olaparib or cediranib. (A) PK effects of durvalumab with olaparib. There was a significant ($P = .004$) matched-pairs difference (Wilcoxon matched-pairs signed rank test) in dose-normalized area under the curve ($\text{AUC}_{\text{inf}}/\text{D}$; nine of 10 patients had increasing exposure), consistent with prior multiple-dose olaparib tablet monotherapy (ratio of approximately 1.5 and reflecting time-dependent cytochrome P450 3A4 [CYP3A4] inhibition), although the mean values (unpaired analysis from Mann-Whitney test, $P = .089$) were not statistically different, suggesting that durvalumab does not affect the PK of olaparib. (B) Exposure to durvalumab increases cediranib AUC and (C) maximum plasma concentration (C_{max}) with the daily cediranib schedule, because of (D) decreased cediranib clearance. Two of eight patients had no samples after durvalumab for PK analysis. Seven of eight patients before durvalumab and five of six patients after durvalumab had calculable elimination rates for AUC calculation. There did seem to be greater $\text{AUC}_{\text{inf}}/\text{D}$ in two patients who developed pulmonary hypertension (one; gold open square) and colitis (one; gold open circle). (E, F) Exposure to durvalumab does not increase cediranib AUC and C_{max} with intermittent cediranib schedule. The cediranib schedule of 5 days on, 2 days off provided sufficient washout time to avoid measurable cediranib PK changes in the presence of durvalumab. AUC_{inf} , area under the plasma concentration versus time curve from time zero to infinity; CL/F , apparent oral total systemic clearance (first dose); $\text{CL}_{\text{ss}}/\text{F}$, apparent oral total systemic clearance at steady state.

expression induced by PARPi will be examined.²¹ Another study with durvalumab plus olaparib, using our defined RP2D, is now ongoing in women with platinum-sensitive recurrent ovarian carcinoma associated with germline *BRCA* mutation ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02734004) identifier: NCT02734004). The optimal target population of PARPi plus immune checkpoint blockade is still under investigation. Randomized phase II trials will be needed to assess differential activity of the combinations against single agent.

Our phase I study findings demonstrated an interesting activity with durvalumab plus cediranib combination compared with historical studies of either cediranib (17%)²² or PD-1/PD-L1 pathway inhibition alone (11% to 17%) in the treatment of ovarian cancer.¹³ This could be due to higher-than-expected exposure to cediranib, although no dose-response relationship has been shown for cediranib in women's cancers. We observed

duration, continued benefit (> 4 months) beyond the cessation of anti-PD-L1 therapy in our patient with cervical cancer who had grade 3 colitis, similar to reports with other immune checkpoint inhibitors.²³ Nivolumab in combination with the VEGFR TKI sunitinib or pazopanib yielded a high response rate in metastatic renal cell cancer, 52% and 45%, respectively.²⁴ Both nivolumab combinations were associated with significant grade 3 and 4 AEs ($\geq 70\%$), mostly hepatic and renal toxicities,²⁴ which led to closure of the nivolumab/pazopanib arm of the study.²⁴ Bevacizumab and pembrolizumab seem more tolerable in metastatic renal cell cancer than PD-1/PD-L1 blockade and VEGFR TKI combinations, with no serious AEs or unexpected toxicities observed.²⁵ In this study, daily cediranib was discontinued or dose reduced because of recurrent grade 2, or grade 3 or 4 AEs in seven of eight patients. We observed a similar pattern of AEs with an intermittent schedule,

Fig 3. Carcinoma cell PD-L1 labeling is seen in responders and nonresponders. Patient 012 had a partial response ≥ 15 months. Her high-grade serous ovarian cancer (arrow) contained (A) 3+ tumor-infiltrating lymphocytes (TILs; stars; hematoxylin and eosin, $\times 200$), with (B) both TIL (stars) and carcinoma cell (arrow) PD-L1 labeling (PD-L1, $\times 200$). Patient 002 had progressive disease while in the trial. (C) Her primary high-grade serous ovarian cancer (arrow) contains minimal TILs (hematoxylin and eosin, $\times 200$), but (D) exhibits carcinoma cell (arrow) PD-L1 positivity (PD-L1, $\times 200$).

but it was less severe, and none had dose reduction. Moreover, the patients did not lose clinical benefit with intermittent cediranib. Building on these results, we have initiated a safety and early activity evaluation of the three-drug combination (durvalumab plus olaparib plus intermittent cediranib).

