Olaparib plus Durvalumab, with or without Bevacizumab, as Treatment in PARP Inhibitor-Naïve Platinum-Sensitive Relapsed Ovarian Cancer: A Phase II Multi-Cohort Study

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ABSTRACT

Purpose: Early results from the phase II MEDIOLA study (NCT02734004) in germline *BRCA1*- and/or *BRCA2*-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSROC) showed promising efficacy and safety with olaparib plus durvalumab. We report efficacy and safety of olaparib plus durvalumab in an expansion cohort of women with gBRCAm PSROC (gBRCAm expansion doublet cohort) and two cohorts with non-gBRCAm PSROC, one of which also received bevacizumab (non-gBRCAm doublet and triplet cohorts).

Patients and Methods: In this open-label, multicenter study, PARP inhibitor-naïve patients received olaparib plus durvalumab treatment until disease progression; the non-gBRCAm triplet cohort also received bevacizumab. Primary endpoints were objective response rate (ORR; gBRCAm expansion doublet cohort), disease control rate (DCR) at 24 weeks (non-gBRCAm cohorts), and safety (all cohorts).

Results: The full analysis and safety analysis sets comprised 51, 32, and 31 patients in the gBRCAm expansion doublet, non-gBRCAm doublet, and non-gBRCAm triplet cohorts, respectively. ORR was 92.2% [95% confidence interval (CI), 81.1–97.8] in the gBRCAm expansion doublet cohort (primary endpoint); DCR at 24 weeks was 28.1% (90% CI, 15.5–43.9) in the non-gBRCAm doublet cohort (primary endpoint) and 74.2% (90% CI, 58.2–86.5) in the non-gBRCAm triplet cohort (primary endpoint). Grade ≥ 3 adverse events were reported in 47.1%, 65.6%, and 61.3% of patients in the gBRCAm expansion doublet, non-gBRCAm doublet, and non-gBRCAm triplet cohorts, respectively, most commonly anemia.

Conclusions: Olaparib plus durvalumab continued to show notable clinical activity in women with gBRCAm PSROC. Olaparib plus durvalumab with bevacizumab demonstrated encouraging clinical activity in women with non-gBRCAm PSROC. No new safety signals were identified.

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Translational Relevance

Early results from the phase II open-label multi-cohort MEDIOLA study in germline *BRCA1*- and/or *BRCA2*-mutated (gBRCAm) platinum-sensitive relapsed ovarian cancer (PSROC) showed promising efficacy and safety with the PARP inhibitor olaparib plus the anti—programmed death-ligand 1 (PD-L1) antibody durvalumab. MEDIOLA was expanded to further characterize the efficacy and safety of olaparib plus durvalumab in a larger cohort of patients with gBRCAm PSROC and to determine whether the benefit extends beyond gBRCAm ovarian cancer with the doublet combination or with the addition of the antiangiogenic agent bevacizumab in a triplet combination. Olaparib plus durvalumab continued to show notable clinical activity in women with gBRCAm PSROC. Olaparib plus durvalumab and bevacizumab demonstrated encouraging clinical activity in women with non-gBRCAm PSROC, with objective responses seen in patients regardless of genomic instability status and across PD-L1 subgroups. Findings warrant further investigation of combination therapies for patients with non-gBRCAm ovarian cancer.

Introduction

For women with relapsed, advanced ovarian cancer, chemotherapy may be limited by toxicity, resistance, and impaired health-related quality of life (1, 2) and new treatments that improve outcomes are needed.

Olaparib, a PARP inhibitor, causes both PARP enzyme inhibition and PARP trapping at sites of single-strand DNA damage, inhibiting single-strand break repair (3). Tumors with homologous recombination deficiency (HRD), such as a *BRCA1* and/or *BRCA2* mutation (BRCAm), cannot accurately repair DNA damage generated from unrepaired single-strand breaks, leading to cell death (3). PARP inhibitors also induce antitumor immune responses via stimulator of interferon genes (STING) pathway activation (and subsequent cytotoxic T-cell response; refs. 4, 5) and STING-dependent type I interferon production (6).

For patients with newly diagnosed advanced ovarian cancer in response to first-line platinum-based chemotherapy, maintenance olaparib is standard of care either as monotherapy in BRCAm ovarian cancer or in combination with bevacizumab in HRD-positive ovarian cancer (defined by a BRCAm and/or genomic instability; refs. 7, 8). For patients with platinum-sensitive relapsed ovarian cancer (PSROC), although maintenance olaparib demonstrated benefit regardless of biomarker status (9, 10), patients with a BRCAm derived the greatest benefit (11, 12), suggesting potential roles for combination therapies to improve outcomes in patients without a BRCAm (non-BRCAm).

Durvalumab, a selective, high-affinity, human immunoglobulin G1 monoclonal antibody, blocks binding of the surface protein programmed death-ligand 1 (PD-L1) to its receptors, promoting antitumor immune responses (13). Durvalumab is approved in multiple tumor types, as monotherapy (unresectable stage III non–small cell lung cancer) or combination therapy (extensive-stage small cell lung cancer, metastatic biliary tract cancer, and unresectable hepatocellular carcinoma; ref. 14); however, single-agent activity of immune checkpoint inhibitors in ovarian cancer has been modest (15).

Bevacizumab, an anti-VEGF monoclonal antibody with antiangiogenic effects, is a standard treatment option for first-line and recurrent advanced ovarian cancer (16–20). Combination therapy with other anti-VEGF agents, including receptor tyrosine kinase inhibitors, and immune checkpoint inhibitors have previously shown activity in other tumor types (21).

MEDIOLA is a phase II multi-cohort study of olaparib plus durvalumab in patients with selected solid tumors. In an initial MEDIOLA germline BRCAm (gBRCAm) PSROC cohort, olaparib plus durvalumab showed promising efficacy and safety in the initial treatment (as opposed to maintenance) setting (22). MEDIOLA was expanded to further characterize efficacy and safety of olaparib plus durvalumab as treatment in a larger cohort of patients with gBRCAm PSROC who were naïve both to PARP inhibitors and to immune checkpoint inhibitors and/or biologics targeting T-cell co-regulatory proteins and to determine whether the benefit extends beyond gBRCAm ovarian cancer, including the additional effect of bevacizumab. The hypotheses tested were that PARP inhibition leads to increased DNA damage, thus increasing antitumor immunity and potentiating the effect of immune checkpoint inhibition. Furthermore, the addition of a VEGF inhibitor may help overcome the immunosuppressive microenvironment and further enhance the antitumor immune response. Preclinical (23–28) and clinical (29–32) data support these hypotheses.

Here, we report expanded efficacy and safety data for olaparib plus durvalumab as treatment in patients with gBRCAm PSROC (gBRCAm expansion doublet cohort) and results from two new cohorts of patients with non-gBRCAm PSROC, one of which also received bevacizumab (non-gBRCAm doublet and triplet cohorts, respectively); patients in all three cohorts were naïve both to PARP inhibitors and to immune checkpoint inhibitors and/or biologics targeting T-cell co-regulatory proteins.

