"Latest Advancements in Ovarian Cancer: The Role of Olaparib in Management".

Module III

Clinical Efficacy of Olaparibin Ovarian Cancer

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Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

Introduction

Standard therapy for patients with newly diagnosed advanced ovarian cancer consists of cytoreductive surgery and platinum-based chemotherapy.1,2 Although the majority of such patients have no evidence of disease after treatment, approximately 70% have a relapse within the subsequent 3 years.2 Recurrent ovarian cancer is typically incurable, with most patients receiving multiple additional lines of treatment before ultimately dying from the disease. In primary analyses of phase 3 trials, the addition of intravenous bevacizumab to carboplatin plus paclitaxel (followed by bevacizumab alone) led to prolonged progression-free survival among patients with newly diagnosed advanced ovarian cancer, with hazard ratios for disease progression or death of 0.72 (Burger et al.3) and 0.81 (Perren et al.4). However, there was no improvement in overall survival.5 Poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors, such as olaparib, trap PARP on DNA at sites of single-strand breaks, thereby preventing the repair of the single-strand breaks and generating double-strand breaks that cannot be repaired accurately in tumors that have defects in homologous recombination repair, such as tumors with a mutation in BRCA1 or BRCA2. The use of PARP inhibitors leads to an accumulation of DNA damage and tumor-cell death.6 Olaparib has been approved in the United States and Europe as maintenance treatment for women with platinum-sensitive relapsed ovarian cancer who have a response to their most recent platinum-based regimen, regardless of BRCA mutation status.7,8 It has also been approved in the United States for the treatment of women with advanced ovarian cancer and a deleterious or suspected deleterious germline BRCA mutation who have been treated with three or more lines of chemotherapy, regardless of sensitivity to platinum-based therapy.7 National Comprehensive Cancer Network guidelines state that maintenance therapy with a PARP inhibitor should be considered in patients with relapsed ovarian cancer with sensitivity to platinum-based therapy, regardless of BRCA mutation status.1 We conducted the phase 3 SOLO1 trial to evaluate the efficacy of maintenance therapy with a PARP inhibitor (olaparib) in patients with newly diagnosed advanced ovarian cancer with a germline or somatic mutation in BRCA1, BRCA2, or both (BRCA1/2) who had a complete or partial clinical response after platinum-based chemotherapy. Methods Patients Patients were eligible if they were 18 years of age or older and had newly diagnosed, histologically confirmed advanced (International Federation of Gynecology and Obstetrics stage III or IV) highgrade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof). Those with stage III disease had undergone an attempt at cytoreductive surgery before the start chemotherapy (up front) or after the start but before the end of chemotherapy (interval). Those with stage IV disease had undergone either biopsy or up-front or interval cytoreductive surgery. Eligible patients had a deleterious or suspected deleterious germline or somatic BRCA1/2 mutation, as determined by local or central testing, with the use of the BRACAnalysis test (Myriad) or, in China, with the use of a BRCA1/2 genetic testing assay (BGI). Germline BRCA1/2 mutation status that was determined locally was confirmed centrally at Myriad or BGI, and tumor BRCA1/2 mutation status was assessed retrospectively at Foundation Medicine.

Eligible patients also had received platinumbased chemotherapy without bevacizumab and were having a complete clinical response (no evidence of disease on imaging after chemotherapy and a normal CA-125 level) or a partial clinical response (a ≥30% decrease in tumor volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range). Further details and a complete list of eligibility criteria are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org. All the patients provided written informed consent. Trial Design and Interventions This randomized, double-blind, placebo-controlled, phase 3 trial was conducted in 15 countries. Randomization was performed centrally with a block design, with stratification according to clinical response after platinum-based chemotherapy (complete or partial). Patients were assigned to a trial group through an interactive Web-based or voice-response system. After completion of platinum-based chemotherapy, patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. The trial intervention was continued until investigator-assessed objective disease progression on imaging (according to modified Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), provided that the patient was having a benefit and did not meet any discontinuation criteria. Patients who had no evidence of disease at 2 years stopped receiving the trial intervention, but patients who had a partial response at 2 years were permitted to continue receiving the trial intervention in a blinded manner. Crossover between trial groups was not specified in the protocol. After discontinuation of the trial intervention, patients could receive treatments at the investigators' discretion. End Points and Assessments The primary end point was progression-free survival as assessed by investigators. Progressionfree survival was defined as the time from randomization to objective disease progression on imaging (according to modified RECIST, version 1.1) or death from any cause. Computed tomography or magnetic resonance imaging was performed at baseline and every 12 weeks for up to 3 years and then every 24 weeks, until objective disease progression. A sensitivity analysis of progression-free survival as assessed by blinded independent central review was performed. Other sensitivity analyses of progression-free survival were also performed (see the Methods section in the Supplementary Appendix). Secondary end points were second progression– free survival (the time from randomization to second disease progression or death), overall survival, the time from randomization to the first subsequent therapy or death, the time from randomization to the second subsequent therapy or death, and health-related quality of life, which was assessed with the use of the Trial Outcome Index score on the Functional Assessment of Cancer Therapy–Ovarian Cancer (FACT-O) questionnaire (see the Methods section in the Supplementary Appendix). Trial Outcome Index scores range from 0 to 100, with higher scores indicating better health-related quality of life and a difference of 10 points indicating a clinically meaningful difference. FACT-O questionnaires were completed at baseline, on day 29, and every 12 weeks for 3 years and then every 24 weeks, until the time of data cutoff for the primary efficacy analysis. The analysis of healthrelated quality of life evaluated the change from baseline in the Trial Outcome Index score for the first 2 years. Adverse events were graded with the use of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Trial Oversight This trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy of bioethics,8 under the auspices of an independent data and safety monitoring committee.
The trial was designed by the first and last authors in collaboration with AstraZeneca and the Gynecologic Oncology Group. AstraZeneca was responsible for overseeing the collection, analysis, and interpretation of the data. All the authors had full access to the data. The manuscript was written by the authors, with medical writing assistance funded by AstraZeneca and Merck.

