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Authors

Liu, Joyce
Gaillard, Stéphanie
Wahner Hendrickson, Andrea
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Niraparib, Dostarlimab, and Bevacizumab as Combination Therapy in Pretreated, Advanced Platinum-Resistant Ovarian Cancer: Findings From Cohort A of the OPAL Phase II Trial

Joyce F. Liu, MD, MPH[1]; Stéphanie Gaillard, MD, PhD[2]; Andrea E. Wahner Hendrickson, MD[3]; Oladapo Yeku, MD, PhD[4]; Elisabeth Diver, MD[5]; Camille Gunderson Jackson, MD[6]; Rebecca Arend, MD[7]; Elena Ratner, MD, MBA[8]; Vivek Samnotra, MD[9]; Divya Gupta, MD[9]; Jon Chung, PhD[9]; Hailei Zhang, PhD[9]; Natalie Compton, MSc[10]; Amanda Baines, BSc[11]; Emeline Bacqué, PharmD[9]; Xiaohong Liu, PhD[9]; Brunella Felicetti, PhD[11]; and Gottfried E. Konecny, MD[12]

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ABSTRACT

PURPOSE To report the results of OPAL (ClinicalTrials.gov identifier: NCT03574779) cohort A, a single-arm substudy of niraparib plus dostarlimab and bevacizumab for the treatment of advanced, platinum-resistant ovarian cancer (PROC).

METHODS Participants with PROC who received 1-2 previous lines of therapy were treated with niraparib (200 or 300 mg once daily), dostarlimab (500 mg once every 3 weeks for four 21-day cycles, followed by 1,000 mg once every 6 weeks), and bevacizumab (15 mg/kg once every 3 weeks). The primary end point was investigator-assessed objective response rate (ORR) per RECIST v1.1. Safety was also assessed. Exploratory biomarker end points included evaluation of changes in the tumor molecular profile and microenvironment using baseline and on-treatment tumor samples.

RESULTS Of 41 enrolled participants (median age, 66.0 years [range, 37-83 years]), 9.8% had tumors that were *BRCA*-mutated, 19.5% were homologous recombination (HR)–deficient, and 17.1% were HR repair (HRR)–mutated. As of the cutoff date, all participants discontinued treatment. The ORR was 17.1% (80% CI, 9.8 to 27.0), including one complete response (2.4%); the disease control rate was 73.2% (80% CI, 62.3 to 82.2). Two participants withdrew before first post-baseline scan because of adverse events (AEs). Grade ≥3 treatment-emergent AEs were reported in 92.7% of participants, with the most common being hypertension (26.8%). Response was not correlated with *BRCA*, HRR, HR deficiency (HRD), or PD-L1 status. Changes suggesting immune activation were observed in on-treatment samples after triplet therapy.

CONCLUSION Results demonstrated modest activity of niraparib, dostarlimab, and bevacizumab in participants with PROC, many of whom had prognostic factors for poor treatment response. Most participants with response were bevacizumab-naïve. No association was found with HRD, *BRCA*, or PD-L1 status. AEs were consistent with previous monotherapy reports, except that hypertension was reported more frequently.

ACCOMPANYING CONTENT

- Data Sharing Statement
- Data Supplement
- Protocol

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INTRODUCTION

Ovarian cancer (OC) is the second leading cause of gynecologic cancer–related deaths globally, with approximately 207,000 deaths in 2020.[1] Most patients with OC present with advanced disease, are treated with primary surgery and platinum-based chemotherapy, and may also receive maintenance therapy with a poly(ADP-ribose) polymerase (PARP) inhibitor, bevacizumab, or both.[2-5] Unfortunately, most patients will experience repeated recurrences of their disease; patients who experience recurrence within 6 months of a platinum-based chemotherapy are considered to have developed platinum-resistant OC (PROC).[6] Treatment options for PROC are limited, and overall survival (OS) estimates range from 1 to 2 years.[6-8]

Maintenance treatment with niraparib, a highly selective PARP 1/2 inhibitor,[9,10] significantly improved progression-free survival (PFS) compared with placebo in patients with advanced platinum-sensitive OC.[11,12] Dostarlimab, an immune

CONTEXT

Key Objective

Effective therapy for platinum-resistant ovarian cancer (PROC) is an unmet medical need. The OPAL-A study (ClinicalTrials.gov identifier: NCT03574779) was conducted to assess the activity of triplet combination therapy with niraparib plus dostarlimab and bevacizumab for the treatment of advanced PROC.

Knowledge Generated

In patients with PROC, triplet therapy with niraparib plus dostarlimab and bevacizumab showed an objective response rate (ORR) of 17.1% (80% CI, 9.8 to 27.0), a disease control rate of 73.2% (80% CI, 62.3 to 82.2), a median progression-free survival of 7.9 months (95% CI, 4.2 to 10.9 months), and a median overall survival of 22.1 months (95% CI, 11.1 to 26.3 months).

Relevance

Triplet combination therapy with niraparib, dostarlimab, and bevacizumab showed only modest activity as measured by ORR in participants with PROC. Further studies of biomarkers for response to triplet therapy in PROC are warranted.

checkpoint inhibitor (ICI) blocking the interaction between PD-1 and PD-L1 or PD-L2,[13] improved PFS and OS in combination with chemotherapy as first-line therapy for primary advanced or recurrent endometrial cancer.[14,15] However, data on the activity of ICIs in OC are currently limited.

