

ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

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ABSTRACT

BACKGROUND

Olaparib has shown significant clinical benefit as maintenance therapy in women with newly diagnosed advanced ovarian cancer with a *BRCA* mutation. The effect of combining maintenance olaparib and bevacizumab in patients regardless of *BRCA* mutation status is unknown.

METHODS

We conducted a randomized, double-blind, international phase 3 trial. Eligible patients had newly diagnosed, advanced, high-grade ovarian cancer and were having a response after first-line platinum–taxane chemotherapy plus bevacizumab. Patients were eligible regardless of surgical outcome or *BRCA* mutation status. Patients were randomly assigned in a 2:1 ratio to receive olaparib tablets (300 mg twice daily) or placebo for up to 24 months; all the patients received bevacizumab at a dose of 15 mg per kilogram of body weight every 3 weeks for up to 15 months in total. The primary end point was the time from randomization until investigator-assessed disease progression or death.

RESULTS

Of the 806 patients who underwent randomization, 537 were assigned to receive olaparib and 269 to receive placebo. After a median follow-up of 22.9 months, the median progression-free survival was 22.1 months with olaparib plus bevacizumab and 16.6 months with placebo plus bevacizumab (hazard ratio for disease progression or death, 0.59; 95% confidence interval [CI], 0.49 to 0.72; $P < 0.001$). The hazard ratio (olaparib group vs. placebo group) for disease progression or death was 0.33 (95% CI, 0.25 to 0.45) in patients with tumors positive for homologous-recombination deficiency (HRD), including tumors that had *BRCA* mutations (median progression-free survival, 37.2 vs. 17.7 months), and 0.43 (95% CI, 0.28 to 0.66) in patients with HRD-positive tumors that did not have *BRCA* mutations (median progression-free survival, 28.1 vs. 16.6 months). Adverse events were consistent with the established safety profiles of olaparib and bevacizumab.

CONCLUSIONS

In patients with advanced ovarian cancer receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib provided a significant progression-free survival benefit, which was substantial in patients with HRD-positive tumors, including those without a *BRCA* mutation. (Funded by ARCADY Research and others; PAOLA-1 ClinicalTrials.gov number, NCT02477644.)

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*A list of the PAOLA-1 principal investigators is provided in the Supplementary Appendix, available at NEJM.org.

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NEWLY DIAGNOSED ADVANCED OVARIAN cancer is treated with curative intent. However, owing to late diagnosis with advanced-stage disease, the vast majority of patients have a relapse (after a median of 10 to 18 months),^{1,2} despite being treated with cytoreductive surgery and platinum-based chemotherapy.³

The addition of the antiangiogenic agent bevacizumab to carboplatin plus paclitaxel, followed by bevacizumab alone, is a standard option in patients with newly diagnosed advanced ovarian cancer.^{1,2,4-7} Recently, in the phase 3 SOLO1 trial, the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib provided a substantial progression-free survival benefit as maintenance monotherapy in patients with newly diagnosed advanced ovarian cancer whose tumors had a *BRCA1* or *BRCA2* mutation (*BRCA* mutation) and who had a complete or partial clinical response after platinum-based chemotherapy (hazard ratio for disease progression or death, 0.30; 95% confidence interval [CI], 0.23 to 0.41; $P < 0.001$).⁸

PARP inhibitors trap PARP on DNA at sites of single-strand breaks, preventing the repair of these breaks and generating double-strand breaks that cannot be repaired accurately in tumors with homologous-recombination deficiency (HRD).⁹ HRD is not limited to tumors with *BRCA* mutations and is present in approximately 50% of high-grade serous ovarian tumors.¹⁰ Indeed, in platinum-sensitive relapsed ovarian cancer,¹¹⁻¹³ PARP inhibitors are active as maintenance monotherapy in patients who have tumors without *BRCA* mutations, although the magnitude of benefit appears lower than in patients with *BRCA*-mutated tumors. Moreover, the addition of an antiangiogenic agent to a PARP inhibitor in phase 2 studies involving patients with relapsed platinum-sensitive ovarian cancer¹⁴⁻¹⁶ resulted in longer progression-free survival than the use of a PARP inhibitor alone. In the phase 3 PAOLA-1 (PAOLA-1/ENGOT-ov25) trial, we evaluated maintenance therapy with a PARP inhibitor (olaparib) as compared with placebo in patients with newly diagnosed advanced ovarian cancer who were receiving chemotherapy plus bevacizumab followed by bevacizumab, regardless of *BRCA* mutation status.

METHODS

PATIENTS

Eligible patients were 18 years of age or older and had newly diagnosed advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV), high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer. (For details on the FIGO staging system, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Patients with other nonmucinous epithelial ovarian cancers were eligible, provided they had a deleterious germline *BRCA1* or *BRCA2* mutation. Patients were eligible irrespective of previous surgical outcome (residual macroscopic disease or no residual macroscopic disease after upfront or interval surgery). After first-line treatment with platinum-taxane chemotherapy plus bevacizumab, patients were required to have no evidence of disease or to have had a clinical complete or partial response (definitions in Table 1). Patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 (on a 5-point scale in which higher numbers reflect greater disability), and a tumor sample had to be available for central testing to determine *BRCA* mutation status. Details of *BRCA* testing and full eligibility criteria are provided in the Supplementary Appendix. All the patients provided written informed consent.