Olaparib is being codeveloped by AstraZeneca and Merck, and Merck provided input regarding the interpretation of the data. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol (available at NEJM.org). Statistical Analysis We determined that 206 primary end-point events (disease progression or death) would provide the trial with 90% power, at a two-sided significance level of 0.05, to show a significant difference in progression-free survival between the olaparib group and the placebo group, with a corresponding hazard ratio for disease progression or death of 0.62 (assuming a median progression-free survival of 13 months in the placebo group). Because the rate of primary end-point events was lower than projected, the protocol was amended such that the primary analysis of progression-free survival was to be performed when approximately 196 events had occurred (data maturity, approximately 50%) or when the last patient to undergo randomization had done so at least 3 years earlier, whichever came first. Data on efficacy and health-related quality of life were summarized and analyzed in the intention-to-treat population (all patients who underwent randomization, regardless of the intervention that they actually received). Data on safety were summarized in the safety population (all patients who received ≥1 dose of the trial intervention). A multiple-testing procedure was used to control the type I error rate, with a test for progression-free survival to be performed first, a test for second progression–free survival to be performed if the null hypothesis for progression-free survival were rejected, and a test for overall survival to be performed if the results for progressionfree survival and second progression–free survival were significant. The analyses of time to the first subsequent therapy and time to the second subsequent therapy were not adjusted for multiple comparisons. To describe the potential benefit of olaparib, tests for time to the first subsequent therapy, time to the second subsequent therapy, and change from baseline in the Trial Outcome Index score were performed at a two-sided significance level of 0.05. The analysis of progression-free survival was performed with a stratified log-rank test, with calculation of a hazard ratio, an accompanying 95% confidence interval, and a P value (see the Methods section in the Supplementary Appendix). Analyses of second progression–free survival, overall survival, time to the first subsequent therapy, and time to the second subsequent therapy were performed with a method similar to that used for the analysis of progression-free survival. The analysis of change from baseline in the Trial Outcome Index score was performed with a mixed-effects model for repeated measures. The statistical analysis plan is available with the protocol at NEJM.org. Results Patients From September 3, 2013, to March 6, 2015, a total of 391 patients underwent randomization. All 260 patients who were assigned to the olaparib group and 130 of the 131 patients who were assigned to the placebo group received the trial intervention; 1 patient in the placebo group decided to withdraw before receiving the intervention (Fig. 1). The baseline characteristics were well balanced between the trial groups (Table 1). At baseline, the majority of patients had no evidence of disease, a good performance status, and a CA-125 level within the normal range. With regard to BRCA mutation status, 210 patients underwent randomization on the basis of results of local testing and 181 on the basis of results of central testing (at Myriad or BGI). Central germline testing confirmed that 388 of the 391 patients had a BRCA1/2 mutation, 1 had a BRCA variant of uncertain significance, and 2 had wild-type BRCA. Testing at Foundation Medicine showed that the 2 patients with wild-type BRCA on central germline testing had somatic BRCA mutations (see the Results section in the Supplementary Appendix). Overall, of the 210 locally determined BRCA mutations, 207 (99%) were confirmed by central germline testing. The median duration of follow-up was 40.7 months (interquartile range, 34.9 to 42.9) in the olaparib group and 41.2 months (interquartile range, 32.2 to 41.6) in the placebo group.

A total of 123 patients (47%) in the olaparib group and 35 (27%) in the placebo group completed the trial intervention at 2 years, in accordance with the protocol, and 26 (10%) and 3 (2%), respectively, continued to receive the trial intervention beyond 2 years. Of the patients who received the trial intervention beyond 2 years, 13 were still receiving olaparib and 1 was still receiving placebo at the time of data cutoff for the primary analysis (May 17, 2018). Efficacy The analysis of the primary end point was performed after 198 of the 391 patients had had investigator-assessed disease progression or had died (data maturity, 51%). In the primary analysis, the Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years was 60% in the olaparib group, as compared with 27% in the placebo group (hazard ratio for disease progression or death, 0.30; 95% confidence interval [CI], 0.23 to 0.41; P <0.0001 (Fig. 2A). The median progression-free survival from the end of chemotherapy was 13.8 months in the placebo group. In the analysis of progression-free survival as assessed by blinded independent central review (data maturity, 38%), the Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years was 69% in the olaparib group, as compared with 35% in the placebo group (hazard ratio for disease progression or death, 0.28; 95% CI, 0.20 to 0.39; P<0.0001 (Fig. 2B); these results are consistent with the benefit of olaparib with regard to progressionfree survival as assessed by investigators. In a sensitivity analysis of investigator-assessed progression-free survival that was performed to evaluate for possible attrition bias, the median progression-free survival was approximately 36 months longer in the olaparib group than in the placebo group (see the Results section and Table S3 of the Supplementary Appendix). The Kaplan–Meier estimate of the rate of freedom from investigator-assessed disease progression and from death was 88% in the olaparib group and 51% in the placebo group at 1 year; 74% and 35%, respectively, at 2 years; 60% and 27% at 3 years; and 53% and 11% at 4 years (Fig. S1 of the Supplementary Appendix). Subgroup analyses of progression-free survival are shown in Figure 3. In the analysis of second progression–free survival (data maturity, 31%), the Kaplan–Meier estimate of the rate of freedom from second disease progression and from death at 3 years was 75% in the olaparib group, as compared with 60% in the placebo group (hazard ratio for second disease progression or death, 0.50; 95% CI, 0.35 to 0.72; P< 0.0001). The median second progression–free survival was 41.9 months in the placebo group (Fig. S2 of the Supplementary Appendix). In an interim analysis of overall survival (data maturity, 21%), the Kaplan–Meier estimate of the rate of freedom from death at 3 years was 84% in the olaparib group and 80% in the placebo group (hazard ratio for death, 0.95; 95% CI, 0.60 to 1.53). The median time to the first subsequent therapy or death was 51.8 months in the olaparib group and 15.1 months in the placebo group (hazard ratio, 0.30; 95% CI, 0.22 to 0.40). The Kaplan–Meier estimate of the rate of freedom from the use of a second subsequent therapy and from death at 3 years was 74% in the olaparib group and 56% in the placebo group (hazard ratio for the use of a second subsequent therapy or death, 0.45; 95% CI, 0.32 to 0.63), with a median time to the second subsequent therapy or death of 40.7 months in the placebo group.