Combining PARP inhibition with an ICI and/or an antiangiogenic agent has demonstrated promising antitumor activity.[16-19] In the multicenter, single-arm, TOPACIO/KEYNOTE-162 study, treatment of patients with recurrent PROC with niraparib combined with the ICI pembrolizumab led to an 18% objective response rate (ORR) and a 65% disease control rate (DCR), regardless of *BRCA* status.[19] OPAL (ClinicalTrials.gov identifier: NCT03574779) is an ongoing, open-label, multicohort phase II study designed to evaluate the safety and efficacy of novel niraparib-containing treatment combinations in patients with advanced, relapsed, high-grade OC. Herein, we report results from OPAL Cohort A (OPAL-A), a single-arm substudy designed to evaluate niraparib in combination with dostarlimab and bevacizumab to treat PROC.

METHODS

Study Design

OPAL-A was a single-arm study designed to evaluate the triplet combination of niraparib-dostarlimab-bevacizumab in patients with previously treated, recurrent, advanced PROC (Data Supplement, Fig S1). The study protocol was approved by an independent ethics committee or institutional review board at every participating institution. The study was performed in accordance with the Declaration of Helsinki, within Good Clinical Practice Guidelines defined by the International Conference on Harmonisation, and according to all applicable local, state, and federal laws and regulatory requirements. All participants provided informed written consent before enrollment.

Participants

Eligible participants were 18 years and older with advanced, high-grade, histologically diagnosed recurrent epithelial (serous, endometrioid, mucinous, clear cell, or mixed) ovarian, fallopian tube, or primary peritoneal cancer, or recurrent carcinosarcoma of the ovary, with relapsed disease after one or two previous lines of therapy. Disease progression within 6 months after completing the platinum-based treatment was required immediately before enrollment. Included participants had platinum-resistant but not platinum-refractory disease (defined as disease progression during or within 4 weeks of first platinum-based chemotherapy completion) and were naïve to both PARP inhibitors and anti–PD-1/PD-L1 therapies. Hormonal agents or single-agent bevacizumab were not counted as previous lines of therapy (Supplementary Methods, Data Supplement, Table S1).

Interventions

Participants received dostarlimab 500 mg intravenously every 3 weeks for four cycles (21 days each), followed by dostarlimab 1,000 mg once every 6 weeks, plus bevacizumab 15 mg/kg intravenously once every 3 weeks for up to 15 months, and niraparib 300 mg (or 200 mg if the body weight was <77 kg or the platelet count was <150,000/μL at screening) orally once daily until disease progression, unacceptable toxicity, or study withdrawal.

Study Assessments

The primary end point was investigator-assessed confirmed ORR per RECIST v1.1. Secondary end points included

investigator-assessed PFS, OS, duration of response (DOR), DCR, safety, and tolerability.

Tumor response was assessed using computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis at baseline and every 9 weeks for 1 year and then every 12 weeks (or at any time on suspicion of progression). Adverse events (AEs) were assessed per the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0, and AE toxicities were assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Baseline tumor samples (archival or collected at screening) were assessed for tumor *BRCA* mutation status, homologous recombination repair (HRR) gene mutation status, and HR deficiency (HRD) status (HR-deficient [HRd] defined as tumor *BRCA*-mutated [t*BRCA*m] or HRD score ≥42; HR-proficient [HRp] defined as tumor *BRCA* wild-type [t*BRCA*wt] and HRD score <42) using the Myriad MyChoice HRD Plus assay (Myriad Genetics). Tumor PD-L1 combined positive score was assessed using the DAKO 22C3 immunohistochemistry assay (NeoGenomics, Fort Myers, FL). Outcomes were correlated with tumor biomarker status.

Whole-transcriptome sequencing (WTS) of baseline tumor samples and paired on-treatment tumor samples (collected between cycle 2/day 1 and cycle 3/day 1) was performed using the ImmunoID NeXT assay (Personalis), and gene set enrichment analysis (GSEA) was used to evaluate biologic processes associated with response and disease control (complete response [CR], partial response [PR], or stable disease [SD]). Measured and derived markers by multiplex immunofluorescence using the MultiOmyx platform (NeoGenomics) are listed in the Data Supplement (Table S2).

Statistical Analysis

The efficacy population comprised all participants with measurable disease per RECIST v1.1 at baseline and included participants without a postbaseline assessment. The response-evaluable population included all efficacy population participants with one or more evaluable postbaseline tumor assessments. The safety population comprised all participants who received one or more study treatment doses. Biomarkers were assessed in all participants with at least one follow-up tumor assessment and a tumor sample.

Baseline demographic and disease characteristics were summarized descriptively. Time-to-event analyses were performed using Kaplan-Meier methods. ORR was defined as the proportion of participants who achieved investigator-assessed confirmed CR or PR per RECIST v1.1. PFS was defined as the time from the first study treatment dose to the earliest assessment date of progression per RECIST v1.1 or death. OS was defined as the time from the first study treatment dose to the date of death. DOR was defined as the time from documentation of first response (CR or PR) until the date of first documentation of progressive disease (PD) per RECIST v1.1 or death. DCR was defined as the percentage of participants achieving a best confirmed overall response (CR, PR, or SD). AEs were coded using MedDRA and tabulated by MedDRA system organ class and preferred term. Exploratory biomarker analyses were summarized descriptively. A paired Wilcoxon test compared paired baseline with on-treatment samples in the multiplex immunofluorescence analysis. Safety and efficacy analyses were conducted using SAS version 9.4. Biomarker analyses were conducted using R version 4.3.0.

RESULTS

Baseline Characteristics and Participant Disposition

Among 54 participants screened for OPAL-A, 41 were enrolled (median age, 66.0 years) at 10 sites across the United States between November 15, 2018, and April 1, 2022; 9.8% of participants had t*BRCA*m, 19.5% had HRd tumors, and 68.3% had PD-L1–positive tumors. Over half (56.1%) of participants had two previous lines of therapy, and 43.9% had one previous line of therapy (Table 1). No HRR gene mutations were detected for 75.6% of participants, whereas 17.1% had an HRR gene mutation; HRR gene mutation status was unknown in 7.3% of participants. The median platinum-free interval before study drug initiation was 3.4 months (range, 0-7 months). All 41 participants discontinued the study (Data Supplement, Fig S2). The most common reason for discontinuation was death (n = 25; 61.0%); 20 participants died because of disease progression, and five because of unknown causes. All deaths occurred during the follow-up period.