We calculated a nearly 40% shorter cediranib half-life (single agent) compared with reported values (12 to 35 hours),² likely due to insufficient terminal sampling (up to 12 hours post dose). Yet, the presence of durvalumab seemed to significantly slow cediranib clearance, suggesting an interaction. We chose to evaluate this because of the novelty of our combination and because there is no known literature for monoclonal antibodies modulating the PK of VEGFR TKIs. Our observation of an interaction between durvalumab and daily cediranib is likely influenced by several factors. The measured decrease in cediranib clearance may be sufficient to explain the effects, although the reason for the decrease in clearance remains a question.² Furthermore, despite cytochrome P450 enzyme having a minor role in the metabolism of cediranib,² the decreased cediranib clearance could be due in part to interactions of cytokines produced by activated T cells with drug transporters or P450 enzyme levels, indirectly affecting exposure to small TKIs.²⁶ Our scheduling for cytokine measurements was not planned to address this question, and, as such, our inability to capture a change in IL-6 concentration with the combination therapy does not negate this hypothesis. The lack of similar effects on olaparib PK²⁷ suggests that this is more likely a complex interaction than strictly a simple competition for clearance. The 2-day interruption in cediranib dosing was sufficient to prevent cediranib accumulation in the presence of durvalumab and obviated the toxicity, apparently without loss of benefit.

A challenge remains to identify and validate effective predictive biomarkers. It has been long known that the presence of TILs is associated with a better prognosis in ovarian carcinoma.¹³ Our data showed all patients attaining a PR had high number of PD-L1–positive TILs in their archival primary tumors. The impact of TILs as a predictive biomarker for immunotherapy has not been established in women's cancers. We found evidence of antitumor activity with both durvalumab combinations, irrespective of carcinoma cell PD-L1 status. Our preliminary findings suggest that the degree of TIL infiltrate and the degree of PD-L1–positive TILs may correlate more closely with response and duration of response to durvalumab combinations than the PD-L1 status of the tumor cells themselves. Similar to our findings, an earlier trial of durvalumab plus tremelimumab, an inhibitor of cytotoxic T-lymphocyte-associated protein 4 (CTLA 4), in advanced non–small-cell lung carcinoma, found no dichotomy of responses in patients with either PD-L1–positive or PD-L1–negative carcinomas.²⁸ In contrast, in a subsequent trial evaluating single-agent durvalumab in patients with advanced urothelial carcinoma, PD-L1 labeling in either $\geq 25\%$ carcinoma cells or $\geq 25\%$ immune cells was associated with improved response to therapy.¹⁴ A different pattern has been observed in melanoma trials, wherein patients with PD-L1–negative tumors had a greater survival benefit with the combination of nivolumab plus ipilimumab (PD-1 inhibitor plus CTLA-4 inhibitor), where benefit was seen for nivolumab monotherapy for patients with PD-L1–positive tumors.²⁹ These observations suggest that different biomarkers may be necessary in monotherapy versus combination immunotherapies. Our correlative findings should be interpreted with caution as hypothesis generating, given the use of small number of archival tissue samples and no significant correlation with clinical outcome.

In conclusion, we demonstrated durvalumab plus olaparib and durvalumab plus intermittent cediranib are tolerable and clinically active combinations in women's cancers. This may be irrespective of carcinoma cell PD-L1 labeling. Our PK data suggest an interaction that led to an intermittent schedule of cediranib administration given with durvalumab. The preliminary activity findings warrant the ongoing single-arm phase II expansions now open to accrual.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study