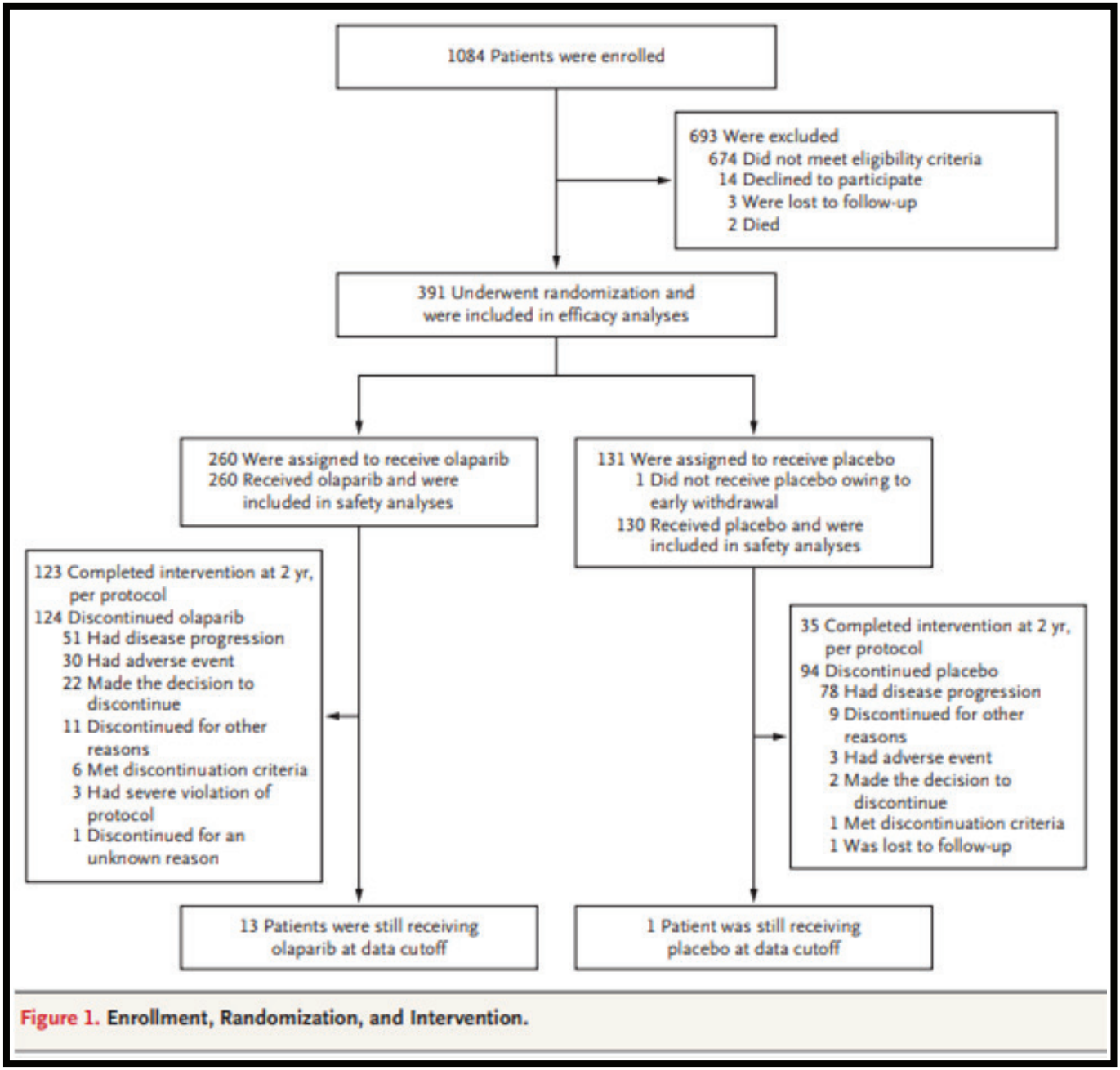

Figure 1. Enrollment, Randomization, and Intervention.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Olaparib Group (N = 260)	Placebo Group (N = 131)
	no. of patients (%)	
Clinical response after platinum-based chemotherapy†		
Complete response	213 (82)	107 (82)
Partial response	47 (18)	24 (18)
No. of cycles of platinum-based chemotherapy		
4	2 (1)	0
5	2 (1)	1 (1)
6	198 (76)	106 (81)
7	17 (7)	10 (8)
8	18 (7)	7 (5)
9	23 (9)	7 (5)
ECOG performance status		
Normal activity	200 (77)	105 (80)
Restricted activity	60 (23)	25 (19)
Missing data	0	1 (1)
Primary tumor location		
Ovary	220 (85)	113 (86)
Fallopian tube	22 (8)	11 (8)
Peritoneum	15 (6)	7 (5)
Other‡	3 (1)	0
International FIGO stage§		
Stage III	220 (85)	105 (80)
Stage IV	40 (15)	26 (20)
CA-125 level		
≤ULN	247 (95)	123 (94)
>ULN	13 (5)	7 (5)
Missing data	0	1 (1)
Histologic type		
Serous	246 (95)	130 (99)
Endometrioid	9 (3)	0
Mixed serous and endometrioid	5 (2)	1 (1)
BRCA mutation¶		
BRCA1	191 (73)	91 (69)
BRCA2	66 (25)	40 (31)
BRCA1 and *BRCA2*	3 (1)	0

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group.
† Complete response was defined as no evidence of disease on imaging (according to modified Response Evaluation Criteria in Solid Tumors, version 1.1) after chemotherapy and a normal CA-125 level. Partial response was defined as a decrease of at least 30% in tumor volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range (ULN).
‡ Other tumor locations included a combination of the ovary, fallopian tube, peritoneum, and omentum (in one patient), a combination of the ovary and peritoneum (one patient), and a combination of the ovary and fallopian tube (one patient).
§ International Federation of Gynecology and Obstetrics (FIGO) stage III indicates involvement of one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis or metastasis to the retroperitoneal lymph nodes (or both), and stage IV indicates distant metastasis excluding peritoneal metastasis.
¶ *BRCA* mutation status was determined centrally (at Myriad or BGI) or locally. For the five patients from China, germline *BRCA* mutation status was determined in China with the use of the BGI test.