Patients and Methods

Study design and patients

MEDIOLA (NCT02734004) is a phase II open-label, multi-cohort basket trial in selected solid tumors. Patients were enrolled into four initial cohorts: gBRCAm PSROC; gBRCAm metastatic breast cancer; relapsed gastric cancer; and relapsed small cell lung cancer (33). We report results from the second-stage ovarian cancer cohorts which enrolled PARP inhibitor-naïve patients aged ≥ 18 years with measurable, relapsed high-grade serous ovarian cancer (including primary peritoneal and/or fallopian tube cancer), considered platinum-sensitive (relapse ≥ 24 weeks after last platinum therapy), with one or two prior lines of chemotherapy including platinum-based therapy and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (**Fig. 1**). Patients were naïve to PARP inhibitors and to biologics targeting immune checkpoints and/or T-cell co-regulatory proteins. Prior bevacizumab treatment was permitted. Full eligibility criteria are provided in the Supplementary Appendix.

Patients were assigned to cohorts based on whether they had a deleterious or suspected deleterious gBRCAm. All patients provided blood samples for central gBRCAm testing (BRACAnalysis CDx; Myriad Genetic Laboratories, Inc., Salt Lake City, UT). Patients with a locally determined gBRCAm-positive status at screening were enrolled into the gBRCAm expansion doublet cohort and underwent retrospective confirmatory central gBRCAm testing (which confirmed all patients enrolled into the gBRCAm expansion doublet cohort had a gBRCAm). Patients with unknown gBRCAm status or locally determined gBRCAm-negative status at screening underwent prospective central gBRCAm testing. In the event of a gBRCAm-positive result, patients were enrolled into the gBRCAm expansion doublet cohort. If the gBRCAm test was negative, patients were enrolled sequentially into

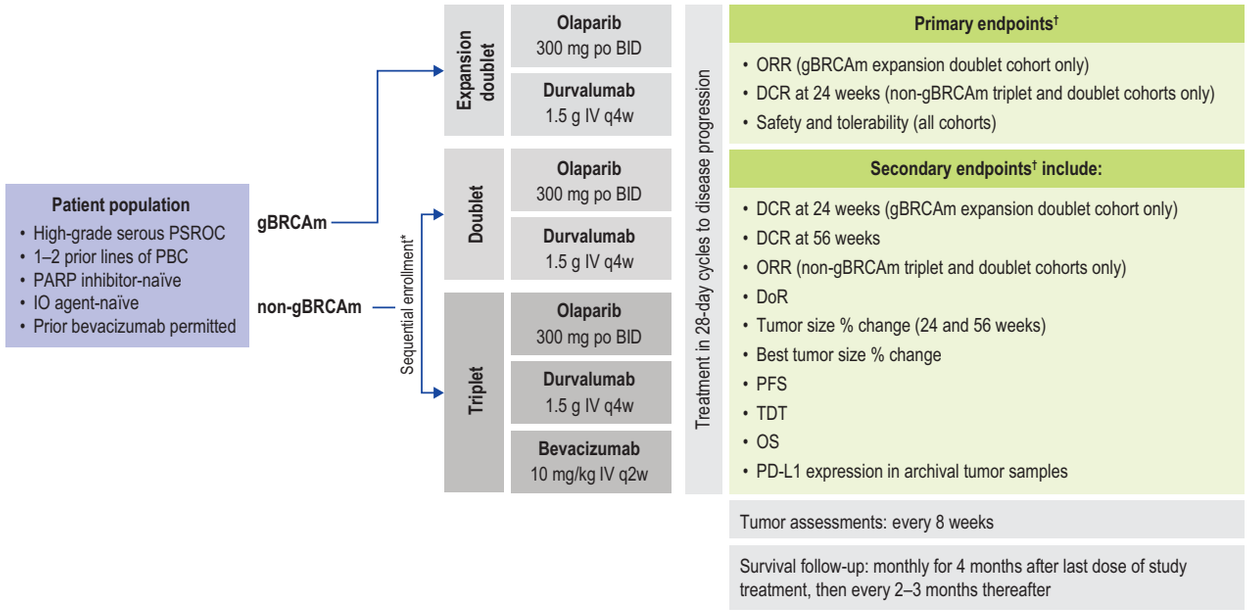


Figure 1.
MEDIOLA second-stage ovarian cancer cohorts: study design. *In the non-gBRCAm cohorts, patients were enrolled into the triplet and doublet cohorts sequentially following confirmation of non-gBRCAm status; patients were enrolled into the doublet cohort once enrollment into the triplet cohort was complete. The gBRCAm expansion doublet cohort was enrolled concurrently alongside the non-gBRCAm cohorts; †All tumor assessment-related endpoints were based on investigator-assessed radiologic response (RECIST 1.1). BID, twice daily; gBRCAm, germline *BRCA1* and/or *BRCA2* mutation; IO, immuno-oncology; IV, intravenous; PBC, platinum-based chemotherapy; po, by mouth; q2w, every 2 weeks; q4w, every 4 weeks.

the non-gBRCAm triplet or doublet cohorts (**Fig. 1** and Supplementary Appendix).

The trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and the AstraZeneca policy of bioethics (34) and was approved by the appropriate Institutional Review Boards. All patients provided written informed consent.

Interventions

All patients received olaparib tablets (300 mg twice daily) plus durvalumab (1.5 g intravenously every 4 weeks); the triplet cohort also received bevacizumab (10 mg/kg intravenously every 2 weeks) in 28-day cycles (**Fig. 1**). Treatment for all cohorts started on day 1 and continued until investigator-assessed objective radiologic disease progression (RECIST version 1.1), or for as long as the investigator considered the patient to be benefitting from treatment and no other discontinuation criteria were met (see Supplementary Appendix). Patients who discontinued one or more study treatment(s) could continue to receive the remaining study treatment(s).

Endpoints and assessments

The primary endpoints were objective response rate (ORR) for the gBRCAm expansion doublet cohort, based on the intent to confirm the response observed with the initial gBRCAm cohort (22), disease control rate (DCR) at 24 weeks in the non-gBRCAm doublet and triplet cohorts, and safety (all cohorts; **Fig. 1**). Adverse events (AE) were monitored using the NCI's Common Terminology Criteria for Adverse Events (version 4.03) throughout the treatment period and for 90 days after discontinuation of the last dose of olaparib, durvalumab, or bevacizumab. Patients were followed for myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and new primary malignancies beyond the 90-day posttreatment safety follow-up period and throughout survival follow-up.

Secondary endpoints were DCR at 24 weeks (gBRCAm expansion doublet cohort only) and 56 weeks, ORR (non-gBRCAm cohorts only), duration of response (DoR), percentage change from baseline in tumor size at 24 and 56 weeks, best percentage change from baseline in tumor size, progression-free survival (PFS), time to study treatment discontinuation or death (TDT), overall survival (OS), and PD-L1 expression in archival tumor samples. All tumor assessment-related endpoints were based on investigator-assessed radiologic response (RECIST 1.1).