TRIAL DESIGN AND INTERVENTION

The randomized, double-blind, placebo-controlled PAOLA-1 trial was conducted in 11 countries. Randomization was performed centrally with the use of a block design with stratification according to the outcome of first-line treatment at screening and tumor *BRCA* status (see the Supplementary Appendix). Patients were assigned to olaparib tablets or matching placebo tablets with the use of an interactive Web or voice response system.

Patients were randomly assigned in a 2:1 ratio to receive olaparib (300 mg twice daily) or placebo at least 3 weeks and no more than 9 weeks after the last dose of chemotherapy. All the major toxic effects that were associated with chemotherapy had to have resolved to grade 1 (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE],

Table 1. Characteristics of the Patients at Baseline.*		
Characteristic	Olaparib plus Bevacizumab (N=537)	Placebo plus Bevacizumab (N=269)
Median age (range) — yr	61.0 (32.0–87.0)	60.0 (26.0–85.0)
ECOG performance status — no. (%)†		
0	378 (70)	189 (70)
1	153 (28)	76 (28)
Missing data	6 (1)	4 (1)
Primary tumor location — no. (%)		
Ovary	456 (85)	238 (88)
Fallopian tube	39 (7)	11 (4)
Peritoneum	42 (8)	20 (7)
FIGO stage — no. (%)‡		
III	378 (70)	186 (69)
IV	159 (30)	83 (31)
Histologic type — no. (%)		
Serous	519 (97)	253 (94)
Endometrioid	12 (2)	8 (3)
Other§	6 (1)	8 (3)
History of cytoreductive surgery		
Upfront — no. (%)	271 (50)	138 (51)
Macroscopic residual disease — no./total no. (%)	111/271 (41)	53/138 (38)
No macroscopic residual disease — no./total no. (%)	160/271 (59)	85/138 (62)
Interval — no. (%)	228 (42)	110 (41)
Macroscopic residual disease — no./total no. (%)	65/228 (29)	35/110 (32)
No macroscopic residual disease — no./total no. (%)	163/228 (71)	75/110 (68)
No surgery — no. (%)	38 (7)	21 (8)
Response after first-line chemotherapy — no. (%)		
No evidence of disease¶	290 (54)	141 (52)
Complete response	106 (20)	53 (20)
Partial response**	141 (26)	75 (28)
Normal serum CA-125 level — no. (%)		
Yes	463 (86)	234 (87)
No	74 (14)	34 (13)
Missing	0	1 (<1)
Deleterious tumor BRCA mutation — no. (%)		
Yes	161 (30)	80 (30)
No	376 (70)	189 (70)
Tumor HRD status — no. (%)††		
Positive	255 (47)	132 (49)
Negative or unknown	282 (53)	137 (51)
Negative	192 (36)	85 (32)
Unknown	90 (17)	52 (19)

Table 1. (Continued.)

- * Percentages may not total 100 because of rounding. CA-125 denotes cancer antigen 125, and HRD homologous-recombination deficiency.
- † Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with higher values reflecting greater disability.
- ‡ Details on the International Federation of Gynecology and Obstetrics (FIGO) staging system are provided in Table S1 in the Supplementary Appendix.
- § “Other” was defined as clear-cell (in 2 patients assigned to olaparib plus bevacizumab), undifferentiated (in 1 patient assigned to olaparib plus bevacizumab and 6 patients assigned to placebo plus bevacizumab), or other (in 3 patients assigned to olaparib plus bevacizumab and 2 patients assigned to placebo plus bevacizumab).
- ¶ No evidence of disease was defined as no measurable or assessable disease after cytoreductive surgery plus no radiologic evidence of disease and a normal CA-125 level after chemotherapy.
- || Clinical complete response was defined as the disappearance of all measurable or assessable disease and normalization of CA-125 levels.
- ** Partial response was defined as radiologic evidence of disease, an abnormal CA-125 level, or both.
- †† HRD positive was defined as a tumor *BRCA* mutation or an HRD score of 42 or higher on the myChoice HRD Plus assay (Myriad Genetic Laboratories). HRD negative was defined as an HRD score of less than 42. “Unknown” was defined as an inconclusive, missing, or failed test.

version 4.03) or had to have resolved completely (except alopecia and peripheral neuropathy).

Administration of olaparib or placebo continued for up to 24 months from randomization or until disease progression (according to investigators' assessment of imaging based on the modified Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1) or unacceptable toxic effects, whichever occurred first, as long as the patient had a benefit and did not meet other discontinuation criteria. Crossover between the trial groups was not planned. After discontinuation of the intervention, patients could receive other treatments at the investigators' discretion. Details of discontinuation criteria and methods for unblinding are provided in the Supplementary Appendix. As part of the intervention, intravenous bevacizumab was initiated in combination with chemotherapy and was continued after randomization as maintenance therapy at a dose of 15 mg per kilogram of body weight every 3 weeks for a total duration of up to 15 months.

END POINTS AND ASSESSMENTS

The primary end point was the time from randomization until investigator-assessed disease progression or death. Tumor assessment scans (computed tomography or magnetic resonance imaging) were performed at baseline and then every 24 weeks (or at planned visits every 12 weeks if there was evidence of clinical progression or progression according to the serum level of cancer antigen 125) up to month 42 or until the date of data cutoff. Subgroup analyses of

progression-free survival and a blinded independent central review of progression-free survival were performed.