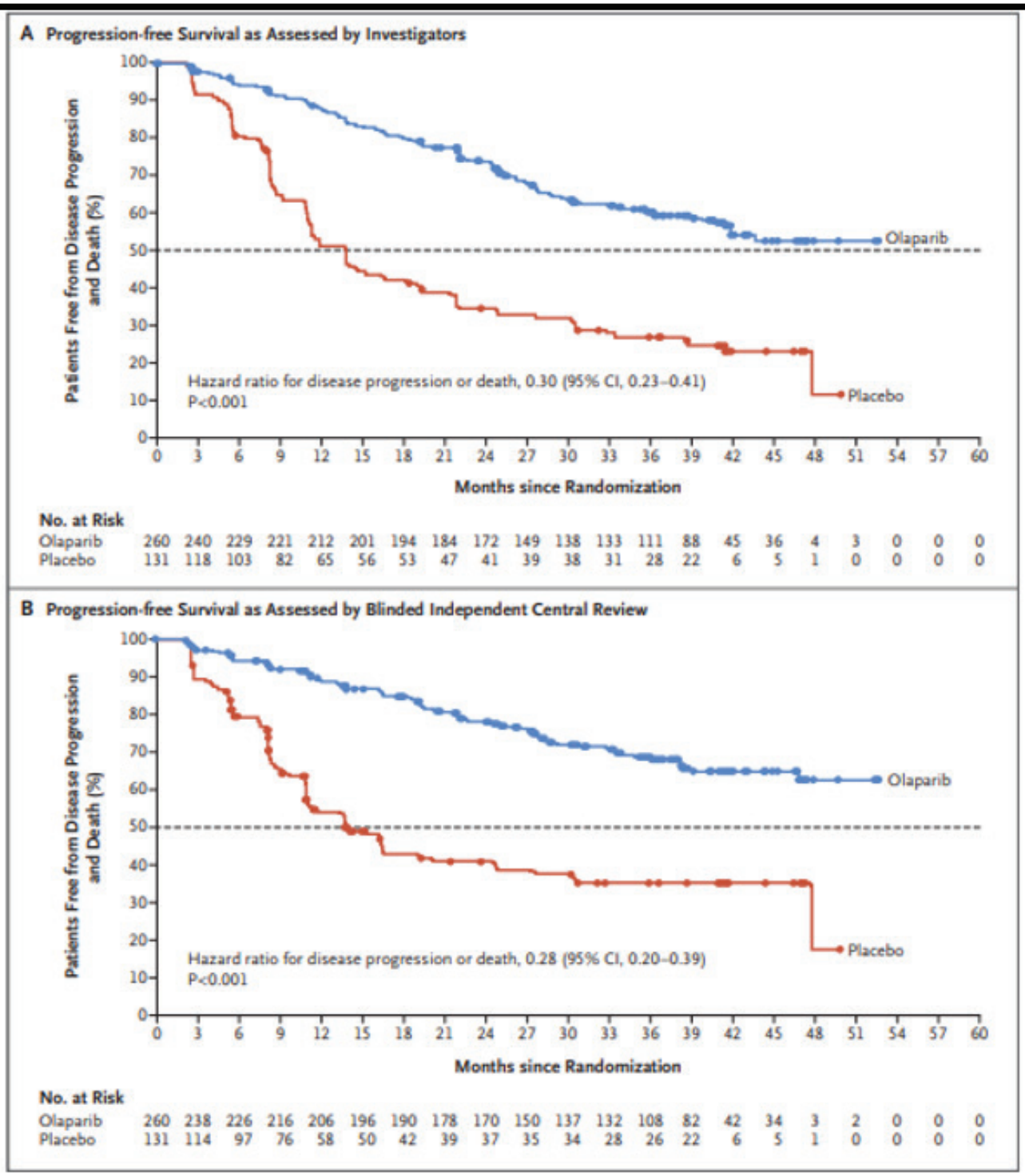

Figure 2. Kaplan–Meier Estimates of Progression-free Survival.

Panel A shows Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by investigators, and from death in the olaparib group and the placebo group. There was no evidence of a change in the shape of the Kaplan–Meier curve for olaparib after 24 months, when patients with no evidence of disease stopped the intervention, in accordance with the protocol; this finding indicates a sustained benefit of olaparib beyond the completion of treatment. In a sensitivity analysis of investigator-assessed progression-free survival that was performed to evaluate for possible attrition bias, the median progression-free survival was approximately 36 months longer in the olaparib group than in the placebo group (see the Supplementary Appendix). Panel B shows Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by blinded independent central review, and from death. The dashed line indicates the median.