Efficacy

One participant (2.4%) achieved a confirmed CR, and six (14.6%) had a confirmed PR, corresponding to a 17.1% ORR (80% CI, 9.8 to 27.0). The DCR, which included 23 participants (56.1%) with SD, was 73.2% (80% CI, 62.3 to 82.2; Table 2). In participants with confirmed or unconfirmed responses (n = 11), the median DOR was 11.8 months (range, 3.4-30.8 months). Twenty participants developed one or more new lesions during the study period (see the Data Supplement, Fig S3, for responses by biomarker status). The investigator-assessed median PFS was 7.9 months (95% CI, 4.2 to 10.9 months; Fig 1A), and the median OS was 22.1 months (95% CI, 11.1 to 26.3 months; Fig 1B).

Safety

All 41 participants experienced treatment-emergent AEs (TEAEs), most commonly fatigue, nausea, vomiting, hypertension, and anemia. Thirty-eight participants (92.7%) had grade ≥3 TEAEs, most frequently hypertension, anemia, and fatigue (Table 3). Six participants (14.6%) developed any-grade small intestinal obstructions. Twenty-two (53.7%) participants had treatment-emergent serious AEs (SAEs), including small intestinal obstruction (n = 4; 9.8%); abdominal pain (n = 3; 7.3%); and anemia, hypertension, thrombocytopenia, and vomiting (n = 2 each; 4.9%).

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	OPAL-A (N = 41)
Age, years, median (range)	66 (37-83)
BMI, kg/m^2, median (range)	27 (17-41)
Race, No. (%)	
White	32 (78.0)
Black/African American	2 (4.9)
Asian	1 (2.4)
Unknown/not reported	6 (14.6)
ECOG PS, No. (%)	
0	18 (43.9)
1	22 (53.7)
Unknown	1 (2.4)
Primary tumor site at diagnosis, No. (%)	
Ovarian	30 (73.2)
Primary peritoneal	3 (7.3)
Fallopian tube	8 (19.5)
Cancer stage at first diagnosis, No. (%)	
Stage I to IC	2 (4.9)
Stage II to IIC	2 (4.9)
Stage III to IIIC	27 (65.9)
Stage IV	10 (24.4)
Previous lines of therapy, No. (%)	
1	18 (43.9)
2	23 (56.1)
Duration of last platinum-based therapy, months, median (range)	4.5 (1-12)
Reason for discontinuation of last platinum-based therapy, No. (%)	
Toxicity	1 (2.4)
Completed the planned course	30 (73.2)
PD	8 (19.5)
Other	2 (4.9)
Best response during last platinum-based therapy, No. (%)	
CR	14 (34.1)
PR	7 (17.1)
SD	3 (7.3)
PD	7 (17.1)
NE	0 (0)
Unknown	10 (24.4)
Platinum-free interval, months, median (range)	3.4 (0-7)
Previous bevacizumab, No. (%)	
Yes	18 (43.9)
No	23 (56.1)
Tumor *BRCA* status, No. (%)	
t*BRCA*m	4 (9.8)
t*BRCA*wt	34 (82.9)
t*BRCA*unk	3 (7.3)

(continued in next column)

TABLE 1. Patient Demographics and Baseline Characteristics (continued)

Characteristic	OPAL-A (N = 41)
HRD status, No. (%)[a]	
HRd	8 (19.5)
t*BRCA*m	4 (9.8)
t*BRCA*wt	4 (9.8)
t*BRCA*unk	0 (0)
HRp	20 (48.8)
HRD status unknown	13 (31.7)
HRR status, No. (%)[b]	
HRR+	7 (17.1)
HRR−	31 (75.6)
HRR status unknown	3 (7.3)
PD-L1 expression, No. (%)	
PD-L1+ (PD-L1 CPS ≥1)	28 (68.3)
PD-L1− (PD-L1 CPS <1)	9 (22.0)
PD-L1 status unknown	4 (9.8)

Abbreviations: CPS, combined positive score; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination–proficient; HRR, homologous recombination repair; m, mutated; NE, not evaluable; OPAL-A, OPAL Cohort A; PD, progressive disease; PR, partial response; SD, stable disease; t*BRCA*, tumor *BRCA*; unk, unknown; wt, wild-type.
[a]Refer to the Methods section for definitions of HRd, HRp, and t*BRCA*- and HRR-mutant status.
[b]Fifteen HRR genes were evaluated: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*.

TABLE 2. Best Overall Response, Efficacy Population

Response Parameter	OPAL-A (N = 41)[a]
BOR per RECIST v1.1, No. (%)	
Confirmed CR	1 (2.4)
Confirmed PR	6 (14.6)
SD	23 (56.1)
PD	8 (19.5)
Inconclusive/NE	1 (2.4)
Missing	2 (4.9)[a]
ORR, % (80% CI)	17.1 (9.8 to 27.0)[b]
DCR, % (80% CI)	73.2 (62.3 to 82.2)

Abbreviations: BOR, best overall response; CR, complete response; DCR, disease control rate; NE, not evaluable; OPAL-A, OPAL Cohort A; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Two participants who withdrew from the study before their first postbaseline scans were included in the efficacy population (N = 41) and were listed with best response missing.
[b]One-sided *P* value, .8794; null hypothesis ORR ≤25%.