Secondary end points were the time from randomization until second disease progression or death, overall survival, the time until the first subsequent therapy or death, and the global health status–quality of life dimension of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30; scores range from 0 to 100, with higher scores indicating better health-related quality of life and with a minimal clinically important difference defined as 10 points).¹⁷ The EORTC QLQ-C30 was completed at baseline and then every 12 weeks for 2 years or until the date of data cutoff. Adverse events were graded with the use of the CTCAE, version 4.03. Tumor HRD status was determined with the use of the myChoice HRD Plus assay (Myriad Genetic Laboratories). An HRD score of 42 or higher indicated a positive test, and an HRD score of less than 42 indicated a negative test. Details of trial end points and analyses are provided in the Supplementary Appendix.

TRIAL OVERSIGHT

The trial was performed in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines under the auspices of an independent data monitoring committee. The trial was designed by the European Network for Gynecological Oncological Trial Groups (ENGOT) lead group, Groupe d'Investi-

gateurs Nationaux pour l'Etude des Cancers Ovariens, and sponsored by Association de Recherche Cancers Gynécologiques (ARCAGY) Research, according to the ENGOT model A (academic sponsor; details of this research model are provided in the Supplementary Appendix).^{18,19} ARCAGY Research was responsible for overseeing the collection, analysis, and interpretation of the data. AstraZeneca, Merck Sharp & Dohme (a subsidiary of Merck), and F. Hoffmann–La Roche were given the opportunity to review drafts of the manuscripts but were not asked to approve the final content because this was an academic-sponsored trial. The authors wrote the manuscript, with medical writing assistance funded by ARCAGY Research, AstraZeneca, and Merck Sharp & Dohme. The authors attest to the accuracy and completeness of the data and to the adherence of the trial to the protocol (available at NEJM.org).

STATISTICAL ANALYSIS

The trial was designed to detect a treatment effect (hazard ratio for disease progression or death) of 0.75, translating to an improvement in median progression-free survival from 15.8 months in the placebo group to 21.1 months in the olaparib group²⁰; 458 primary end-point events (disease progression or death) would give the trial more than 80% power at a two-sided significance level of 5% to show a significant difference in progression-free survival between the olaparib group and the placebo group. The randomization of 762 patients would result in data being mature once approximately 60% of the patients had had disease progression or had died; an additional 24 patients underwent randomization in Japan.

All efficacy data were summarized and analyzed in the intention-to-treat population, which included all the patients who had undergone randomization, regardless of the intervention received. In this analysis, we used the electronic case-report form data set, except for the prespecified HRD analysis, which used the Myriad myChoice Plus HRD test. Safety data were summarized in the safety analysis set (all patients who received at least one dose of olaparib or placebo). Analyses of health-related quality of life used an imputation-based approach for missing questionnaires.

The Kaplan–Meier method was used to estimate progression-free survival, with the strati-

fied log-rank test used to assess the difference between the olaparib group and the placebo group. The hazard ratio and associated 95% confidence interval were calculated with the use of a stratified Cox proportional-hazards model. In order to show consistency of the treatment effect in prespecified subgroups, a preplanned progression-free survival analysis was performed in which the hazard ratio and 95% confidence interval were calculated with the use of an unstratified Cox model.

Analyses of secondary efficacy end points used a method similar to that used in the progression-free survival analysis. A hierarchical-testing procedure was used to control for type I error at 5% for progression-free survival, second progression-free survival, and overall survival, in that order.

The change from baseline in the global health status–quality of life score was assessed with the use of a mixed model for repeated measures.²¹ Adverse events were analyzed descriptively; an interim safety analysis was planned and conducted. Details of the statistical analyses are provided in the Supplementary Appendix. The statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

PATIENTS

From July 2015 through September 2017, a total of 806 patients underwent randomization. A total of 535 of the 537 patients assigned to olaparib plus bevacizumab (olaparib group) and 267 of the 269 patients assigned to placebo plus bevacizumab (placebo group) received the trial intervention; 2 patients in each group withdrew before receiving the trial intervention (Fig. S1).

The baseline characteristics were well balanced between the trial groups (Table 1 and Tables S2 through S4). A total of 30% of the patients had stage IV disease, and most patients had no evidence of disease owing to complete cytoreduction or were having a complete response after first-line treatment. A total of 30% of the patients had a deleterious tumor *BRCA* mutation.

EFFICACY

The primary analysis of investigator-assessed progression-free survival was performed after 474 of 806 patients had had disease progression or had died (data maturity, 59%) (data cutoff,