Baseline PD-L1 expression levels were measured using the VENTANA PD-L1 immunohistochemistry assay. Genomic instability status was determined by Foundation Medicine Inc. (Cambridge, MA) tumor analysis. Patients with genome-wide loss of heterozygosity (LOH) ≥ 14, a somatic BRCAm, or a deleterious or suspected deleterious mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, or *RAD54 L* were considered positive. Genomic instability negative was defined as genome-wide LOH < 14, no somatic BRCAm, and no deleterious or suspected deleterious mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, or *RAD54L*. An unknown genomic instability status was due to the sample not being analyzable (i.e., poor quality, technical failure, or inadequate tissue). During the study, the threshold for LOH changed from ≥ 14 to ≥ 16; however, at the time of analysis, the prespecified cutoff for genome-wide LOH of 14% (35) was used for all analyses of genomic instability. Further information on the assessment schedule, outcome measures, and PD-L1 expression analysis is provided in the Supplementary Appendix.

Statistical methods

In the gBRCAm expansion doublet cohort, a total of 80 patients were planned for enrollment based on ORR; a two-sided 95% confidence interval (CI) for a single proportion using the large sample normal approximation extended 0.090 from the observed proportion for an expected proportion of 0.785. However, during enrollment of the gBRCAm expansion doublet cohort, PARP inhibitors became standard of care in the first-line setting for patients with a gBRCAm, limiting the number of PARP inhibitor-naïve patients eligible for inclusion in the gBRCAm expansion doublet cohort; recruitment was therefore closed after 51 patients had been enrolled. In each of the non-gBRCAm doublet and triplet cohorts, a total of 30 patients were planned for enrollment based on a target DCR of 80% at 24 weeks. The target DCR was determined on the basis of an estimated median PFS for these cohorts of 17.7 months, which suggested that approximately 80% of patients would be progression-free after 24 weeks; the target DCR was therefore 80%. Stopping guidelines are provided in the Supplementary Appendix.

The full analysis set included all patients who received one or more doses of study treatment and were not excluded from the study because of prespecified protocol deviations (see Supplementary Appendix) and was used for all efficacy analyses. The safety analysis set included all patients who received one or more doses of study treatment.

ORR was summarized with 95% CIs. DCR at 24 weeks was summarized with 90% CIs. CIs were calculated using the Clopper–Pearson method.

Patients who did not complete the DCR assessment at week 24 were considered not to have controlled disease at 24 weeks. Efficacy analyses were not adjusted for baseline patient or disease characteristics because of the small sample size in each cohort.

The Kaplan–Meier method was used to calculate DoR, PFS, TDT, and OS. ORR was also summarized by PD-L1 expression. Exploratory *post hoc* analyses summarized ORR by genomic instability status in the non-gBRCAm cohorts.

AEs were analyzed descriptively.

All statistical analyses were performed using SAS software version 9 (SAS Institute Inc., Cary, NC; RRID: SCR_008567).

Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available, outlining further details: https://vivli.org/ourmember/astrazeneca/.

Results

Patients were enrolled between May 4, 2018 and March 10, 2020 at 33 sites across seven countries (Supplementary Appendix). Patient characteristics were generally similar between cohorts (**Table 1**) and were representative of the overall target populations with PSROC, although patients in the gBRCAm expansion doublet cohort were younger than those in the non-gBRCAm cohorts and patients in the non-gBRCAm triplet cohort were more likely to have had two prior lines of chemotherapy and less likely to have experienced disease progression > 12 months after their last platinum therapy than those in the gBRCAm and non-gBRCAm doublet cohorts. Two patients (6.3%) in the non-gBRCAm doublet cohort and 2 patients (6.5%) in the non-gBRCAm triplet cohort had somatic BRCAm identified on Foundation Medicine Inc. testing (**Table 1**). MEDIOLA is generally representative of real-world patients with PSROC, although enrolled patients were predominantly white or Asian (Supplementary Table S1).

In the gBRCAm expansion doublet cohort, 51 patients were included in the full analysis and safety analysis sets (Supplementary Fig. S1). At the time of the final data cutoff (DCO; September 17, 2021), 15 patients (29.4%) were still receiving olaparib plus durvalumab and 17 (33.3%) were receiving olaparib alone (Supplementary Fig. S1). Thirty-two patients were included in the full analysis and safety analysis sets in the non-gBRCAm doublet cohort; no patients were receiving olaparib or durvalumab at the time of DCO (Supplementary Fig. S1). Thirty-one patients were included in the full analysis and safety analysis sets in the non-gBRCAm triplet cohort (Supplementary Fig. S1). At DCO, 2 patients (6.5%) were still receiving olaparib plus durvalumab and bevacizumab, 2 (6.5%) were receiving olaparib plus durvalumab, and 1 (3.2%) was receiving olaparib alone.

The median duration of follow-up for OS was 24.2 months in the gBRCAm expansion doublet cohort, 23.2 months in the non-gBRCAm doublet cohort, and 31.9 months in the non-gBRCAm triplet cohort.

In the gBRCAm expansion doublet cohort, ORR (primary endpoint) was 92.2% (95% CI, 81.1–97.8; **Table 2**). A best overall response of complete response (CR) was reported for 22 (43.1%) patients and median DoR was 14.8 months [interquartile range (IQR), 9.0–not calculable (NC)]. DCR was 88.2% (90% CI, 78.1–94.8) at 24 weeks and 41.2% (90% CI, 29.5–53.7) at 56 weeks.

In the non-gBRCAm cohorts, DCR at 24 weeks (primary endpoint) was 28.1% (90% CI, 15.5–43.9) in the doublet cohort and 74.2% (90% CI, 58.2–86.5) in the triplet cohort and DCR at 56 weeks was 9.4% (90% CI, 2.6–22.5) and 38.7% (90% CI, 24.1–55.0), respectively (**Table 2**). In the non-gBRCAm doublet and triplet cohorts, ORR was 34.4% (95% CI, 18.6–53.2) and 87.1% (95% CI, 70.2–96.4), respectively, and median DoR was 6.9 months (IQR, 5.4–11.1) and 11.1 months (IQR, 7.4–22.1), respectively. Percentage change from baseline in tumor size alongside genomic instability status is shown in **Fig. 2A–C**; Supplementary Fig. S2A–S2C.

ORR of ≥ 75% was observed regardless of genomic instability status in the non-gBRCAm triplet cohort (**Fig. 2D**). ORR by PD-L1 status is shown in **Fig. 2E**.

In the gBRCAm expansion doublet, non-gBRCAm doublet, and non-gBRCAm triplet cohorts, median (95% CI) PFS was 15.0 (12.9–24.1), 5.5 (3.6–7.5), and 14.7 (9.2–18.1) months, respectively (**Fig. 3A–C**), and median (95% CI) TDT was 19.3 (14.7–26.2), 6.6 (4.4–8.5), and 15.9 (10.3–18.4) months, respectively. In the gBRCAm expansion doublet cohort, OS data were immature (25.5%) and median OS was not reached (**Fig. 3D**). Median (95% CI) OS was 26.1 (18.7–NC) and 31.9 (22.1–NC) months in the non-gBRCAm doublet and triplet cohorts, respectively (**Fig. 3E** and **F**). OS rates at 24 months were 76.7%, 50.8%, and 64.5% in the gBRCAm expansion doublet, non-gBRCAm doublet, and non-gBRCAm triplet cohorts, respectively.