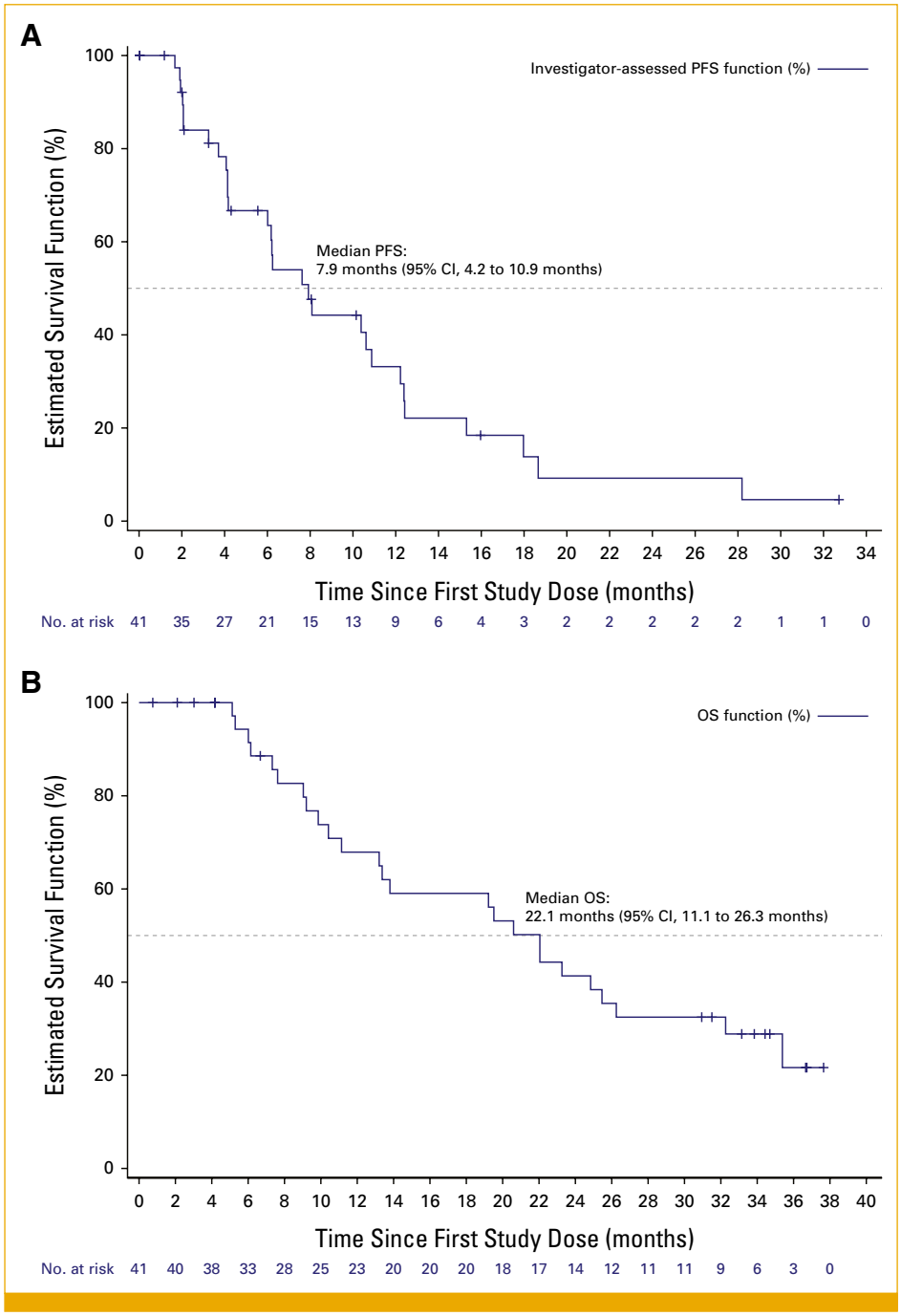

FIG 1. Kaplan-Meier estimates of investigator-assessed (A) PFS and (B) OS. OS, overall survival; PFS, progression-free survival.

TEAEs led to niraparib dose reductions in 26 (63.4%) participants and dose delays in 27 (65.9%) participants (Data Supplement, Table S3). Dose reductions were most commonly due to decreased platelet count (19.5%), anemia, fatigue, and thrombocytopenia (9.8% each). Dose delays were most commonly due to decreased platelet count (24.4%), anemia, fatigue, thrombocytopenia, and vomiting (12.2% each). For dostarlimab, TEAEs led to infusion interruptions in three participants (7.3%), two because of infusion-related reactions. Dostarlimab dose delays occurred in 17 (41.5%) participants; attributed events in one or more participants included rash (n = 3) and fatigue, increased alanine aminotransferase, decreased platelet count, and pneumonitis (n = 2 each). No bevacizumab infusion interruptions occurred, but delays were necessary for 19 (46.3%) participants, including delays attributed to proteinuria (n = 3), anemia, fatigue, hypertension, decreased platelet count, rash, and thrombocytopenia (n = 2 each).