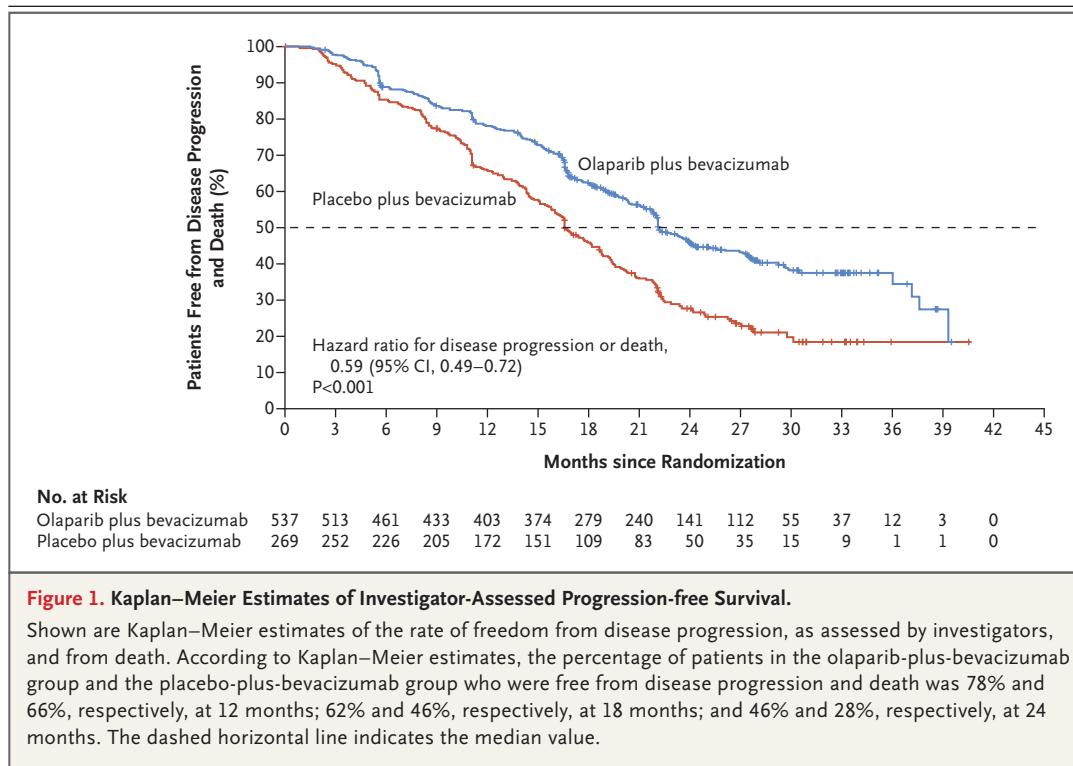


Figure 1. Kaplan–Meier Estimates of Investigator-Assessed Progression-free Survival.

Shown are Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by investigators, and from death. According to Kaplan–Meier estimates, the percentage of patients in the olaparib-plus-bevacizumab group and the placebo-plus-bevacizumab group who were free from disease progression and death was 78% and 66%, respectively, at 12 months; 62% and 46%, respectively, at 18 months; and 46% and 28%, respectively, at 24 months. The dashed horizontal line indicates the median value.

March 22, 2019). The median duration of follow-up for the primary analysis was 22.7 months (range, 18.0 to 27.7) in the olaparib group and 24.0 months (range, 18.7 to 27.7) in the placebo group; the median duration of follow-up in the combined groups was 22.9 months.

The duration of investigator-assessed progression-free survival was significantly longer in the olaparib group than in the placebo group (median, 22.1 months vs. 16.6 months; hazard ratio for disease progression or death, 0.59; 95% CI, 0.49 to 0.72; $P < 0.001$) (Fig. 1). Results of the analysis of progression-free survival as assessed by blinded independent review (Fig. S2) were consistent with the results of the primary analysis (median, 26.1 months in the olaparib group and 18.3 months in the placebo group; hazard ratio for disease progression or death, 0.63; 95% CI, 0.51 to 0.77). Results of subgroup analyses of progression-free survival showed a benefit in the majority of predefined subgroups (Fig. 2).

In patients with a tumor *BRCA* mutation, the median progression-free survival was 37.2 months in the olaparib group and 21.7 months in the placebo group (hazard ratio for disease progression or death, 0.31; 95% CI, 0.20 to 0.47) (Fig. 3A). In patients without a tumor *BRCA* mutation, the median progression-free survival was

18.9 months in the olaparib group and 16.0 months in the placebo group (hazard ratio for disease progression or death, 0.71; 95% CI, 0.58 to 0.88) (Fig. 3B).

In patients with tumors positive for HRD (tumor score of ≥ 42 on the myChoice HRD Plus assay or tumor *BRCA* mutation), the median progression-free survival was 37.2 months in the olaparib group and 17.7 months in the placebo group (hazard ratio for disease progression or death, 0.33; 95% CI, 0.25 to 0.45) (Fig. 3C). In patients with HRD-positive tumors that did not have *BRCA* mutations, the median progression-free survival was 28.1 months in the olaparib group and 16.6 months in the placebo group (hazard ratio for disease progression or death, 0.43; 95% CI, 0.28 to 0.66) (Fig. 3D).

In patients with HRD-negative tumors or whose tumor HRD status was unknown (total, 419 patients), the median progression-free survival was 16.9 months in the olaparib group and 16.0 months in the placebo group (hazard ratio for disease progression or death, 0.92; 95% CI, 0.72 to 1.17) (Fig. S3A). In patients with HRD-negative tumors (277 patients), the median progression-free survival was 16.6 months in the olaparib group and 16.2 months in the placebo group (hazard ratio for disease progression or