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Appendix

Methods

This open-label phase I dose-escalation study examined dose optimization of the two independent durvalumab combinations: durvalumab plus olaparib and durvalumab plus cediranib. Eligible patients were ≥ 18 years of age and had confirmed advanced or recurrent solid tumor with evaluable disease on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Biomarker-only disease was not considered evaluable. Patients did not respond to or relapsed after or were not eligible for standard treatment. Patients had to be immunotherapy-naïve and may have received any number of other systemic therapies, including prior poly (ADP-ribose) polymerase inhibitors (PARPi), and/or anti-angiogenesis therapy. However, patients who received both olaparib and cediranib, either in combination or sequentially, were not eligible. Other inclusion criteria included an Eastern Cooperative Oncology Group performance status 0 to 2, life expectancy ≥ 12 weeks, and adequate organ and marrow function, defined as hemoglobin ≥ 10 g/dL or hemoglobin 9 to 9.9 g/dL on two readings within 2 weeks before enrollment, in the absence of packed RBC transfusion within 28 days before study treatment, absolute neutrophil count $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN), ALT and AST $\leq 2.5 \times$ ULN, and serum creatinine $\leq 1.5 \times$ ULN or measured creatinine clearance ≥ 50 mL/min/1.73 m², and spot urine protein/creatinine ratio ≤ 1 . Adequately controlled blood pressure (systolic blood pressure < 140 mm Hg and diastolic blood pressure < 80 mm Hg) on a maximum of three antihypertensive medications was required. Female patients must have been of nonreproductive potential (ie, postmenopausal by history, ≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause, history of hysterectomy, history of bilateral tubal ligation, or history of bilateral oophorectomy) or must have had serum pregnancy test on study entry and agreed to use contraception or abstinence for female patients with reproductive potential. Study exclusion criteria included concurrent anticancer therapy, any investigational anticancer therapy, or live attenuated vaccine ≤ 4 weeks before first doses of study drugs (6 weeks for nitrosoureas or mitomycin); CNS metastases, leptomeningeal disease or cord compression ≤ 1 year before enrollment; concomitant or prior invasive malignancies ≤ 5 years before enrollment; severe prior immune-related adverse events (AEs); persistent AEs from prior anticancer therapy $\geq$ grade 2 per Common Terminology Criteria for Adverse Events Version 4.03; baseline features suggestive of myelodysplastic syndrome or acute myelogenous leukemia on peripheral blood smear or bone marrow biopsy; increased risk of cardiac toxicities ≤ 1 year before durvalumab plus olaparib and ≤ 2 years before durvalumab plus cediranib enrollment, such as prior myocardial infarction, clinically significant pericardial effusion, myocarditis, prior cardiac arrhythmia including atrial fibrillation and atrial flutter, or requiring concurrent use of drugs or biologics with proarrhythmic potential or New York Heart Association class II or greater heart failure; current or prior use (≤ 28 days before first doses of study drugs) of immunosuppressive medication (except intranasal/inhaled corticosteroids or systemic corticosteroids ≤ 10 mg prednisone equivalent); history of primary immunodeficiency; and HIV or hepatitis B or C. Additional exclusion criteria included signs and/or symptoms of bowel obstruction < 28 days, abdominal fistula or perforation < 6 months, and history of cerebrovascular accident or transient ischemic attack < 1 year before study enrollment.

Dose-limiting toxicity was defined as grade 3 or 4 nonhematologic and grade 4 hematologic AEs related to study medications occurring during the first cycle. The following were exceptions: grade 3 lymphopenia or leukopenia in the absence of grade 3 or higher neutropenia, grade 3 hypertension controlled with antihypertensive therapy, or grade 3 asymptomatic electrolytes imbalance with optimal repletion that downgrades to grade 1 or better within 3 days, grade 3 asymptomatic increase in amylase or lipase that downgrades to grade 1 or better within 7 days after onset of the event, or grade 3 asymptomatic endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.

Study Oversight

The study has been conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council on Harmonization guidelines on Good Clinical Practice, all applicable laws and regulatory requirements, and all conditions required by a regulatory authority and/or institutional review board. The study protocol was reviewed and approved by the institutional review board of the Center for Cancer Research, National Cancer Institute. Written informed consent was obtained from all patients.