TABLE 3. Treatment-Emergent Adverse Events of Any Grade Occurring in ≥20% of Participants and/or of Grade ≥3 Occurring in ≥5% of Participants, Safety Population

	OPAL-A (N = 41)	
Preferred Term, No. (%)	Any Grade TEAE	Grade ≥3 TEAE
Any TEAE	41 (100)	38 (92.7)
Fatigue	30 (73.2)	7 (17.1)
Nausea	28 (68.3)	2 (4.9)
Vomiting	23 (56.1)	3 (7.3)
Hypertension	21 (51.2)	11 (26.8)
Anemia	19 (46.3)	8 (19.5)
Platelet count decreased	17 (41.5)	6 (14.6)
Headache	16 (39.0)	0 (0)
Constipation	15 (36.6)	1 (2.4)
Decreased appetite	15 (36.6)	0 (0)
Abdominal pain	14 (34.1)	3 (7.3)
Aspartate aminotransferase increased	14 (34.1)	2 (4.9)
Diarrhea	14 (34.1)	0 (0)
Dyspnea	14 (34.1)	1 (2.4)
Hyponatremia	14 (34.1)	5 (12.2)
Insomnia	14 (34.1)	0 (0)
Arthralgia	12 (29.3)	1 (2.4)
Blood creatinine increased	11 (26.8)	0 (0)
Neutrophil count decreased	11 (26.8)	4 (9.8)
Alanine aminotransferase increased	10 (24.4)	2 (4.9)
Cough	10 (24.4)	0 (0)
Myalgia	10 (24.4)	0 (0)
Rash	10 (24.4)	2 (4.9)
Back pain	9 (22.0)	1 (2.4)
Blood alkaline phosphatase increased	9 (22.0)	1 (2.4)
Thrombocytopenia	8 (19.5)	5 (12.2)
Small intestinal obstruction	6 (14.6)	5 (12.2)

Abbreviations: OPAL-A, OPAL Cohort A; TEAE, treatment-emergent adverse event.

Nineteen participants (46.1%) discontinued ≥1 drugs because of TEAEs: 15 (36.6%) niraparib, 10 (24.4%) dostarlimab, 11 (26.8%) bevacizumab, and five (12.2%) all three drugs (Data Supplement, Table S3). There were no TEAEs leading to death.

The most common (in ≥30% of participants) treatment-related AEs (TRAEs) were fatigue (65.9%), nausea (46.3%), anemia (41.5%), platelet count decreased (41.5%), and vomiting (34.1%) in participants treated with niraparib; fatigue (39%) in participants treated with dostarlimab; and hypertension (43.9%) in participants treated with bevacizumab (Data Supplement). Among 18 participants with treatment-related hypertension, 11 cases were considered related to both niraparib and bevacizumab and seven were considered related to bevacizumab only (Data Supplement, Table S4). Observed irAE rates are reported in the Data Supplement (Table S5).

Exploratory Subgroup Analyses

ORR was consistent across most subgroups, on the basis of t*BRCA*, HRD, HRR, or PD-L1 (Data Supplement, Tables S6 and S7). Of seven participants with a confirmed response, one received previous bevacizumab and six did not. Best percent change in lesion size was assessed according to t*BRCA*, HRR, HRD, and PD-L1 status (Fig 2). Twelve participants achieved a ≥30% decrease in lesion size from baseline as their best response.

Paired on-treatment biopsies were available from 17 participants (one responder, 15 nonresponders [12 SD, three PD], and one NE). Interferon (IFN)-gamma response was the most significantly enriched pathway in on-treatment versus baseline samples; IFN-alpha response was also significantly enriched on treatment (Fig 3). In the multiplex immunofluorescence analysis, the paired Wilcoxon test was applied to 14 participants with paired samples (11 SD, three PD). On treatment, T cells (cluster of differentiation [CD]3^+), cytotoxic T cells ($CD3^+CD8^+$), helper T cells ($CD3^+CD4^+$), granzyme B^+ cytotoxic T cells ($CD3^+/CD8^+$/granzyme B^+), and M2 macrophage markers ($CD163^+$ and percent M2 macrophages) were significantly increased within the tumor (Data Supplement, Table S8, Fig 3) after treatment. Neither baseline immune cell markers nor changes in immune cell markers on treatment were associated with clinical benefit (data not shown).

Baseline samples for WTS were available from 25 participants (four responders [PR], 21 nonresponders [17 SD, four PD]). In GSEA analysis of baseline samples, epithelial to mesenchymal transition signaling was the most significantly enriched pathway in responders (compared with nonresponders) and in participants with clinical benefit (compared with no clinical benefit). In baseline tissue specimens, the IFN-alpha pathway was significantly enriched in nonresponders, whereas a nonsignificant increase was noted in participants with clinical benefit (Data Supplement, Figs S4A and S4B).

DISCUSSION

In this phase II study, the triplet combination of niraparib-dostarlimab-bevacizumab resulted in a confirmed investigator-assessed 17.1% ORR. This modest ORR might have been due to most participants having t*BRCA*wt or HRRwt tumors, which are predictive of poorer response to therapy and poorer survival.[20–23] No subgroup demonstrated increased ORR; however, the analysis was limited by the small sample size and number of responses. While OPAL-A did not meet its primary end point, the DCR was appreciable (73.2%), with 56.1% of participants achieving SD. This response translated into a PFS of 7.9 months and an OS of