No clear patterns in progression or survival outcomes according to line of therapy, genomic instability status, or PD-L1 status were seen; however, small subgroup sizes and unknown biomarker status made interpretation difficult (Supplementary Fig. S3A and S3B). Genomic instability status was unknown in 50.0% and 41.9% of patients in the non-gBRCAm doublet and triplet cohorts, respectively, due to non-analyzable samples (**Table 1**).

Table 1. Baseline demographics and clinical characteristics.

	gBRCAm expansion doublet (*N* = 51)	Non-gBRCAm doublet (*N* = 32)	Non-gBRCAm triplet (*N* = 31)
Median (range) age, years	56.0 (36–86)	68.5 (40–86)	64.0 (33–77)
Age group (years), *n* (%)			
< 50	14 (27.5)	4 (12.5)	3 (9.7)
≥ 50 to < 65	24 (47.1)	8 (25.0)	14 (45.2)
≥ 65	13 (25.5)	20 (62.5)	14 (45.2)
Race, *n* (%)			
White	34 (66.7)	24 (75.0)	20 (64.5)
Asian	12 (23.5)	3 (9.4)	10 (32.3)
Black or African American	1 (2.0)	0	0
Other	0	0	1 (3.2)
Missing[a]	4 (7.8)	5 (15.6)	0
ECOG performance status, *n* (%)			
0 (fully active)	33 (64.7)	16 (50.0)	21 (67.7)
1 (restricted in physically strenuous activity)	17 (33.3)	16 (50.0)	10 (32.3)
Missing	1 (2.0)	0	0
Time to progression after completion of last platinum therapy, *n* (%)			
> 6 to 12 months	20 (39.2)	14 (43.8)	17 (54.8)
> 12 months	30 (58.8)	18 (56.3)	14 (45.2)
Not applicable	1 (2.0)	0	0
Primary tumor location, *n* (%)			
Ovary	47 (92.2)	30 (93.8)	29 (93.5)
Fallopian tubes	2 (3.9)	1 (3.1)	2 (6.5)
Primary peritoneal	2 (3.9)	1 (3.1)	0
Histology, *n* (%)			
Serous	48 (94.1)	32 (100)	31 (100)
Mixed epithelial	1 (2.0)	0	0
Other	2 (3.9)	0	0
FIGO stage at primary diagnosis, *n* (%)			
IC	0	1 (3.1)	0
II	3 (5.9)	1 (3.1)	1 (3.2)
III	30 (58.8)	14 (43.8)	16 (51.6)
IV	18 (35.3)	15 (46.9)	14 (45.2)
Missing	0	1 (3.1)	0
Prior lines of chemotherapy,[b] *n* (%)			
1	44 (86.3)	24 (75.0)	20 (64.5)
2	7 (13.7)	8 (25.0)	11 (35.5)
Prior bevacizumab, *n* (%)			
Yes	10 (19.6)	12 (37.5)	12 (38.7)
No	41 (80.4)	20 (62.5)	19 (61.3)
Myriad-determined *BRCA* status,[c] *n* (%)			
g*BRCA1* mutation	33 (64.7)	0	0
g*BRCA2* mutation	18 (35.3)	0	0
Negative	0	32 (100)	31 (100)
Genomic instability status, *n* (%)			
Positive[d]	–	10 (31.3)	10 (32.3)
Negative[e]	–	6 (18.8)	8 (25.8)
Unknown[f]	–	16 (50.0)	13 (41.9)
PD-L1 expression, *n* (%)			
≥ 1% PD-L1 tumor cell expression	12 (23.5)	8 (25.0)	6 (19.4)
< 1% PD-L1 tumor cell expression	34 (66.7)	20 (62.5)	21 (67.7)
Missing	5 (9.8)	4 (12.5)	4 (12.9)
≥ 1% PD-L1 immune cell expression	32 (62.7)	16 (50.0)	19 (61.3)
< 1% PD-L1 immune cell expression	14 (27.5)	12 (37.5)	8 (25.8)
Missing	5 (9.8)	4 (12.5)	4 (12.9)

Abbreviations: BRCAm, *BRCA1* and/or *BRCA2* mutation; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline BRCAm; sBRCAm, somatic BRCAm.

[a]It was not permitted to collect race or ethnicity data from patients enrolled in France.

[b]Number of prior lines of chemotherapy was by medical review.

[c]Determined using a central laboratory. Myriad *BRCA* mutation status could be assessed retrospectively on a sample collected after initiation of study treatment.

[d]Defined as genome-wide LOH ≥ 14, s*BRCA*m or a deleterious or suspected deleterious mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, or *RAD54 L* as determined by Foundation Medicine Inc. (Cambridge, MA) tumor analysis. Two patients in the non-gBRCAm doublet cohort and 2 patients in the non-gBRCAm triplet cohort had an sBRCAm. At the time of analysis, the cutoff for genome-wide LOH was 14% (35).

[e]Defined as genome-wide LOH < 14, no sBRCAm, and no deleterious or suspected deleterious mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, or *RAD54L*, as determined by Foundation Medicine Inc. tumor analysis.

[f]Unknown status due to sample not being analyzable (i.e., poor quality, technical failure, or inadequate tissue).

Table 2. Treatment response and DCR.

	gBRCAm expansion doublet (*N* = 51)	Non-gBRCAm doublet (*N* = 32)	Non-gBRCAm triplet (*N* = 31)
ORR,[a] *n* (%)	47 (92.2)	11 (34.4)	27 (87.1)
95% CI	81.1–97.8	18.6–53.2	70.2–96.4
Best overall response,[a] *n* (%)			
CR	22 (43.1)	0	5 (16.1)
Partial response	25 (49.0)	11 (34.4)	22 (71.0)
DCR[b] at 24 weeks, *n* (%)	45 (88.2)	9 (28.1)	23 (74.2)
90% CI	78.1–94.8	15.5–43.9	58.2–86.5
Not evaluable/missing[c]	3 (5.9)	6 (18.8)	3 (9.7)
DCR[b] at 56 weeks, *n* (%)	21 (41.2)	3 (9.4)	12 (38.7)
90% CI	29.5–53.7	2.6–22.5	24.1–55.0
Not evaluable/missing[d]	11 (21.6)	3 (9.4)	5 (16.1)
Median DoR (IQR), months	14.8 (9.0–NC)	6.9 (5.4–11.1)	11.1 (7.4–22.1)
Confirmed response rate,[e] *n* (%)	47 (92.2)	10 (31.3)	23 (74.2)
95% CI	81.1–97.8	16.1–50.0	55.4–88.1

Abbreviations: gBRCAm, germline *BRCA1* and/or *BRCA2* mutation; NC, not calculable.
Assessments were based on investigator review of radiologic scans.
[a]Response did not require confirmation. ORR was defined as the number (%) of patients with at least one visit response of CR or partial response.
[b]DCR was defined as the percentage of patients who had at least one visit response of CR or partial response or demonstrated stable disease that was maintained until the RECIST 1.1 assessment at 24 or 56 weeks.
[c]Patients with no evaluable post-baseline assessment or patients who did not experience disease progression and had their week 24 assessment prior to day 161.
[d]Patients with no evaluable post-baseline assessment or patients who did not experience disease progression and had their week 56 assessment prior to day 385.
[e]A response of CR or partial response was recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed, with no evidence of progression between the initial and confirmation visit.