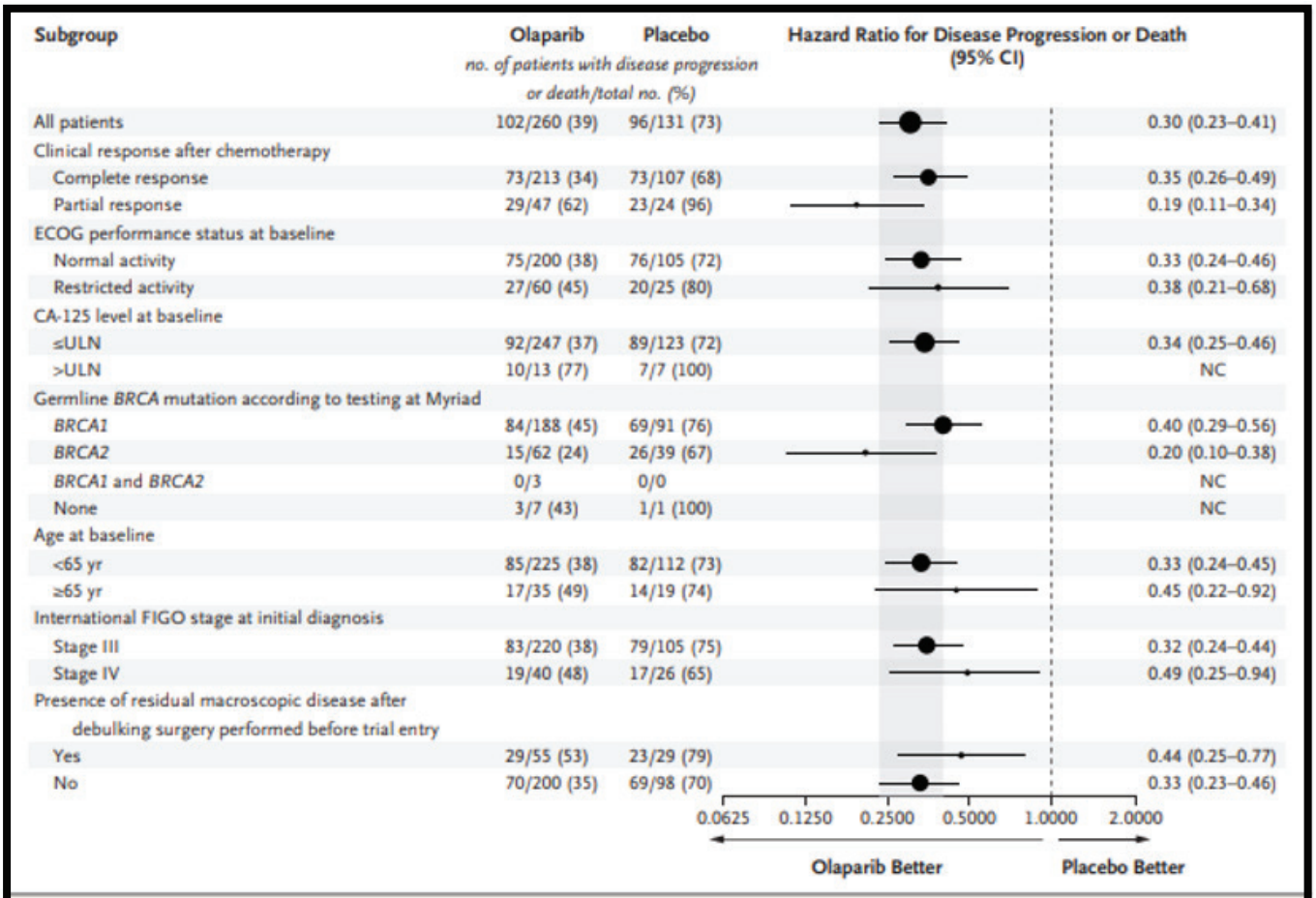

Figure 3. Subgroup Analysis of Progression-free Survival.

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 all patients, and the dashed line indicates the point of no effect. International Federation of Gynecology and Obstetrics (FIGO) stage III indicates involvement of one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis or metastasis to the retroperitoneal lymph nodes (or both), and stage IV indicates distant metastasis excluding peritoneal metastasis. NC denotes not calculated, ECOG Eastern Cooperative Oncology Group, and ULN upper limit of the normal range.

Safety

The median duration of the trial intervention in the olaparib group was 24.6 months (range, 0.0 to 52.0), a finding consistent with the 2-year treatment cap. The median duration in the placebo group was 13.9 months (range, 0.2 to 45.6), a finding consistent with the median progression-free survival in that group. The most common adverse events that occurred during the trial intervention or up to 30 days after discontinuation of the intervention are shown in Table 2; most were grade 1 or 2 events. Serious adverse events occurred in 21% of the patients in the olaparib group and 12% of the patients in the placebo group. Anemia was the most common serious adverse event (in 7% of the patients in the olaparib group and in no patients in the placebo group). No adverse events that occurred during the trial intervention or up to 30 days after discontinuation of the intervention resulted in death. Adverse events were usually managed by dose interruption or dose reduction, rather than discontinuation (Table 2). The most common adverse events that led to discontinuation were nausea and anemia. Acute myeloid leukemia occurred in 3 of 260 patients (1%) in the olaparib group and in none of 130 patients in the placebo group, new primary cancers occurred in 5 (2%) and 3 (2%), respectively, and pneumonitis or interstitial lung disease occurred in 5 (2%) and none (see the Results section in the Supplementary Appendix).

All three cases of acute myeloid leukemia occurred more than 30 days after the end of treatment with olaparib. Health-Related Quality of Life The mean Trial Outcome Index score at baseline was 73.6 in the olaparib group and 75.0 in the placebo group. The score remained stable in the olaparib group (237 patients), with an adjusted mean change from baseline to 2 years of 0.30 points (95% CI, −0.72 to 1.32), as compared with a change of 3.30 points (95% CI, 1.84 to 4.76) in the placebo group (125 patients). The estimated between-group difference in change was −3.00 points (95% CI, −4.78 to −1.22); the difference was not considered to be clinically meaningful. Discussion In the phase 3 SOLO1 trial, the use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-freesurvival among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo. Results of a sensitivity analysis and the time to first subsequent therapy or death support an estimated difference in median progression-free survival between the olaparib group and the placebo group of approximately 3 years. The median progression-free survival of 13.8 months in the placebo group, which was measured from the end of chemotherapy rather than from the start of chemotherapy, is consistent with results reported in studies of carboplatin plus paclitaxel in patients with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation.9,10 The results of sensitivity analyses and subgroup analyses of progression-free survival were consistent with the results of the primary analysis. The absolute longer progression-free survival with olaparib than with placebo that was seen in a sensitivity analysis in this trial was substantially greater than the increases in progression-free survival that were seen with PARP inhibitors in relapsed disease,11-13 and some patients (e.g., those who have platinum resistance) are not eligible to receive olaparib as a second-line therapy. Some patients in this trial were able to stop receiving the trial intervention at 2 years and to live progression-free for months without treatment. Patients with newly diagnosed advanced ovarian cancer are the only patients with ovarian cancer in whom treatment has curative potential. Ongoing follow-up of patients in this trial would be necessary to evaluate whether a subgroup has a durable long-term benefit with olaparib (which has been seen in relapsed disease with sensitivity to platinum-based therapy14) or even a cure. A significant increase in time to second disease progression was also noted with olaparib, a finding that suggests that olaparib did not diminish patients' ability to benefit from subsequent therapy. This finding was observed despite the use of PARP inhibitors in 33 of 94 patients (35%) in the placebo group who received subsequent therapy, which may potentially explain the median second progression–free survival of 42 months in the placebo group. Data on overall survival are currently immature but show no evidence that olaparib had a detrimental effect on survival. Most patients in this trial had a germline BRCA1/2 mutation. However, the results of other studies11,12 suggest that the findings could be applicable to patients with a somatic BRCA1/2 mutation. The safety profile of olaparib in the SOLO1 trial was consistent with that seen in patients with relapsed disease (i.e., in patients in the SOLO2 trial13), despite the longer duration of treatment. Rates of adverse events that led to dose reduction or discontinuation were relatively low. The safety profile of olaparib appeared to be generally acceptable in patients receiving maintenance treatment for newly diagnosed advanced ovarian cancer. The incidence of acute myeloid leukemia that was reported in the SOLO1 trial (1%) is consistent with the incidence of the myelodysplastic syndrome or acute myeloid leukemia that was reported in the SOLO2 trial (2%)13 and other trials of PARP inhibitors.11,12,15 Comparative data regarding the incidence of the myelodysplastic syndrome or acute myeloid leukemia after the use of platinum-based chemotherapy alone in patients with newly diagnosed ovarian cancer are limited. In this trial, neither trial group had a clinically significant change in health-related quality of life.