Noncompartmental Pharmacokinetic Analysis

Plasma samples for olaparib and cediranib pharmacokinetic (PK) analysis were collected at 0.5, 1, 2, 4, 8, and 12 hours during cycle one, day 1 (in the absence of durvalumab) and during cycle one, day 15 at dose level (DL)1 and 2 (in the presence of durvalumab) or cycle two, day 1 (DL3, in the presence of durvalumab) to assess drug-drug interaction. Samples were stored at -80°C until measurement. PK parameters (concentration, area under the concentration–time curve, clearance, and half-life of olaparib or cediranib in the absence and presence of durvalumab) were calculated using noncompartmental methods (Phoenix WinNonlin v6.4; Certara Pharsight, Cary, NC), expressed as geometric mean $\pm$ standard deviation, and compared in both an unpaired and pairwise manner against the absence or presence of durvalumab to assess drug-drug interactions. The maximum plasma concentration and the time of maximum plasma concentration were recorded as measured values. For cycle one, day 1 kinetics, the area under the concentration–time curve extrapolated to infinity (AUC_{inf}) was calculated using the linear up–log down trapezoidal method via extrapolation of AUC_{last} (AUC to the last quantifiable time point) by dividing C_{last} (the last measurable drug concentration, typically at 10 to 12 hours post first daily dose) by the rate constant of the terminal phase, λ_z . This constant was determined from the slope of the terminal phase of the concentration–time curve using weighted least squares as the estimation procedure. It should be noted that olaparib exhibits a bi-exponential elimination, with the terminal elimination occurring roughly 10 to 12 hours post dose. Because a second daily dose was administered 12 hours after the first, a true terminal elimination rate (λ_z) for olaparib is likely not possible on the basis of the study design. Cediranib is known to have a long half-life, roughly 22 hours;² thus, sampling through 12 hours also may not fully capture the true λ_z . Estimated PK parameters also included the apparent oral volume of distribution during the terminal phase (V_z/F) and the apparent oral systemic clearance ($\text{CL}/\text{F} = \text{dose}/\text{AUC}_{\text{inf}}$). For steady-state kinetics (cycle one, day 15), AUC_{τ} (AUC for the dosing interval; 12 hours for olaparib, 24 hours for cediranib) was calculated. Apparent oral total systemic clearance at steady state ($\text{CL}_{\text{ss}}/\text{F}$) was calculated as $\text{dose}/\text{AUC}_{\tau}$. Comparison of PK and clinical parameters by group was performed using a nonparametric Mann-Whitney test (for unpaired analyses) or a nonparametric Wilcoxon matched-pairs signed rank test (for paired analyses) using GraphPad Prism, v6. A two-sided P value $< .05$ was considered to be significant.

Programmed Death-Ligand 1 Labeling and Tumor-Infiltrating Lymphocytes Analysis

Programmed death-ligand1 (PD-L1) labeling and the presence of tumor-infiltrating lymphocytes (TILs) were assessed using available archival tissue samples. Hematoxylin and eosin–stained slides were evaluated to confirm diagnosis and to assign a qualitative TIL distribution score (0, none; 1, mild/focal, $< 5\%$ tumor area; 2, moderate, 5% to 50% tumor area; 3, brisk, $> 50\%$ tumor area; A.C.M.; Cimino-Mathews A, et al: Hum Pathol 47:52–63, 2016). The presence or absence of peritumoral lymphoid aggregates was recorded as absent, focal (1; rare, isolated lymphoid aggregates), present (2; multiple lymphoid aggregates), and well-developed (3; present with well-developed germinal centers; Cimino-Mathews A, et al: Hum Pathol 47:52–63, 2016). Unstained slides were labeled by immunohistochemistry for PD-L1 (clone SP142; Spring Bioscience, Pleasanton, CA) paired with an isotype-matched mouse IgG1 (H.X. and A.O; Herbst RS, et al: Nature 515:563–567, 2014). PD-L1 labeling of cancer cells and TILs were scored for percentage of positive cells with membranous labeling (A.C.M. and E.T.). At least 100 cells were counted. The cancer cells exhibiting clear membrane PD-L1 expression were scored in 5% increments from 0% to 100%, with $< 5\%$ labeling considered negative.¹⁶ TILs with PD-L1 expression were recorded in 5% increments and scored as none, focal (1+; $< 5\%$), moderate (2+; 5% to 50%), or brisk (3+; 51% to 100%; Cimino-Mathews A, et al: Hum Pathol 47:52–63, 2016).