Median (range) treatment duration in the gBRCAm expansion doublet, non-gBRCAm doublet, and non-gBRCAm triplet cohorts was 81.9 (12.3–142.7), 28.9 (2.1–131.9), and 69.1 (7.9–162.7) weeks, respectively, for olaparib, and 78.3 (4.0–144.0), 30.0 (4.0–131.9), and 60.0 (8.0–152.1) weeks, respectively, for durvalumab. Median (range) treatment duration for bevacizumab in the non-gBRCAm triplet cohort was 62.0 (8.0–164.1) weeks. Median relative dose intensity across cohorts was similar for durvalumab and for olaparib (Supplementary Table S2).

Across the three cohorts, the most commonly reported AEs of any grade included nausea (66.7% of patients in the gBRCAm expansion doublet cohort, 87.5% of patients in the non-gBRCAm doublet cohort, and 74.2% of patients in the non-gBRCAm triplet cohort), fatigue/asthenia (66.7%, 68.8%, and 54.8%, respectively), and anemia (51.0%, 40.6%, and 58.1%, respectively; **Table 3**; see Supplementary Table S3 for AEs by grade). Anemia was the most commonly reported grade ≥ 3 AE (**Table 3**; Supplementary Table S3). Grade ≥ 3 hypertension was reported in 3.9% of patients in the gBRCAm expansion doublet cohort, 3.1% of patients in the non-gBRCAm doublet cohort and 16.1% of patients in the non-gBRCAm triplet cohort.

In the gBRCAm expansion doublet, non-gBRCAm doublet, and non-gBRCAm triplet cohorts, serious AEs were reported in 25.5%, 25.0%, and 19.4% of patients, respectively (Supplementary Table S4). AEs leading to death (excluding deaths due to disease progression) were reported in 1 of 32 (3.1%) patients in the non-gBRCAm doublet cohort (septic shock; Supplementary Table S3) and no patients in the gBRCAm expansion doublet or non-gBRCAm triplet cohorts.

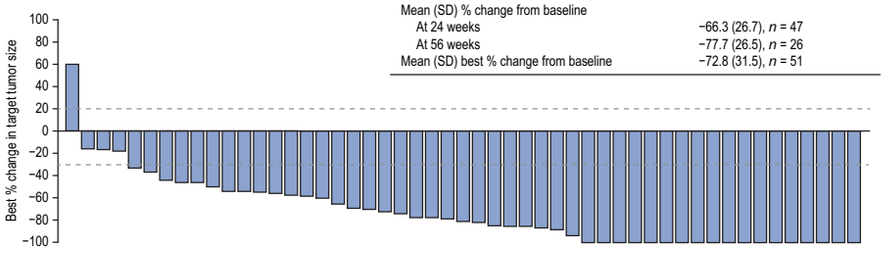
MDS/AML was reported in 1 of 31 (3.2%) patients in the non-gBRCAm triplet cohort and no new primary malignancies were reported (**Table 3**). Immune-mediated AEs occurred in 29.4%, 15.6%, and 35.5% of patients in the gBRCAm expansion doublet, non-gBRCAm doublet, and non-gBRCAm triplet cohorts, respectively (**Table 3**; see Supplementary Table S5).

The incidence of AEs leading to discontinuation of any study treatment was 15.7% in the gBRCAm expansion doublet cohort, 3.1% in the non-gBRCAm doublet cohort, and 32.3% in the non-gBRCAm triplet cohort (**Table 3**). The incidence of AEs leading to discontinuation of olaparib was similar in the gBRCAm expansion doublet and non-gBRCAm triplet cohorts (11.8% and 12.9%, respectively), as was the incidence of AEs leading to discontinuation of durvalumab (13.7% and 16.1%, respectively). The incidence of AEs leading to discontinuation of olaparib and durvalumab was 3.1% and 3.1%, respectively, in the non-gBRCAm doublet cohort. AEs led to discontinuation of bevacizumab in 29.0% of patients in the non-gBRCAm triplet cohort. Proteinuria was the most common AE leading to discontinuation of bevacizumab in the non-gBRCAm triplet cohort [4 (12.9%) patients] and, across cohorts, anemia was the most common AE leading to discontinuation of olaparib [2 (3.9%) patients in the gBRCAm expansion doublet cohort, no patients in the non-gBRCAm doublet cohort, and 1 (3.2%) patient in the non-gBRCAm triplet cohort; Supplementary Table S6]. AEs leading to discontinuation of durvalumab were not reported in more than 1 patient in each cohort (Supplementary Table S6). Dose modifications are summarized in Supplementary Table S7.

Discussion

In MEDIOLA, we evaluated chemotherapy-free treatment with olaparib plus durvalumab in PARP inhibitor-naïve patients with gBRCAm PSROC and report the first data for olaparib plus durvalumab with or without bevacizumab in non-gBRCAm PSROC.

A



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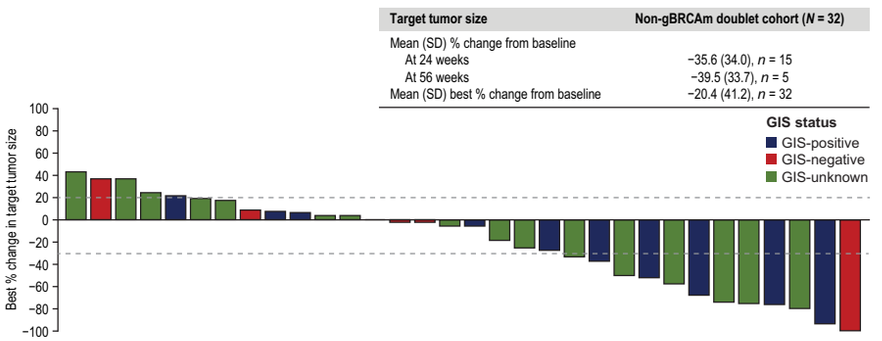

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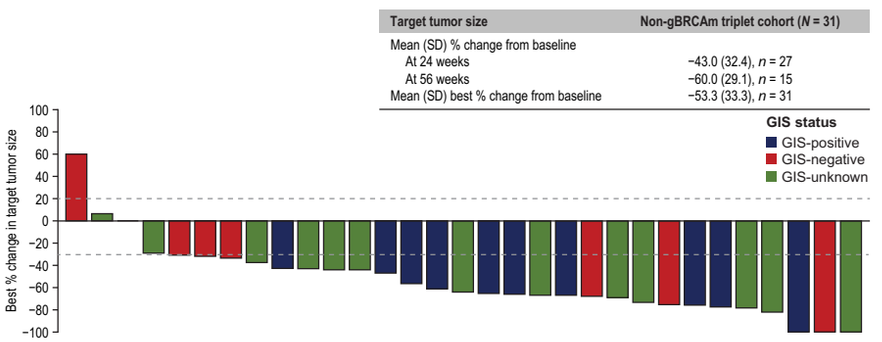