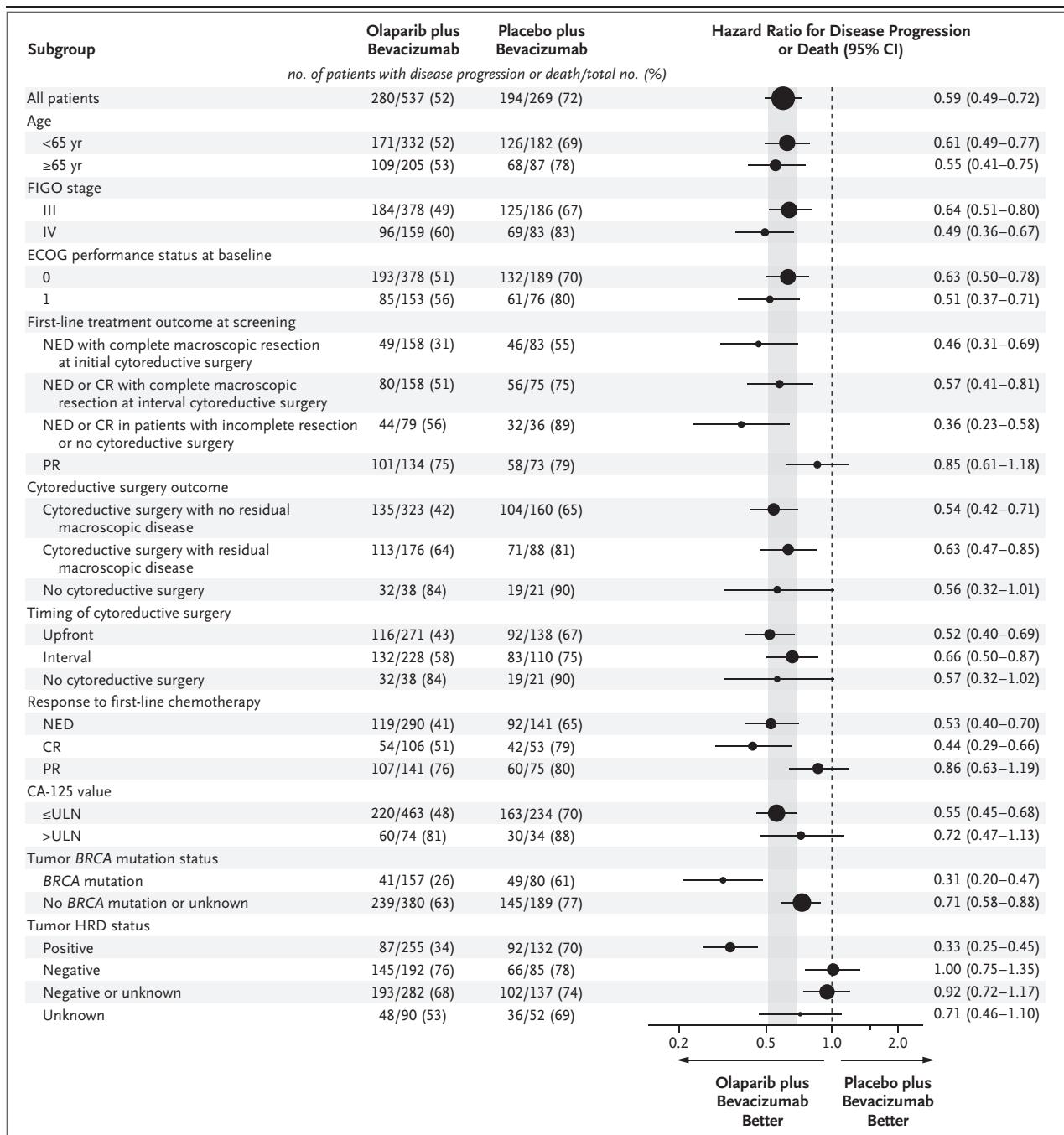


Figure 2. Subgroup Analysis of Progression-free Survival.

All subgroups presented here were predefined, except for two post hoc subgroups: homologous-recombination deficiency (HRD) negative or unknown and HRD unknown. The outcome of first-line treatment at screening was determined according to the electronic case-report form. For the hazard ratios, the size of the circle is proportional to the number of events. The gray band represents the 95% confidence interval for the overall population, and the dashed line indicates the point of no effect. CA-125 denotes cancer antigen 125, CR complete response, ECOG Eastern Cooperative Oncology Group, FIGO International Federation of Gynecology and Obstetrics, NED no evidence of disease, PR partial response, and ULN upper limit of the normal range.

death, 1.00; 95% CI, 0.75 to 1.35) (Fig. S3C). (Data for patients whose tumor HRD status was unknown are shown in Fig. S3B.)

The median time until the first subsequent treatment for all patients was 24.8 months in the olaparib group and 18.5 months in the placebo

group (hazard ratio, 0.59; 95% CI, 0.49 to 0.71). In an interim analysis of second progression-free survival (data maturity, 39%), the Kaplan-Meier estimate of the rate of freedom from second disease progression and death at 18 months was 79% in the olaparib group and 80% in the placebo group (hazard ratio, 0.86; 95% CI, 0.69 to 1.09) (Fig. S4). Overall survival data are immature.

SAFETY

The median duration of the randomized intervention was 17.3 months (range, 0.0 to 33.0) for olaparib and 15.6 months (range, 0.1 to 26.2) for placebo. The median duration of treatment with bevacizumab since randomization was 11.0 months (range, 0.7 to 21.4) in the olaparib group and 10.6 months (range, 0.7 to 17.1) in the placebo group.

The most common adverse events and the incidence of associated grade 3 or higher adverse events for the entire maintenance treatment period are shown in Table 2 and Table S5. The most common adverse events (all grades) that occurred at a higher incidence among patients receiving olaparib plus bevacizumab than among those receiving placebo plus bevacizumab were fatigue, nausea, and anemia (Table 2). The most common adverse event (all grades) that occurred at a higher incidence among patients receiving placebo plus bevacizumab than among those receiving olaparib plus bevacizumab was hypertension (Table 2). Serious adverse events occurred in 31% of the patients in both trial groups (Table S6). The most common serious adverse event that occurred at a higher incidence with olaparib plus bevacizumab than with placebo plus bevacizumab was anemia (34 patients [6%] in the olaparib group and 1 patient [$<1\%$] in the placebo group). The most common serious adverse event that occurred at a higher incidence with placebo plus bevacizumab than with olaparib plus bevacizumab was hypertension (35 patients [13%] in the placebo group and 48 patients [9%] in the olaparib group). Fatal adverse events occurred during the trial intervention or up to 30 days after discontinuation of the intervention in 1 of 535 patients ($<1\%$) in the olaparib group and in 4 of 267 patients (1%) in the placebo group. (Details of serious and fatal adverse events are provided in the Supplementary Appendix.)