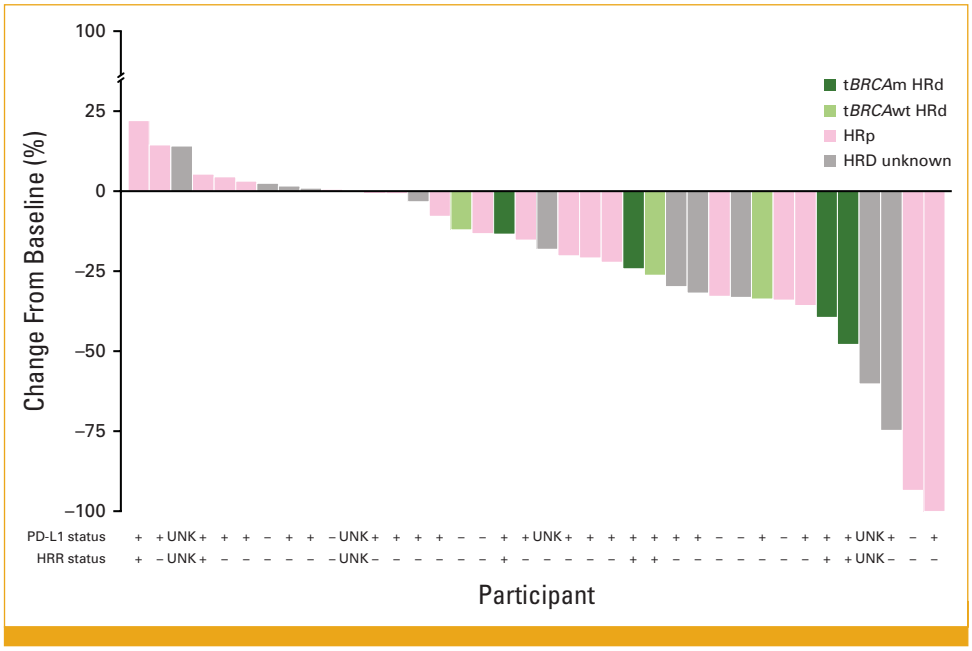

FIG 2. Waterfall plot of best percent change in lesion size from baseline, with biomarker status. Tumor response assessments were conducted per RECIST v1.1. Best percent change in target lesion size was defined as the maximum reduction from baseline or, in the absence of reduction, the minimum increase (least growth) in lesion size from baseline. Results are shown for 38 of 39 participants with postbaseline scans. The remaining participant had one postbaseline scan showing progression; at this scan, the investigator was unable to evaluate one of the target lesions, so the target lesion percent change from baseline was not calculable for this participant. PD-L1 status and HRR status: +, positive; −, negative; or UNK, unknown status. For HRR status, 15 genes were evaluated: *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. HRD status: HRd, HRp, HRD unknown. HRd was defined as t*BRCA*m or HRD score ≥42; HRp was defined as t*BRCA*wt and HRD score <42; HRD status unknown was defined as *BRCA*wt or unknown and HRD score unknown. HRd, homologous recombination–deficient; HRD, homologous recombination deficiency; HRp, homologous recombination–proficient; HRR, homologous recombination repair; m, mutated; t*BRCA*, tumor *BRCA*; UNK, unknown; wt, wild-type.

22.1 months, both longer than those seen in historical controls in the platinum-resistant population.[6] Analysis of paired on-treatment tumor samples revealed that the most significantly enriched gene set between the on-treatment and baseline samples was an IFN-gamma response, suggesting that the triplet therapy induced changes in immune activity. Similarly, multiplex immunofluorescence demonstrated both that $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells were significantly increased in the on-treatment samples. However, there was also a significant increase in the M2 macrophage ratio, suggesting potential for concomitant enhanced immunosuppression.

Treatment of PROC remains an area of high unmet need.[24] Although recent advances include approval of the folate receptor alpha–targeting antibody-drug conjugate mirvetuximab soravtansine in folate receptor alpha–high PROC,[25] available treatment options for patients with PROC continue to have generally limited efficacy. One question has been whether targeted therapy with PARP inhibitors can be leveraged to generate effective therapeutic treatments with high tolerability. As monotherapy, PARP inhibitors have only modest activity in PROC. In the phase II QUADRA study of niraparib monotherapy for late-line OC treatment, a 5.9% ORR (17 of 289 participants) was observed in participants with known PROC, and ORR was highest (27%) in participants with a t*BRCA*m.[26] PARP inhibition and immune checkpoint therapy combinations have also been explored, given preclinical data suggesting the potential benefit of combination treatment. In the single-arm TOPACIO/KEYNOTE-162 study, an 18% ORR and a 65% DCR were reported with niraparib plus pembrolizumab, including activity in non-*BRCA*m tumors.[19] However, a subsequent phase II, single-arm study of niraparib with dostarlimab in participants with PROC (MOONSTONE/GOG-3032) was terminated for futility.[27] A doublet combination (niraparib-dostarlimab) trial in PROC remains ongoing (NITCHE/MITO 33).[28]

In OPAL-A, the addition of bevacizumab to the PARP inhibitor–ICI combination of niraparib and dostarlimab had only modest clinical activity. These results contrast more promising results reported in platinum-sensitive and first-line therapies for OC. In the MEDIOLA trial in platinum-sensitive nongermline *BRCA*m OC, the triplet of bevacizumab-olaparib-durvalumab resulted in an 87.1% ORR and a median PFS of 14.7 months, whereas olaparib-