D

	Non-gBRCAm doublet cohort		Non-gBRCAm triplet cohort	
GIS* subgroup	ORR (95% CI), %	*n/N* patients	ORR (95% CI), %	*n/N* patients
GIS-positive	50.0 (18.7–81.3)	5/10	100.0 (69.2–100.0)	10/10
GIS-negative	16.7 (0.4–64.1)	1/6	75.0 (34.9–96.8)	6/8
GIS-unknown	31.3 (11.0–58.7)	5/16	84.6 (54.6–98.1)	11/13

E

gBRCAm expansion doublet cohort (*N* = 51)		Non-gBRCAm doublet cohort (*N* = 32)		Non-gBRCAm triplet cohort (*N* = 31)	
PD-L1 staining	ORR (%)†	PD-L1 staining	ORR (%)†	PD-L1 staining	ORR (%)†
Tumor cells					
<1% (*N* = 34)	30 (88.2)	<1% (*N* = 20)	7 (35.0)	<1% (*N* = 21)	17 (81.0)
≥1% (*N* = 12)	12 (100)	≥1% (*N* = 8)	3 (37.5)	≥1% (*N* = 6)	6 (100)
Immune cells					
<1% (*N* = 14)	13 (92.9)	<1% (*N* = 12)	5 (41.7)	<1% (*N* = 8)	7 (87.5)
≥1% (*N* = 32)	29 (90.6)	≥1% (*N* = 16)	5 (31.3)	≥1% (*N* = 19)	16 (84.2)

Figure 2.

Percentage change from baseline in target tumor size in the (**A**) gBRCAm expansion doublet cohort, (**B**) non-gBRCAm doublet cohort and (**C**) non-gBRCAm triplet cohort, (**D**) ORR by GIS in non-gBRCAm doublet and triplet cohorts and (**E**) ORR by PD-L1 status in the gBRCAm expansion doublet cohort and non-gBRCAm doublet and triplet cohorts. Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. The best change is displayed for each patient, by descending percentage change. Dashed reference lines at −30% and 20% indicate RECIST thresholds for partial response and progressive disease, respectively. Values greater than 100% or less than −100% are displayed as 100% and −100%, respectively. *Determined by Foundation Medicine Inc. (Cambridge, MA) tumor analysis: GIS-positive is defined as genome-wide LOH ≥ 14, sBRCAm, or a mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, or *RAD54L*. At the time of analysis, the cutoff for genome-wide LOH was 14% (35). GIS-negative is defined as genome-wide LOH < 14, no sBRCAm and no mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, or *RAD54L*. GIS-unknown status is due to sample not being analyzable (i.e., poor quality, technical failure, or inadequate tissue). †Percentages for ORR are based on the number of patients in that tumor cell or immune cell expression category. BRCAm, *BRCA1* and/or *BRCA2* mutation; gBRCAm, germline BRCAm; GIS, genomic instability status; sBRCAm, somatic BRCAm; SD, standard deviation.

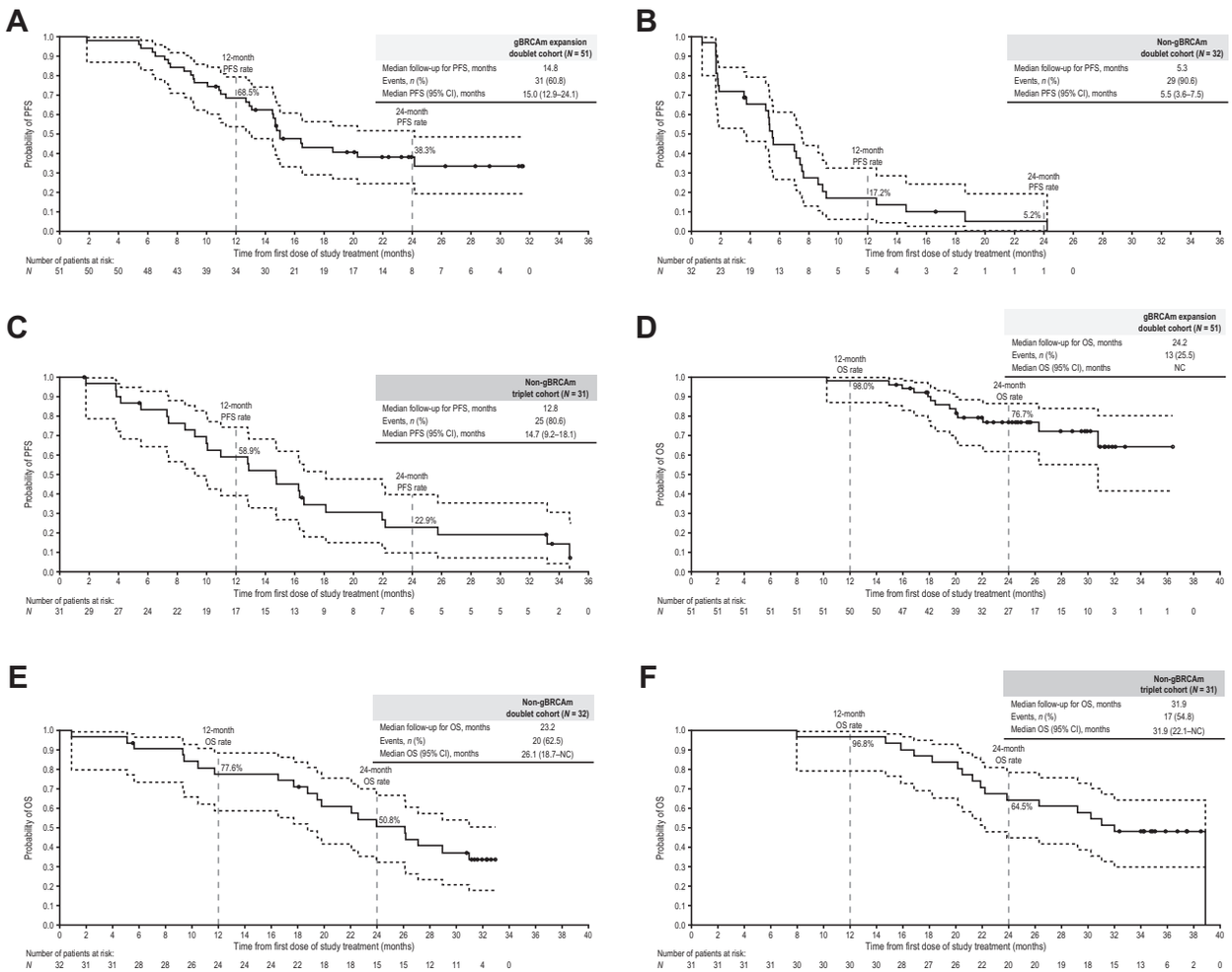

Figure 3.