Myelodysplastic syndromes, acute myeloid leukemia, or aplastic anemia occurred in 6 of 535

patients (1%) receiving olaparib plus bevacizumab and in 1 of 267 patients ($<1\%$) receiving placebo plus bevacizumab. New primary cancers occurred in 7 of 535 patients (1%) in the olaparib group and in 3 of 267 patients (1%) in the placebo group. Grade 1 or 2 pneumonitis, interstitial lung disease, or bronchiolitis occurred in 6 patients (1%) in the olaparib group and no patients in the placebo group.

Adverse events were usually managed by dose modification rather than discontinuation (Table 2). The most common adverse events leading to discontinuation of olaparib were anemia and nausea (Table S7).

Adverse events occurring only in the time period when bevacizumab was being administered as maintenance therapy are summarized in Table S8. Adverse events of special interest for bevacizumab (e.g., hypertension) are shown in Table S9.

HEALTH-RELATED QUALITY OF LIFE

The mean global health status-quality of life score at baseline was 68.6 in the olaparib group and 67.1 in the placebo group. The adjusted mean change from baseline was -1.33 points (95% CI, -2.47 to -0.19) in the olaparib group (498 patients) and -2.89 points (95% CI, -4.52 to -1.26) in the placebo group (246 patients) (Fig. S5). The estimated between-group difference was 1.56 points (95% CI, -0.42 to 3.55). None of these changes were considered to be clinically significant.

DISCUSSION

In the phase 3 PAOLA-1 trial, we evaluated maintenance therapy with the PARP inhibitor olaparib as compared with placebo in patients with newly diagnosed advanced ovarian cancer who were receiving chemotherapy and bevacizumab followed by bevacizumab. The trial met its primary objective by showing a significant progression-free survival benefit in the intention-to-treat population. The PAOLA-1 population was representative of the majority of patients with advanced ovarian cancer because patient selection was not restricted on the basis of surgical outcome or *BRCA* mutation status.

Prespecified subgroup analyses showed a progression-free survival benefit with olaparib in patients with *BRCA*-mutated and HRD-positive tumors. The results in patients with HRD-positive tumors without a *BRCA* mutation (comprising