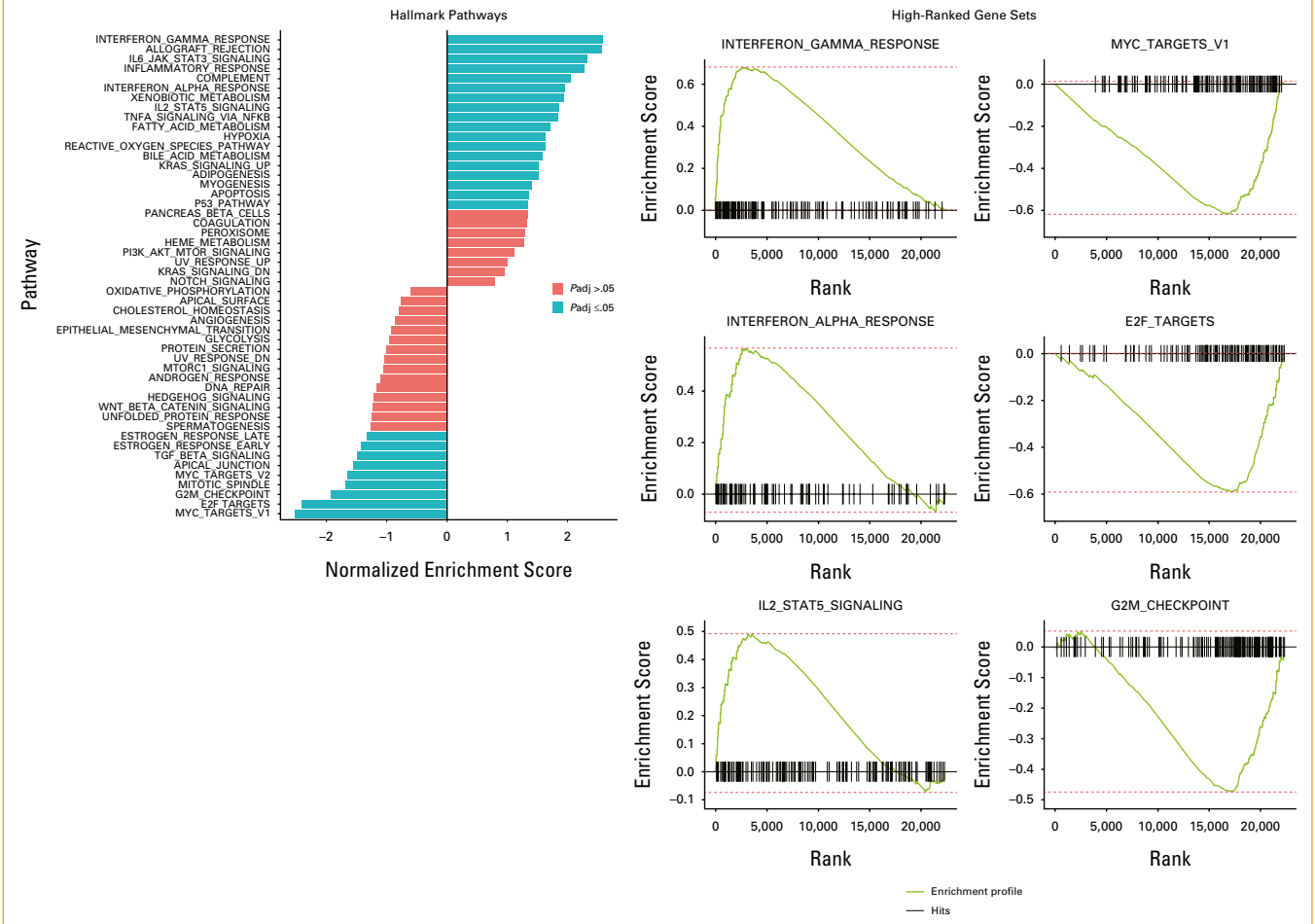

FIG 3. Comparison of on-treatment and baseline tumor biopsies using (A) GSEA pathway enrichment analysis and (B) multiplex immunofluorescence. For (A), GSEA of WTS data was performed to examine differences in hallmark pathways between baseline tumor biopsies and on-treatment tumor biopsies. Positive normalized enrichment score indicates enrichment on-treatment. Pathways with significant differences (*P* adj ≤.05) are given in blue; pathways with nonsignificant differences (*P* adj >.05) are given in pink. (continued on following page)

FIG 3. (Continued). Example high-ranked gene sets from the analysis are presented to the right of the hallmark pathways–normalized enrichment score from the GSEA bar graph. Red dashed lines indicate enrichment score curve maximum (positive or negative). For (B), tumor samples collected at baseline (screening) and on-treatment (C2D1/C3D1) were evaluated using multiplex immunofluorescence. Changes in markers (cell count/mm^2) or M2 macrophage ratio within the tumor area that were significantly different between on-treatment and baseline tumors are shown. Boxes show median and IQR at screening and on treatment. Changes for participants with BOR PD are shown with pink lines; changes for participants with BOR SD are shown with blue lines. Tumor response assessments were conducted per RECIST v1.1. SD was documented at least once >4 weeks from baseline. PD required no previous SD and no confirmed partial response or complete response. BOR, best overall response; C, cycle; D, day; GSEA, gene set enrichment analysis; *P*adj, adjusted *P* value; PD, progressive disease; SD, stable disease; WTS, whole-transcriptome sequencing.

durvalumab had a 34.4% ORR and a median PFS of 5.5 months.[29] It should be noted that these cohorts were sequentially enrolled, and the trial was not designed for direct comparison between these two regimens; nonetheless, the difference in observed activity suggests that the triplet combination had higher activity than the doublet in platinum-sensitive OC. Recently, the first-line DUO-O study results demonstrated improved PFS with the combination of chemotherapy with bevacizumab-durvalumab followed by triplet maintenance of bevacizumab-olaparib-durvalumab compared with chemotherapy with bevacizumab followed by bevacizumab maintenance in participants with newly diagnosed stage III to IV high-grade epithelial cancer.[30] However, DUO-O did not have an olaparib-durvalumab maintenance arm to assess whether the triplet combination had added activity beyond the doublet PARP inhibitor–ICI in this setting.