Post Hoc Analysis of Circulating Plasma Interferon- γ and Interleukin-6

We measured the pretreatment and cycle 1 day 15 or cycle 2 day 1 of circulating plasma interferon- γ and interleukin-6 by a validated V-PLEX assays (Meso-Scale Diagnostics, Rockville, MD),¹⁸ using plasma samples collected for PK analysis. Calibration standards were used for absolute quantification, and reference samples were included to ensure the satisfactory performance of the tests. Test data were generated with Meso-Scale Diagnostics Discovery Workbench, with all reported data within the quantification range.

Post Hoc Analysis of BRCA1 and RAD51 Methylation

BRCA1 and RAD51 methylation were examined as described.⁶ Briefly, bisulfite conversion of 250-ng tumor DNA was achieved using the EZ DNA Methylation-Direct kit (Zymo Research, Irvine, CA). After bisulfite conversion, the samples underwent desulphonation and clean-up. Two microliters of bisulfite-converted DNA was evaluated with methylation-sensitive polymerase chain reaction for BRCA1, as previously described.⁶ Methylation-specific polymerase chain reaction for RAD51C was performed with newly designed primers. Primer sequences for the methylated reaction were 5'-TGTAAGGTTTCGGAGTTTCGTGC-3' (sense)

and 5'-TCGCTAAAACGTACGACGTAACG-3' (antisense) and for the unmethylated reaction 5'-GTGTAAAGTTGTAAGGTTTG-GAGTTTTGTGTG-3' (sense) and 5'-CACACACCCTCACTAAAACATACAACATAACA-3' (antisense). The unmethylated product is 103 nt, and the methylated product is 85 nt.

Homologous Recombination Deficiency Definition¹⁷

Homologous recombination deficiency was defined as *RAD51C* or *BRCA1* promoter hypermethylation or a damaging germline or somatic mutation identified by BROCA-HR sequencing present in > 10% of the neoplastic fraction in one of the following genes: *ATM*, *ATR*, *BARD1*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, *SLX4*, *RBBP8*, and *XRCC2*.

Fig A1. CA125 response. Serial serum CA125 measurements were performed in 18 patients with ovarian cancer (10 who received durvalumab plus olaparib [D + O] and eight who received durvalumab plus cediranib [D + C]). Color code defines dose level of treatment with arbitrary patient number assignment: blue, gold, and gray horizontal bars represent dose levels (DL) 1 to 3, respectively.

Fig A2. Pharmacokinetic parameters. Exposure to durvalumab does not affect olaparib (A) maximum plasma concentration (C_{max}) and (B) clearance. There were no significant differences in any dose-normalized or dose-independent pharmacokinetic parameters for olaparib alone before durvalumab (first dose) versus olaparib after durvalumab (steady state). (C) Exposure to durvalumab does not decrease cediranib clearance with intermittent cediranib schedule. The cediranib intermittent schedule (5 days on/2 days off) demonstrated sufficient washout of cediranib in the presence of durvalumab. CL/F, apparent oral total systemic clearance (first dose); CLss/F, apparent oral total systemic clearance at steady state.

Fig A3. Interferon (IFN)- γ and interleukin (IL)-6. There were no significant differences in IFN- γ and IL-6 between pretreatment and (A, E) post durvalumab plus olaparib (D + O) or (B, F) durvalumab plus cediranib (D + C), irrespective of the schedule of cediranib (once-daily cediranib [C, G] and intermittent cediranib [D, H]). (G) There was no significant increase of IL-6 in two patients who developed pulmonary hypertension (one; gold open square) and colitis (one; gold open circle).