Although there was a between-group difference in the change in the Trial Outcome Index score, the difference was less than 10 points and thus was not considered to be clinically meaningful.16 In conclusion, the SOLO1 trial showed that the use of maintenance therapy with olaparib, as compared with placebo, after platinum-based chemotherapy provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation.

Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial

Introduction

The ultimate goal of treatment in women newly diagnosed with ovarian cancer is cure. However, disease is often advanced at the time of diagnosis and approximately 70% of patients who receive cytoreductive surgery followed by first-line platinum-based chemotherapy will relapse within 3 years,with a 10-year survival of 17% in patients with advanced epithelial ovarian cancer.2Relapsed advanced ovarian cancer is typically incurable, highlighting the need for effective first-line treatments that delay relapse, prolong survival, and enhance the potential for cure. The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib represents the new standard of care in the management of patients with newly diagnosed advanced ovarian cancer and a BRCA1 and/or BRCA2 (BRCA) mutation. In the pivotal SOLO1/GOG 3004 trial, maintenance olaparib provided a sustained progression-free survival (PFS) benefit beyond the end of treatment, which was capped at 2 years, in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation.In the primary analysis (data cutoff [DCO]: May 17, 2018), maintenance olaparib provided a significant PFS benefit compared with placebo (hazard ratio [HR], 0.30; 95% CI, 0.23 to 0.41; P < .001). In an updated PFS analysis conducted after a 5-year follow-up (DCO: March 5, 2020), the median PFS was 56.0 months in the olaparib group compared with 13.8 months in the placebo group (HR, 0.33; 95% CI, 0.25 to 0.43).4 On the basis of Kaplan-Meier estimates, 48.3% versus 20.5% of patients, respectively, were progression-free at 5 years; overall survival (OS) data were immature.

We report a descriptive analysis of OS after a 7-year follow-up in SOLO1. To our knowledge, this is the longest follow-up for any PARP inhibitor in newly diagnosed advanced ovarian cancer and the first report of long-term OS data for any PARP inhibitor in this setting. Seven years is considered a clinically relevant time point for survivorship, as modeling indicates that most ovarian cancer–related deaths occur within 7 years of diagnosis, with mortality approaching that of women in the general population after a 9-year follow-up.

Methods

Study Design and Patients

The design of the randomized, double-blind, placebo-controlled, international, phase III SOLO1/GOG 3004 study has been reported previously.3 In brief, eligible patients had newly diagnosed, histologically confirmed advanced (International Federation of Gynaecology and Obstetrics [FIGO] stage III or IV) high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer.

Patients were eligible for SOLO1 regardless of the timing of cytoreductive surgery or surgical outcome. Patients with FIGO stage III disease had undergone an attempt at optimal upfront or interval cytoreductive surgery, and those with FIGO stage IV disease had undergone a biopsy and/or upfront or interval cytoreductive surgery. Patients had a germline or somatic BRCA1 and/or BRCA2 mutation on local or central testing and were in clinical complete or partial response after first-line platinum-based chemotherapy (without bevacizumab). Patients who had received prior PARP inhibitor therapy or who had a history or myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) were ineligible. Full eligibility criteria are given in the Data Supplement (online only).

The study Protocol (online only) was approved by the ethics committees at each participating site and performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy on bioethics.6 All patients provided written informed consent.

Treatment

Patients were randomly assigned (2:1) to receive olaparib tablets (300 mg twice daily) or placebo within 8 weeks of receiving their last dose of chemotherapy. Random assignment was stratified according to clinical response (complete or partial) after platinum-based chemotherapy. Patients received treatment for up to 2 years or until investigator-assessed objective radiologic disease progression (according to modified RECIST, version 1.1), whichever occurred first, or treatment was stopped if other discontinuation criteria were met (Data Supplement). Patients with no evidence of disease at 2 years stopped receiving study treatment, but patients with evidence of disease at 2 years could continue to receive study treatment in a blinded manner if, in the opinion of the investigator, this was in the patient's best interest. Within the study, crossover between the treatment groups was not permitted. After study treatment discontinuation, patients could receive subsequent therapies at the investigators' discretion.

Outcomes

Secondary end points reported in this analysis are OS (defined as the time from random assignment to death because of any cause), time from random assignment to first subsequent therapy or death (TFST), time from random assignment to second subsequent therapy or death (TSST), time from random assignment to discontinuation of study treatment or death (TDT), and safety and tolerability. Adverse events (AEs) were monitored using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0) throughout the treatment period and for 30 days after discontinuation of study treatment. In addition, patients were proactively followed for MDS/AML and new primary malignancies beyond the 30-day post-treatment safety follow-up period. Investigator-assessed PFS, the primary end point, and additional end points have been reported previously.

Statistical Analysis

Efficacy was analyzed in all randomly assigned patients (full analysis set), and safety was analyzed in all patients who received at least one dose of randomized treatment.