The varied levels of efficacy of triplet therapy observed in OPAL-A, MEDIOLA, and DUO-O suggest that clinical setting and tumor biology may be important for triplet PARP inhibitor–antiangiogenic–ICI activity. PARP inhibitor–induced DNA damage is hypothesized to lead to stimulator of interferon genes (STING) pathway activation.[31] Cells that have acquired platinum resistance by restoration of HR may endure minimal DNA damage from the PARP inhibitor, potentially decreasing the clinical impact of triplet combination in PROC. Notably, some participants experienced a durable response in OPAL-A; the median DOR was 11.8 months (range, 3.4-30.8 months). The observation that PD-L1 status did not correlate with triplet efficacy is consistent with other studies in OC where ICI activity was not clearly associated with PD-L1 expression.[32]

In this study, we conducted an extensive set of biomarker analyses, including collection of baseline or archival tumor samples for all participants, and paired on-treatment tumor samples. Availability of paired baseline and on-treatment samples for WTS and multiplex immunofluorescence analysis was limited. In total, screening samples for WTS were available from 25 participants, and we successfully collected paired on-treatment tumor samples in 17 participants. Our overall sample size was small, and given the limited number of responders, there was limited power to observe any significant associations. Nonetheless, analysis of the paired on-treatment tumor samples yielded some interesting observations. An interferon gamma response was the most significantly enriched gene set between the on-treatment and baseline samples, and CD8$^+$ cytotoxic T cells were significantly increased in the on-treatment samples, suggesting that immune activation did occur with triplet therapy. In OPAL-A, the small number of responders who had available paired samples meant that meaningful clinical correlation could not be seen. However, it would be of interest to investigate whether a clinical correlation exists for similar upregulation of immune activity in settings where treatment demonstrates increased activity.

No unexpected safety signals were observed with the niraparib-dostarlimab-bevacizumab triplet combination, and TRAEs were consistent with previous monotherapy reports. Grade ≥3 TEAEs were reported in 92.7% of participants, and TRAEs leading to discontinuation of one or more study drugs occurred in 17 participants (41.5%), suggesting that this triplet combination may be difficult to maintain in this population; however, in less heavily pretreated populations, this may not be the case. Both niraparib and bevacizumab monotherapies are associated with hypertension (≤21% and ≤42%, respectively).[9,33] The rate of hypertension in OPAL-A was 51.2%, with grade 3 hypertension in 26.8%; this increased rate may represent overlapping AEs.

OPAL-A had several limitations, including a small sample size and lack of a comparator arm. Notably, most confirmed responses were in participants who were bevacizumab-naïve, with one exception; however, small participant numbers limit the conclusions that can be drawn from this finding. Given the limited number of responders, specific correlations of clinical activity with potential biomarkers of interest could not be adequately assessed. Biomarker analyses were limited to participants with available tumor samples; reasons why tumor samples were unavailable or unsuitable for analysis were not recorded as part of this study. However, OPAL-A demonstrated that collection of paired samples is feasible and valuable to incorporate in early proof-of-concept studies, and the OPAL-A study design is a scalable model that works well for analysis of exploratory data sets in early-phase testing of novel combinations.

In conclusion, OPAL-A reported only modest ORR activity for the triplet combination of niraparib-dostarlimab-bevacizumab in participants with PROC although the median PFS of 7.9 months and the median OS of 22.1 months

compared favorably with historical controls in a PROC population. It should be noted that most responders were bevacizumab-naïve (six of seven responders [85.7%]). Exploratory biomarkers from paired pretreatment and on-treatment samples suggest that this triplet regimen does mediate immune activation; further exploration of whether these biomarkers could predict clinical activity of triplet therapy is of interest.

AFFILIATIONS

[1]Dana-Farber Cancer Institute, Boston, MA
[2]Johns Hopkins University, Baltimore, MD
[3]Mayo Clinic, Rochester, MN
[4]Massachusetts General Cancer Center, Boston, MA
[5]Stanford Women's Cancer Center, Palo Alto, CA
[6]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK
[7]University of Alabama at Birmingham, Birmingham, AL
[8]Yale University, New Haven, CT
[9]GSK, Waltham, MA
[10]GSK, Brentford, United Kingdom
[11]GSK, Stevenage, United Kingdom
[12]University of California Los Angeles, Los Angeles, CA

CORRESPONDING AUTHOR

Joyce F. Liu, MD, MPH; e-mail: joyce_liu@dfci.harvard.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Provision of study materials or patients: Joyce F. Liu, Stéphanie Gaillard, Andrea E. Wahner Hendrickson, Oladapo Yeku, Elisabeth Diver, Camille Gunderson Jackson, Rebecca Arend, Elena Ratner, Vivek Samnotra, Gottfried E. Konecny
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Joyce F. Liu
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Stéphanie Gaillard
Consulting or Advisory Role: Arcus, Elevar Therapeutics, GSK Diagnostics, Immunogen, Lumanity, Novartis, Organon, SignPath Pharma
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Andrea E. Wahner Hendrickson
Consulting or Advisory Role: Oxcia
Research Funding: Mayo Ovarian Cancer SPORE P50 CA1363939 (Inst), Prolynx, TORL

Oladapo Yeku
Employment: Massachusetts General Hospital Cancer Center, Massachusetts Medical Society
Consulting or Advisory Role: Celldex Therapeutics, GIMV NV, hC Bioscience, TigaTx
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Travel, Accommodations, Expenses: ASCO

Elisabeth Diver
Employment: Immunogen
Stock and Other Ownership Interests: Immunogen
Leadership: Society for Gynecologic Oncology
Honoraria: CCO, Curio, OncLive, SurvivorNet
Consulting or Advisory Role: EMD Serono, GSK, Novartis
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Travel, Accommodations, Expenses: Tempus

Rebecca Arend
Consulting or Advisory Role: GSK
Research Funding: NCI – DETECT contract, cervical SPORE, cancer center grant

Vivek Samnotra
Employment: GSK
Stock and Other Ownership Interests: GSK

Divya Gupta
Employment: GSK

Jon Chung
Employment: GSK
Stock and Other Ownership Interests: GSK

Hailei Zhang
Employment: GSK
Stock and Other Ownership Interests: GSK

Natalie Compton
Employment: GSK
Consulting or Advisory Role: GSK

Amanda Baines
Employment: GSK
Stock and Other Ownership Interests: GSK

Emeline Bacqué
Employment: GSK

Xiaohong Liu
Employment: GSK

Brunella Felicetti
Employment: GSK
Stock and Other Ownership Interests: GSK

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