Phase I Study of Durvalumab With Olaparib or Cediranib

Table A1. Pathologic Characteristics and Immune Correlates

Characteristic	All Patients (n = 21)	Durvalumab Plus Cediranib Arm (n = 9)	Durvalumab Plus Olaparib Arm (n = 12)
Primary organ site			
Breast	2 (10)	0	2 (17)
Cervix	1 (5)	1 (11)	0
Ovary/fallopian tube	16 (76)	6 (67)	10 (83)
Uterus	2 (10)	2 (22)	0
Primary tumor histology			
Clear cell adenocarcinoma	1 (5)	1 (11)	0
Endometrioid carcinoma	2 (10)	2 (22)	0
High-grade serous carcinoma	15 (71)	5 (56)	10 (83)
Squamous cell carcinoma	1 (5)	1 (11)	0
Triple-negative breast carcinoma	2 (10)	0	2 (17)
Tumor tissue available for correlative studies			
Primary tumor*	15 (71)	5 (56)	10 (83)
Metastasis at the time of diagnosis	3 (14)	2 (22)	1 (8)
Recurrent tumor	3 (14)	2 (22)	1 (8)
Treatment response			
Progressive disease	2 (10)	1 (11)	1 (8)
Stable disease	12 (57)	3 (33)	9 (75)
Partial response	7 (33)	5 (56)	2 (17)
Carcinoma cell PD-L1 labeling in primary or recurrent tumor	(n = 21 evaluable)	(n = 9 evaluable)	(n = 12 evaluable)
Absent	7 (33)	3 (33)	4 (33)
> 5% carcinoma cell labeling	14 (67)	6 (67)	8 (67)
Primary carcinoma cell PD-L1 labeling	(n = 15 evaluable)	(n = 5 evaluable)	(n = 10 evaluable)
Absent	6 (40)	2 (40)	4 (40)
> 5% carcinoma cell labeling	9 (60)	3 (60)	6 (60)
Primary tumor TIL infiltrate	(n = 15 evaluable)	(n = 5 evaluable)	(n = 10 evaluable)
Mild infiltrate (score 1)	4 (27)	1 (20)	3 (30)
Moderate infiltrate (score 2)	8 (53)	3 (60)	5 (50)
Brisk infiltrate (score 3)	3 (20)†	1 (20)	2 (20)‡
Primary tumor TIL PD-L1 labeling†	(n = 15 evaluable)	(n = 5 evaluable)	(n = 10 evaluable)
Focal PD-L1–positive TIL (score 1+)	3 (20)	0	3 (30)
Moderate PD-L1–positive TIL (score 2+)	5 (33)	1 (20)	4 (40)
Brisk PD-L1–positive TIL (score 3+)	7 (47)	4 (80)	3 (30)

NOTE. Data presented as No. (%). The tumor-associated macrophages (TAM) were diffusely distributed through the tumors in 14 of the 15 patients with HGSOC. Abbreviations: HGSOC, high-grade serous ovarian cancer; PD-L1, programmed death-ligand 1; TIL, tumor-infiltrating lymphocyte.

*Primary archival tissues of all 15 patients were chemotherapy naïve.

†All patients with HGSOC contained tumor-infiltrating macrophages with cytoplasmic PD-L1 positivity.

‡One patient's primary HGSOC tumor (A012), which had brisk TILs, also displayed tertiary lymphoid structures/lymphoid aggregates.