Kaplan–Meier estimates of PFS in the (**A**) gBRCAm expansion doublet cohort, (**B**) non-gBRCAm doublet cohort and (**C**) non-gBRCAm triplet cohort, and OS in the (**D**) gBRCAm expansion doublet cohort, (**E**) non-gBRCAm doublet cohort and (**F**) non-gBRCAm triplet cohort. Dashed lines represent 95% CIs. **A–C,** Progression events that occurred after two or more missed visits, or within two visits of baseline where the patient had no evaluable visits or did not have a baseline assessment, were censored. **D–F,** Patients who had not died were censored at their last known alive date. gBRCAm, germline *BRCA1* and/or *BRCA2* mutation; NC, not calculable.

A very high ORR (92.2%) was observed with olaparib plus durvalumab doublet in patients with a gBRCAm, with CR in over 40% of patients. The non-randomized design and absence of an olaparib-only control cohort limits interpretation of these findings. An ORR (assessed by blinded independent central review) of 84.6% was previously reported with olaparib monotherapy in patients with gBRCAm PSROC and two prior lines of chemotherapy in a *post hoc* analysis of the phase III SOLO3 trial (36). In the phase III ARIEL2 trial, an ORR of 80% was seen with rucaparib treatment in the subgroup of PSROC patients with a BRCAm (35), although comparisons across trials should be made with caution given differences in study design and patient populations (e.g., 86.3% of patients in the gBRCAm expansion doublet cohort of MEDIOLA had received one prior line of chemotherapy compared with 42.5% of patients in ARIEL2). While PARP inhibitor approvals in first-line gBRCAm ovarian cancer have resulted in fewer PARP inhibitor-naïve patients who may benefit from olaparib plus durvalumab treatment in the recurrent setting, these data suggest olaparib plus durvalumab may be an effective treatment option for patients with gBRCAm, although the contribution of durvalumab to these findings remains uncertain.

Olaparib plus durvalumab doublet demonstrated modest activity in women with non-gBRCAm PSROC, while olaparib plus durvalumab and bevacizumab triplet demonstrated high-level, durable efficacy in women with non-gBRCAm PSROC. While an olaparib plus bevacizumab cohort may have provided additional insight into these targeted chemotherapy-sparing combinations, the benefit with the addition of bevacizumab encourages further evaluation of this triplet combination that also demonstrated a manageable safety profile.

It should be noted that across the MEDIOLA second-stage ovarian cancer cohorts, the primary efficacy endpoint differed between the gBRCAm expansion doublet cohort (ORR) and the non-gBRCAm cohorts (DCR at 24 weeks). This is because the purpose of the gBRCAm expansion cohort was to confirm the signal that had been observed in the gBRCAm ovarian cancer initial cohort for which the

Table 3. Summary of AEs.

Patient with AE	gBRCAm expansion doublet (*N* = 51), *n* (%)	Non-gBRCAm doublet (*N* = 32), *n* (%)	Non-gBRCAm triplet (*N* = 31), *n* (%)
Any-grade AE[a]	51 (100.0)	32 (100.0)	31 (100.0)
Hematologic			
Anemia[b]	26 (51.0)	13 (40.6)	18 (58.1)
Non-hematologic			
Nausea	34 (66.7)	28 (87.5)	23 (74.2)
Fatigue/asthenia	34 (66.7)	22 (68.8)	17 (54.8)
Constipation	21 (41.2)	8 (25.0)	9 (29.0)
Vomiting	20 (39.2)	5 (15.6)	16 (51.6)
Diarrhea	17 (33.3)	14 (43.8)	12 (38.7)
Abdominal pain	16 (31.4)	6 (18.8)	8 (25.8)
Dyspnea	13 (25.5)	4 (12.5)	4 (12.9)
Decreased appetite	10 (19.6)	9 (28.1)	12 (38.7)
Headache	8 (15.7)	7 (21.9)	11 (35.5)
Urinary tract infection	8 (15.7)	6 (18.8)	9 (29.0)
Arthralgia	6 (11.8)	8 (25.0)	9 (29.0)
Hypertension	4 (7.8)	2 (6.3)	8 (25.8)
Proteinuria	0	0	9 (29.0)
Grade ≥ 3 AE[c]	24 (47.1)	21 (65.6)	19 (61.3)
Hematologic			
Anemia[b]	7 (13.7)	7 (21.9)	6 (19.4)
Neutropenia[d]	3 (5.9)	5 (15.6)	3 (9.7)
Decreased WBC count	0	0	2 (6.5)
Non-hematologic			
Hypertension	2 (3.9)	1 (3.1)	5 (16.1)
Abdominal pain	2 (3.9)	1 (3.1)	0
Fatigue/asthenia	1 (2.0)	2 (6.3)	3 (9.7)
Increased lipase	0	2 (6.3)	2 (6.5)
AEs of special interest for olaparib			
MDS/AML[e]	0	0	1 (3.2)
New primary malignancies[e]	0	0	0
Pneumonitis	2 (3.9)	1 (3.1)	0
Immune-mediated AEs	15 (29.4)	5 (15.6)	11 (35.5)
AEs leading to discontinuation of any study treatment[f,g]	8 (15.7)	1 (3.1)	10 (32.3)
Olaparib[g]	6 (11.8)	1 (3.1)	4 (12.9)
Durvalumab[g]	7 (13.7)	1 (3.1)	5 (16.1)
Bevacizumab[g]	–	–	9 (29.0)

Abbreviations: gBRCAm, germline *BRCA1* and/or *BRCA2* mutation; WBC, white blood cell.

[a]Data are shown for treatment-emergent AEs that occurred in ≥25% of patients in any cohort during study treatment or up to 90 days after discontinuation of study treatment. AEs were monitored using the NCI's Common Terminology Criteria for Adverse Events (version 4.03).

[b]Includes patients with anemia, decreased hemoglobin level, decreased hematocrit, decreased red cell count, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, or normocytic anemia.

[c]Data are shown for treatment-emergent grade ≥ 3 AEs that occurred in ≥ 2 patients in any cohort during study treatment or up to 90 days after discontinuation of study treatment.

[d]Includes patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, or agranulocytosis.

[e]Includes cases reported beyond the 90-day safety follow-up period.

[f]Discontinuation of olaparib, durvalumab, or bevacizumab; patients who discontinued more than one study treatment are only counted once.

[g]Patients with multiple AEs leading to discontinuation are counted once for each preferred term. Patients who discontinued one or more study treatment(s) could continue to receive the remaining study treatment(s).

primary endpoint was DCR at 12 weeks (22). For this reason, ORR was selected as the primary endpoint for the gBRCAm expansion doublet cohort. By contrast, the objective in the non-gBRCAm cohorts was to determine whether combination therapy had activity in a different population and the primary efficacy endpoint was DCR at 24 weeks.