This prespecified descriptive OS analysis was conducted 7 years after the last patient was randomly assigned (DCO: March 7, 2022). A final OS analysis is currently planned to be conducted at approximately 60% data maturity as prespecified in the study Protocol.3 OS was analyzed using a log-rank test stratified by response to first-line platinum-based chemotherapy, with HRs and 95% Cls estimated using a Cox proportional hazards model, including the stratification variable as a covariate. OS was not adjusted for subsequent PARP inhibitor therapy. A two-sided P value of < .0001 was required to declare statistical significance (Haybittle-Peto α = .0001). Kaplan-Meier methods were used to generate time-to-event curves, from which medians and survival proportions were calculated.

Analyses of TFST, TSST, and TDT were performed using a method similar to that used for the analysis of OS. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Results

All 260 patients randomly assigned to olaparib and 130 of the 131 patients randomly assigned to placebo received study treatment (one patient assigned to placebo withdrew before receiving the intervention; Fig 1). Baseline characteristics were well balanced between the treatment groups. For this descriptive OS analysis, DCO (March 7, 2022) took place 7 years after the last patient was randomly assigned, with a median (interquartile range) duration of follow-up for OS of 88.9 (85.7-93.6) months in the olaparib group and 87.4 (84.3-91.7) months in the placebo group. The median (range) duration of treatment in the safety analysis set was 24.6 (0.0-97.5) months in the olaparib group, consistent with the 2-year treatment cap, and 13.9 (0.2-60.9) months in the placebo group. Study treatment was completed at 2 years, per the study Protocol, in 123 olaparib patients (47.3%) and 35 placebo patients (26.9%; Fig 1); 111 patients (42.7%) and 92 patients (70.8%), respectively, discontinued study treatment before 2 years, and 26 patients (10.0%) and three patients (2.3%), respectively, continued study treatment beyond 2 years. Seven of the 13 patients who were receiving olaparib at the primary DCO (May 17, 2018)3 were still receiving olaparib at the current DCO.

At DCO (March 7, 2022), 149 of 391 patients had died (data maturity 38.1%). The median OS was not reached (95% CI, not reached to not reached) in the olaparib group compared with 75.2 months (95% CI, 65.4 to not reached) in the placebo group, with an HR of 0.55 (95% CI, 0.40 to 0.76; P = .0004 [P < .0001 required to declare statistical significance]; Fig 2). This analysis was unadjusted for subsequent therapy, and the OS benefit was achieved despite 44.3% of patients in the placebo group having received a PARP inhibitor in a subsequent line of therapy (Table 1). Of the 122 olaparib patients and 97 placebo patients who received any subsequent therapy (Data Supplement), 31.1% and 59.8%, respectively, received a PARP inhibitor. On the basis of Kaplan-Meier estimates, 67.0% of olaparib patients versus 46.5% of placebo patients were alive 7 years after random assignment. The median TFST (data maturity 59.6%) was 64.0 months (95% CI, 47.7 to 93.2) with olaparib compared with 15.1 months (95% CI, 12.7 to 20.5) with placebo, with an HR of 0.37 (95% CI, 0.28 to 0.48; Fig 3A). On the basis of Kaplan-Meier estimates, 45.3% of olaparib patients versus 20.6% of placebo patients were alive and had not received a first subsequent treatment after a 7-year follow-up. At the time of DCO, 122 (46.9%) patients in the olaparib group and 95 (72.5%) in the placebo group had received a first subsequent therapy. The median TSST (data maturity 48.6%) was 93.2 months (95% CI, 84.2 to not reached) with olaparib compared with 40.7 months (95% CI, 32.9 to 54.4) with placebo, with an HR of 0.50 (95% CI, 0.37 to 0.67; Fig 3B).

On the basis of Kaplan-Meier estimates, 56.9% of olaparib patients versus 32.5% of placebo patients were alive and had not received a second subsequent treatment after a 7-year follow-up. At the time of DCO, 68 (26.2%) patients in the olaparib group and 59 (45.0%) in the placebo group had received a second subsequent therapy (Data Supplement).

Consistent with the results reported previously,4 the median TDT (data maturity 98.2%) was 24.6 months (95% CI, 24.0 to 24.8) in the olaparib group compared with 13.8 months (95% CI, 11.2 to 16.4) in the placebo group, with an HR of 0.63 (95% CI, 0.51 to 0.78; Data Supplement).

After a 7-year follow-up, the safety profile of maintenance olaparib was consistent with that reported at previous DCOs.3,4 The most common AEs of any grade reported in olaparib patients were nausea, fatigue/asthenia, vomiting, and anemia, and the most common grade ≥ 3 AE was anemia (Table 2). Serious AEs occurred in 21.2% of olaparib patients and 13.8% of placebo patients. The most commonly reported serious AEs were anemia (7.3% of olaparib patients v 0.0% of placebo patients) and neutropenia (1.5% v 0.0%). Data on MDS/AML and new primary malignancies were collected both during study treatment and after discontinuation of study treatment up to the time of DCO (March 7, 2022). Since the primary DCO (May 17, 2018), one (0.4%) new case of MDS has been reported in the olaparib group and one (0.8%) new case of acute myelomonocytic leukemia has been reported in the placebo group. In total, after a 7-year follow-up, four (1.5%) cases of MDS/AML were reported in the olaparib group and one (0.8%) case of MDS/AML was reported in the placebo group. In total, after a 7-year follow-up, new primary malignancies were reported in 14 (5.4%) olaparib patients (breast cancer [n = 10], lip and/or oral cavity cancer [n = 1], thyroid cancer [n = 1], pancreatic adenocarcinoma [n = 1], and gall bladder adenocarcinoma [n = 1]) and eight (6.2%) placebo patients (breast cancer [n = 5], lung adenocarcinoma [n = 1], squamous cell carcinoma of the tongue [n = 1], and chronic myeloid leukemia [n = 1]). Six (2.3%) new primary malignancies occurred in olaparib patients, and three (2.3%) occurred in placebo patients since the March 5, 2020, DCO.

AEs were usually managed by dose interruption or reduction, with few patients (11.9% of olaparib patients and 3.1% of placebo patients) requiring treatment discontinuation because of AEs (Table 2).