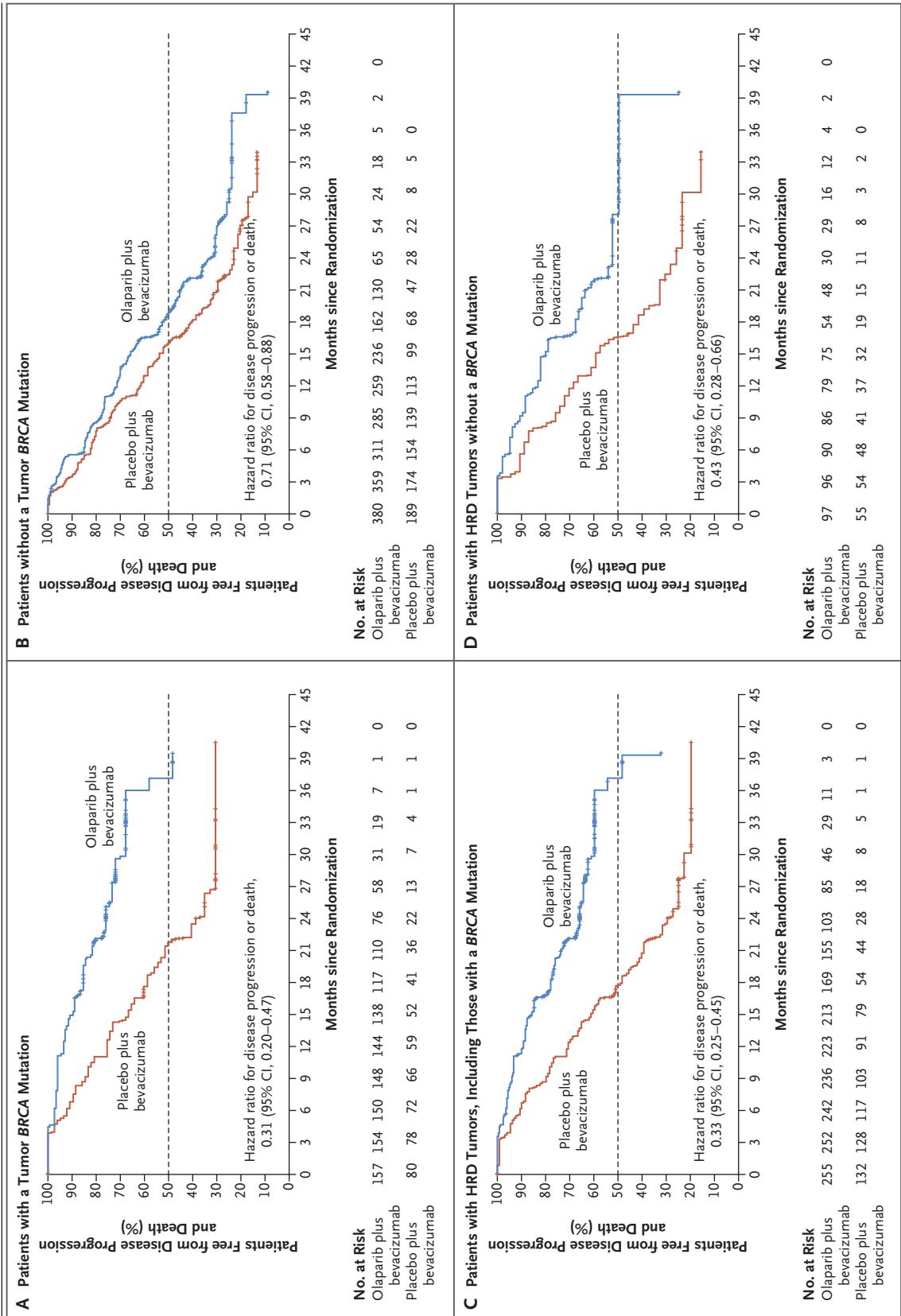


Figure 3 (facing page). Kaplan–Meier Estimates of Investigator-Assessed Progression-free Survival, According to Tumor BRCA Mutation Status and Homologous-Recombination Deficiency (HRD) Status.

Among the patients with a tumor *BRCA* mutation (prespecified subgroup analysis) (Panel A), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 76% in the olaparib-plus-bevacizumab group and 39% in the placebo-plus-bevacizumab group. Among the patients without a tumor *BRCA* mutation (prespecified subgroup analysis) (Panel B), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 33% in the olaparib-plus-bevacizumab group and 23% in the placebo-plus-bevacizumab group. Among the patients with HRD-positive tumors, as defined by a tumor HRD score of 42 or higher or a tumor *BRCA* mutation (prespecified subgroup analysis) (Panel C), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 66% in the olaparib-plus-bevacizumab group and 29% in the placebo-plus-bevacizumab group. Among the patients with HRD-positive tumors without a *BRCA* mutation (prespecified subgroup analysis) (Panel D), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 52% in the olaparib-plus-bevacizumab group and 26% in the placebo-plus-bevacizumab group. Tumor HRD status was determined for 82% of the tumor samples.

nearly 20% of the PAOLA-1 population, which is broadly consistent with expectations¹⁰ identify another patient population who had a substantial clinical benefit from olaparib. A benefit was also seen in patients whose tumor HRD status was unknown, such as those with failed tests or insufficient tumor samples.

In this trial, the progression-free survival benefit seen with olaparib plus bevacizumab in patients with *BRCA*-mutated tumors (hazard ratio for disease progression or death, 0.31; 95% CI, 0.20 to 0.47) is consistent with that observed in the SOLO1 trial (hazard ratio, 0.30; 95% CI, 0.23 to 0.41),⁸ despite the improved outcome of the control group in our trial (median progression-free survival, 21.7 months with placebo plus bevacizumab in the PAOLA-1 trial and 13.8 months with placebo in the SOLO1 trial), which may be due to the addition of bevacizumab or to differences in patient selection.²² Caution is needed when comparing outcomes between patients in the SOLO1 trial and patients with *BRCA*-mutated tumors in the PAOLA-1 trial because of differences between the two trials, including in base-

line characteristics (Table S3). Patients in the PAOLA-1 trial had a higher disease burden, with a lower percentage of patients undergoing upfront cytoreductive surgery (51%, vs. 63% in the SOLO1 trial) and a higher percentage of patients having residual macroscopic disease after cytoreductive surgery (35% vs. 22%) and stage IV disease (30% vs. 17%).

The lack of a maintenance olaparib monotherapy comparator group is a limitation of the PAOLA-1 trial, making it difficult to conclude whether the progression-free survival benefit seen in patients with HRD-positive tumors without *BRCA* mutations (who were not included in the SOLO1 trial) was due largely to the addition of olaparib or whether a synergistic effect occurred with olaparib and bevacizumab. According to preclinical data, hypoxia that is induced by an antiangiogenic treatment can induce, or at least increase, HRD,²³ which means that bevacizumab may increase the activity of olaparib in patients with HRD-positive tumors and, in particular, patients with HRD-positive tumors without a *BRCA* mutation; this hypothesis requires further exploration. Data regarding second progression-free survival and overall survival are currently immature. Although HRD subgroup analyses were prespecified, they were not part of the multiple-testing procedure for this trial.

The safety profile of the olaparib group in the PAOLA-1 trial was generally consistent with that reported for olaparib in the SOLO1 trial⁸ and in patients with relapsed disease (phase 3 SOLO2 trial),²⁴ with the notable exception of hypertension, a frequent toxic effect of bevacizumab, which was more common in the PAOLA-1 trial. The addition of olaparib to bevacizumab did not increase the known toxic effects associated with bevacizumab.

The incidence of myelodysplastic syndromes, acute myeloid leukemia, or aplastic anemia among patients with newly diagnosed disease in the PAOLA-1 trial (1% in the olaparib group and <1% in the placebo group) was similar to that reported in the SOLO1 trial⁸ and in trials involving patients with relapsed disease.^{12,13,24,25} Greater understanding and prospective registries are needed to determine the characteristics of patients at risk for these rare, but potentially fatal, hematologic disturbances.