Biomarker status was unavailable for 50.0% and 41.9% of patients in the non-gBRCAm doublet and triplet cohorts, respectively. Some of these patients may have had undetected somatic BRCAm, which may have influenced outcomes. Although subgroups were small, triplet therapy showed activity in all genomic instability and PD-L1 subgroups in patients with non-gBRCAm PSROC with ORRs of 100% in patients who were genomic instability status-positive or who had PD-L1 tumor cell expression of ≥ 1%. An exploratory *post hoc* analysis in the non-gBRCAm cohorts revealed high ORRs with the triplet combination regardless of genomic instability status, with an ORR of

75.0% in patients who tested negative for genomic instability. These findings warrant confirmation in a larger population.

Initial treatment with PARP inhibitors alone previously showed activity in patients with gBRCA-mutated PSROC (36, 37) as well as in patients without a BRCAm (35, 38–40). For example, in the phase II LIGHT study evaluating initial treatment with olaparib alone, ORR (primary endpoint) was 29.4% and 10.1% in patients with non-gBRCAm PSROC whose tumors tested HRD-positive and HRD-negative, respectively, with median PFS of 7.2 and 5.4 months, respectively (38). Combination therapies are under evaluation to determine whether PARP inhibitor activity can be improved further in non-gBRCAm ovarian cancer.

Addition of bevacizumab to chemotherapy is a standard treatment option for patients with PSROC, including those without a BRCAm. However, the ATLANTE/ov29 study evaluating the immune checkpoint inhibitor atezolizumab plus chemotherapy with or without bevacizumab in PSROC did not meet its co-primary PFS endpoints (41). Augmentation of PARP inhibitor monotherapy by antiangiogenic agents has been investigated previously. Initial treatment with a PARP inhibitor plus an antiangiogenic agent improved outcomes versus a PARP inhibitor alone in patients with PSROC, including in patients without a BRCAm (30–32). However, olaparib plus the antiangiogenic agent cediranib did not improve outcomes versus platinum-based chemotherapy in patients with PSROC, although PFS benefit was seen in the gBRCAm subgroup (42).

Olaparib plus durvalumab and bevacizumab is a combination of growing interest. The single-arm phase II GINECO BOLD trial reported DCR at 6 months of 44% in patients with PSROC receiving olaparib plus durvalumab and bevacizumab, with a median PFS of 4.9 months and median OS of 18.5 months (43). Differences in study design and patient characteristics may account for the outcomes seen with the triplet in GINECO BOLD versus MEDIOLA. For example, 52% of patients in GINECO BOLD had prior PARP inhibitor therapy (43). In the first-line setting, the phase III DUO-O study demonstrated that the combination of durvalumab with platinum-based chemotherapy plus bevacizumab, followed by maintenance olaparib, durvalumab, and bevacizumab provided a statistically significant and clinically meaningful PFS benefit over platinum-based chemotherapy plus bevacizumab in patients with newly diagnosed advanced ovarian cancer without a tumor BRCAm (44). Longer-term results from DUO-O, including OS data, are awaited with interest.

In MEDIOLA, the safety profile of olaparib plus durvalumab, with or without bevacizumab, was consistent with the known safety profiles of the three individual agents, and no new safety signals were identified. A higher rate of AEs leading to discontinuation of any study treatment was seen in the non-gBRCAm triplet cohort (32.3%) versus either the gBRCAm expansion doublet (15.7%) or the non-gBRCAm doublet (3.1%) cohorts. This was driven by AEs resulting in bevacizumab discontinuation (29.0%), most commonly proteinuria (12.9%), noting, however, that in the triplet cohort more discontinuations due to AEs occurred after 24 weeks (7 after 24 weeks vs. 3 prior to 24 weeks; Supplementary Appendix). The higher rates in the non-gBRCAm triplet and gBRCAm expansion doublet cohorts than in the non-gBRCAm doublet cohort were also likely reflective of the longer treatment duration. The bevacizumab discontinuation rate was numerically higher than observed in other bevacizumab trials [e.g., bevacizumab discontinuation rates were 19% due to treatment-related AEs in patients with PSROC receiving niraparib plus bevacizumab in AVANOVA2 (32) and 20% due to treatment-emergent AEs in patients with PSROC receiving chemotherapy plus bevacizumab in OCEANS (18)], although comparisons between trials should be made with caution because of differences in study design and patient populations.

These reported MEDIOLA ovarian cancer cohorts were restricted to patients with PSROC and 1–2 prior lines of chemotherapy, and clinical outcomes appeared similar regardless of number of prior lines of therapy (Supplementary Fig. S3A and S3B). Recently, despite initial positive efficacy data (36, 40, 45), indications for monotherapy with rucaparib (46), olaparib (47), and niraparib (48) in the late-line treatment setting of patients with (g)BRCAm or HRD-positive (niraparib only) ovarian cancer have been voluntarily withdrawn in the United States, prompted by potential detrimental OS results from the final OS analysis of ARIEL4 (49) and *post hoc* final OS subgroup analyses of SOLO3 (50). The ARIEL4 final OS analysis indicated potential OS detriment with rucaparib versus chemotherapy, although this was mainly driven by results in patients with platinum resistance (49). In a *post hoc* subgroup analysis of SOLO3 by line of prior therapy, OS favored olaparib over non-platinum chemotherapy in patients with two prior lines of chemotherapy; however, a potential detrimental effect was observed in patients with three or more prior lines of chemotherapy (50). It should be noted that neither trial was powered to assess between-group differences in OS. These recent changes to the late-line relapsed ovarian cancer treatment setting emphasize the need for novel treatment options or combinations.

MEDIOLA was a signal-seeking study for combination therapy. Limitations include the non-randomized design, as the non-gBRCAm cohorts cannot be directly compared, and lower than planned recruitment into the gBRCAm expansion cohort. Furthermore, lack of olaparib monotherapy and olaparib plus bevacizumab cohorts preclude evaluation of the contribution of components, and small patient numbers present challenges in interpreting subgroup data. It should also be noted that patients enrolled in MEDIOLA were predominantly white or Asian. Despite these limitations, the promising results observed with olaparib combination therapy lay the foundation for further investigation. In particular, the high-level, durable efficacy seen with the olaparib plus durvalumab and bevacizumab triplet in the non-gBRCAm cohort would need to be confirmed in a larger randomized controlled trial in the PSROC setting. The triplet regimen appeared to have activity in all genomic instability and PD-L1 subgroups and it would be important to investigate in a larger study any putative biomarkers for response to better select patients for the olaparib plus durvalumab and bevacizumab triplet.

In summary, olaparib plus durvalumab continued to show notable clinical activity in women with gBRCAm PSROC. Olaparib plus durvalumab and bevacizumab demonstrated encouraging clinical activity in women with non-gBRCAm PSROC. The safety profile of olaparib plus durvalumab, with or without bevacizumab, was consistent with that expected for the individual agents and no new safety signals were identified. Findings warrant further investigation of combination therapies for patients with non-gBRCAm ovarian cancer.

Authors' Disclosures

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