Table A2. Individual Patient Pathologic and Immune Correlates per Treatment Arm

Treatment Arm	Patient Code	Primary Carcinoma Site	Primary Carcinoma Histology	Platinum Sensitivity*	Tissue Available for Correlative Study	Best Response as of October 13, 2016	Response Duration (months) as of October 13, 2016	Degree of TIL Infiltrate	Carcinoma Cell PD-L1 Labeling	TIL PD-L1 Labeling
D + C	A005	Ovary	HGSOC	R	Primary	SD	4	Moderate = 2	Present = 1	Brisk = 3
D + C	A009	Cervix	SQC		Recurrence	PR	5	N/A	Present = 1	N/A
D + C	A011	Ovary	EMCA	S	Primary	SD	6	Brisk = 3	Present = 1	Brisk = 3
D + C	A017	Ovary	HGSOC	S	Metastatic site at first presentation	PR	7	Moderate = 2	Present = 1	Moderate = 2
D + C	A018	Ovary	CCA	S	Recurrence	PR	≥ 8	Mild = 1	Absent = 0	Moderate = 2
D + C	A020	Uterus	HGSOC		Primary	SD	≥ 8	Moderate = 2	Absent = 0	Moderate = 2
D + C	A022	Fallopian tube	HGSOC	S	Primary	PR	≥ 6.5	Mild = 1	Absent = 0	Brisk = 3
D + C	A023	Ovary	HGSOC	R	Metastatic site at first presentation	PD	2	Moderate = 2	Present = 1	Brisk = 3
D + C	A024	Uterus	EMCA		Primary	PR	≥ 5	Moderate = 2	Present = 1	Brisk = 3
D + O	A001	Ovary	HGSOC	R	Primary	SD	9	Mild = 1	Absent = 0	Focal = 1
D + O	A002	Ovary	HGSOC	R	Primary	PD	1	Mild = 1	Present = 1	Focal = 1
D + O	A003	Ovary	HGSOC	S	Primary	SD	≥ 10.5	Moderate = 2	Present = 1	Moderate = 2
D + O	A004	Ovary	HGSOC	R	Primary	SD	9.5	Moderate = 2	Present = 1	Brisk = 3
D + O	A006	Ovary	HGSOC	R	Recurrence	PR	≥ 11	Moderate = 2	Present = 1	Brisk = 3
D + O	A007	Ovary	HGSOC w/foci EMCA	S	Primary	SD	7	Moderate = 2	Absent = 0	Brisk = 3
D + O	A010	Ovary	HGSOC	S	Primary	SD	6	Mild = 1	Present = 1	Focal = 1
D + O	A012	Ovary	HGSOC	S	Primary	PR	≥ 15	Brisk = 3	Present = 1	Brisk = 3
D + O	A014	Ovary	HGSOC	R	Metastatic site at first presentation	SD	3	Brisk = 3	Present = 1	Brisk = 3
D + O	A015	Breast	TNBC		Primary	SD	7	Moderate = 2	Absent = 0	Moderate = 2
D + O	A016	Ovary	HGSOC	S	Primary	SD	4	Moderate = 2	Absent = 0	Moderate = 2
D + O	A021	Breast	TNBC		Primary	SD	14.5	Brisk = 3	Present = 1	Moderate = 2

Abbreviations: C, cediranib; CCA, clear cell adenocarcinoma; D, durvalumab; EMCA, endometrioid carcinoma; HGSOC, high-grade serous ovarian cancer; N/A, not applicable; O, olaparib; PD, progressive disease; PR, partial response; R, platinum-resistant recurrent ovarian cancer; S, platinum-sensitive recurrent ovarian cancer; SD, stable disease; SQC, squamous cell carcinoma; TIL, tumor infiltrating lymphocytes; TNBC, triple-negative breast carcinoma.

*Ovarian cancer only.

Phase I Study of Durvalumab With Olaparib or Cediranib

Table A3. Durvalumab Plus Olaparib Antitumor Activity by BROCA-HR Analysis

Tumor Type	Platinum Sensitivity	Response Duration (months) as of October 13, 2016	Best Response as of October 13, 2016	Mutation in HRR Pathway	BRCA1 Methylation	RAD51C Methylation	HRD Status
Ovarian	Resistant	≥ 11	PR		No	No	No
Ovarian*	Resistant	9.5	SD		No	No	No
Ovarian	Resistant	9	SD		No	Yes	Yes
Ovarian†	Resistant	3	SD		No	No	No
Ovarian	Resistant	1	PD	BRCA2 c.5946delT = 6174delT (0.77vaf), somatic	No	No	Yes
Ovarian	Sensitive	≥ 15	PR		Yes	No	Yes
Ovarian	Sensitive	≥ 10.5	SD		Yes	No	Yes
Ovarian	Sensitive	7	SD	BLM c.1536dupA, subclonal	No	No	No
Ovarian*	Sensitive	6	SD		No	No	No
Ovarian	Sensitive	4	SD	ATM c.5623C >T (p.R1875X) subclonal	No	No	No
TNBC	N/A	14.5	SD		No	No	No
TNBC	N/A	7	SD	BRCA1 c.5545G >T, (p.E1849X), somatic	No	No	Yes

Abbreviations: HRD, homologous recombination deficiency; HRR, homologous recombination repair; N/A, not applicable; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

*Two patients had prior PARP inhibitor (PARPi; veliparib and rucaparib).

†Germline *BRCA* mutation testing was not done; however, tumor testing revealed no germline or somatic *BRCA* mutations. Subclonal: present in < 10% of neoplastic sequences.