Neither trial group had a clinically significant change in health-related quality of life. There

Table 2. Adverse Events with Olaparib or Placebo in Patients Also Receiving Bevacizumab.*

Event	Olaparib plus Bevacizumab (N=535)		Placebo plus Bevacizumab (N=267)	
	All Grades	Grade \geq 3 <i>number (percent)</i>	All Grades	Grade \geq 3
Any	531 (99)	303 (57)	256 (96)	136 (51)
Fatigue or asthenia	283 (53)	28 (5)	86 (32)	4 (1)
Nausea	285 (53)	13 (2)	58 (22)	2 (1)
Hypertension	245 (46)	100 (19)	160 (60)	81 (30)
Anemia†	219 (41)	93 (17)	27 (10)	1 (<1)
Lymphopenia‡	126 (24)	38 (7)	25 (9)	3 (1)
Arthralgia	116 (22)	3 (1)	64 (24)	4 (1)
Vomiting	117 (22)	8 (1)	29 (11)	5 (2)
Abdominal pain	103 (19)	8 (1)	53 (20)	5 (2)
Diarrhea	98 (18)	12 (2)	45 (17)	5 (2)
Neutropenia§	95 (18)	32 (6)	42 (16)	8 (3)
Leukopenia¶	95 (18)	10 (2)	26 (10)	4 (1)
Urinary tract infection	79 (15)	1 (<1)	27 (10)	1 (<1)
Headache	73 (14)	2 (<1)	36 (13)	2 (1)
Constipation	53 (10)	0	28 (10)	1 (<1)
Thrombocytopenia	42 (8)	9 (2)	9 (3)	1 (<1)
Proteinuria	31 (6)	5 (1)	40 (15)	1 (<1)
Leading to dose interruption	291 (54)	NA	65 (24)	NA
Leading to dose reduction	220 (41)	NA	20 (7)	NA
Leading to discontinuation of intervention	109 (20)	NA	15 (6)	NA

* Data are shown for adverse events that occurred in at least 10% of the patients in either trial group (except where noted) during the trial intervention or up to 30 days after discontinuation of the intervention. The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. NA denotes not available.

† The data include patients with anemia, a decreased hemoglobin level, a decreased hematocrit, a decreased red-cell count, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, or normocytic anemia.

‡ The data include patients with a decreased lymphocyte count, lymphopenia, a decreased B-lymphocyte count, or a decreased T-lymphocyte count.

§ The data include patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, a decreased neutrophil count, idiopathic neutropenia, granulocytopenia, a decreased granulocyte count, or agranulocytosis.

¶ The data include patients with leukopenia or a decreased white-cell count.

|| Thrombocytopenia occurred in less than 10% of the patients in each trial group, but the data are provided to complete the profile of hematologic toxic effects. The data include patients with thrombocytopenia, decreased platelet production, a decreased platelet count, or a decreased plateletcrit.

was no evidence of a meaningful difference in health-related quality of life between the trial groups.

Administering maintenance olaparib in addition to bevacizumab to patients with newly diagnosed advanced ovarian cancer who were receiving standard treatment including bevacizumab resulted in a significant progression-free survival benefit, with a substantial benefit in patients with HRD-positive tumors. Previously defined toxic effects of olaparib and bevacizumab were

noted, and rare serious hematologic and mild-to-moderate pulmonary toxic effects also occurred.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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REFERENCES

- Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011;365:2484-96.
- Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365:2473-83.
- Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24:Suppl 6:vi24-vi32.
- Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol* 2019;30:672-705.
- Karam A, Ledermann JA, Kim JW, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer Inter-Group: first-line interventions. *Ann Oncol* 2017;28:711-7.
- Tewari KS, Burger RA, Enserro D, et al. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. *J Clin Oncol* 2019; 37:2317-28.
- Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015;16:928-36.
- Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018;379:2495-505.
- O'Connor MJ. Targeting the DNA damage response in cancer. *Mol Cell* 2015;60: 547-60.
- Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011;474:609-15.
- Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol* 2014;15:852-61.
- Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016;375:2154-64.
- Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;390:1949-61.
- Mirza MR, Avall-Lundqvist E, Birrer MJ, et al. Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer: a randomized controlled chemotherapy-free study — NSGO-AVANOVA2/ENGOT-OV24. *J Clin Oncol* 2019;37:Suppl:5505. abstract.
- Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol* 2014;15:1207-14.
- Liu JF, Barry WT, Birrer M, et al. Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. *Ann Oncol* 2019;30:551-7.
- Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer* 2012;48:1713-21.
- Vergote I, Pujade-Lauraine E, Pignata S, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and pharmaceutical companies. *Int J Gynecol Cancer* 2010;20:476-8.
- du Bois A, Reuss A, Pujade-Lauraine E, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and industry partners — first update 2015. *Int J Gynecol Cancer* 2015;25:1328-30.
- Herzog TJ, Armstrong DK, Brady MF, et al. Ovarian cancer clinical trial endpoints: Society of Gynecologic Oncology white paper. *Gynecol Oncol* 2014;132: 8-17.
- Nnaan A, Laird NM, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med* 1997;16:2349-80.
- Norquist BM, Brady MF, Harrell MI, et al. Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: an NRG Oncology/Gynecologic Oncology Group study. *Clin Cancer Res* 2018;24:777-83.
- Chan N, Pires IM, Bencokova Z, et al. Contextual synthetic lethality of cancer cell kill based on the tumor microenvironment. *Cancer Res* 2010;70:8045-54.
- Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18:1274-84.
- Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol* 2016;17:1579-89.

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