Discussion

The median duration of follow-up of approximately 88 months reported in this descriptive SOLO1 analysis represents the longest follow-up for any PARP inhibitor in newly diagnosed advanced ovarian cancer. With an HR for OS of 0.55 (95% CI, 0.40 to 0.76) observed with maintenance olaparib (administered for ≤ 2 years in most patients) versus placebo and 67.0% of olaparib patients (v 46.5% of placebo patients) alive at 7 years, SOLO1 is the first study to indicate a clinically meaningful improvement in OS with PARP inhibitor maintenance therapy in the first-line setting. Data maturity for OS was 38.1% in the current analysis, and the SOLO1 final OS analysis is currently planned to be conducted once data maturity reaches approximately 60%.3 Given that the event rate for OS is slower than that anticipated at the onset of the study and it may be many years before the threshold to conduct the final OS analysis is met, performing a descriptive OS analysis at 7 years, a clinically relevant time point, was important to help inform treatment decisions.

The Haybittle-Peto α spending function required a P < .0001 to show statistical significance in the current descriptive analysis (administrative α spending), allowing the statistical power of the final OS analysis to be preserved. Although not reaching the threshold for statistical significance, we consider the OS benefit shown in this 7-year descriptive analysis to be clinically meaningful. Given the 5-year survival rate of 38.1% previously reported in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation,9 the 5-year and 7-year OS rates of 73.1% and 67.0%, respectively, seen in SOLO1 patients receiving maintenance olaparib represent an important advance; it should be noted that OS rates in SOLO1 were calculated from the time of random assignment rather than from the time of diagnosis.

It is difficult to demonstrate improvements in OS in ovarian cancer trials because of the number and variety of uncontrolled postprogression treatment options including experimental agents. In this descriptive OS analysis, more than 40% of placebo patients (v 14.6% of olaparib patients) received subsequent therapy with a PARP inhibitor (and 59.8% of placebo patients v 31.1% of olaparib patients who received any subsequent therapy received a PARP inhibitor); this is likely to have affected the OS results, which were unadjusted for subsequent PARP inhibitor therapy. Subsequent treatment with a PARP inhibitor may also partly explain the relatively long median OS of 75.2 months observed in the placebo arm. This compares with a median OS of 58.3 months in patients, irrespective of biomarker status, who were in clinical complete response after first-line platinum-based chemotherapy and enrolled in the surveillance arm of the phase III GOG 0212 trial; < 20% of patients were alive and progression-free after a median follow-up in the overall patient population of 8.1 years.12 BRCA-mutated patients in the placebo arm of the phase III GOG 0218 trial had a median OS of 61.2 months13; it should be noted that compared with SOLO1, patients in GOG 0218 had a worse prognosis (patients with FIGO stage III disease and complete resection after cytoreductive surgery were excluded), and random assignment in GOG 0218 occurred before the start of chemotherapy. Advances in the management of relapsed ovarian cancer, including improvements in the sequencing of therapies and supportive care, might have also contributed to the median OS seen in placebo patients in SOLO1. OS results from other ongoing trials evaluating PARP inhibitor maintenance therapy in the newly diagnosed setting (eg, combination maintenance therapy with olaparib plus bevacizumab in PAOLA-1, maintenance niraparib in PRIMA, and maintenance rucaparib in ATHENA-MONO) are awaited with interest.

The results of SOLO1 emphasize the importance of both testing for both germline and somatic BRCA mutations and providing PARP inhibitor maintenance therapy to all BRCA-mutated patients with advanced disease in the first-line setting, rather than delaying the introduction of PARP inhibitors until patients have experienced relapse. On the basis of the results of SOLO1, maintenance therapy with olaparib is capped at 2 years in the first-line setting although patients with evidence of disease at this time point can be treated beyond 2 years.This descriptive OS analysis (DCO March 7, 2022) confirms findings from earlier PFS analyses in SOLO1 (DCO May 17, 2018, and March 5, 2020) that the benefit of maintenance olaparib extends well beyond its 2-year treatment cap in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation. Indeed, the SOLO1 OS data support the use of maintenance olaparib to achieve long-term remission in BRCA-mutated patients with newly diagnosed advanced ovarian cancer.

It is noteworthy that for a considerable proportion of olaparib patients, the SOLO1 OS data reflect disease-free survival.

Although updated PFS data are not available, TFST was evaluated as a proxy for PFS.TFST data showed a substantial delay with maintenance olaparib versus placebo in the time between random assignment and the first subsequent treatment, with 45.3% of olaparib patients (v 20.6% of placebo patients) alive and still to receive a first subsequent therapy after a 7-year follow-up. These data suggest that maintenance olaparib might enhance the potential for cure although longer follow-up is needed for a more definitive evaluation of cure. Modeling data suggest that 10-year survival appears to be an appropriate surrogate of cure in this setting.

TSST data are also consistent with the previously reported PFS benefit and indicate that the benefit of maintenance olaparib persists beyond the first subsequent therapy.

After a 7-year follow-up, the safety profile of maintenance olaparib was consistent with that reported at earlier DCOs (May 17, 2018, and March 5, 2020), with no new safety signals detected. It is reassuring that the incidence of MDS/AML remained low and the incidence of new primary malignancies remained balanced between the treatment arms after 7 years of active follow-up for these events in SOLO1. Only one new case of MDS/AML has been reported in the olaparib arm since the primary DCO on May 17, 2018. The low risk of MDS/AML observed in SOLO1 is consistent with that reported in other PARP inhibitor maintenance therapy trials in the newly diagnosed setting. A higher incidence of MDS/AML has been observed in PARP inhibitor maintenance therapy trials in patients with relapsed ovarian cancer. The incidence of MDS/AML in the relapsed disease setting should be considered in the context of potential baseline risk factors for MDS/AML (eg, prior chemotherapy with DNA-damaging agents) and the long latency of these events. A contributing role for PARP inhibitors cannot be excluded, and long-term active surveillance for MDS/AML events after discontinuation of PARP inhibitor maintenance therapy is prudent.

In conclusion, after a 7-year follow-up, results indicate a clinically meaningful, albeit not statistically significant according to prespecified criteria, improvement in OS with maintenance olaparib versus placebo in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation. These data support the use of maintenance olaparib to achieve long-term remission in this setting; the potential for cure may also be enhanced.

Figure

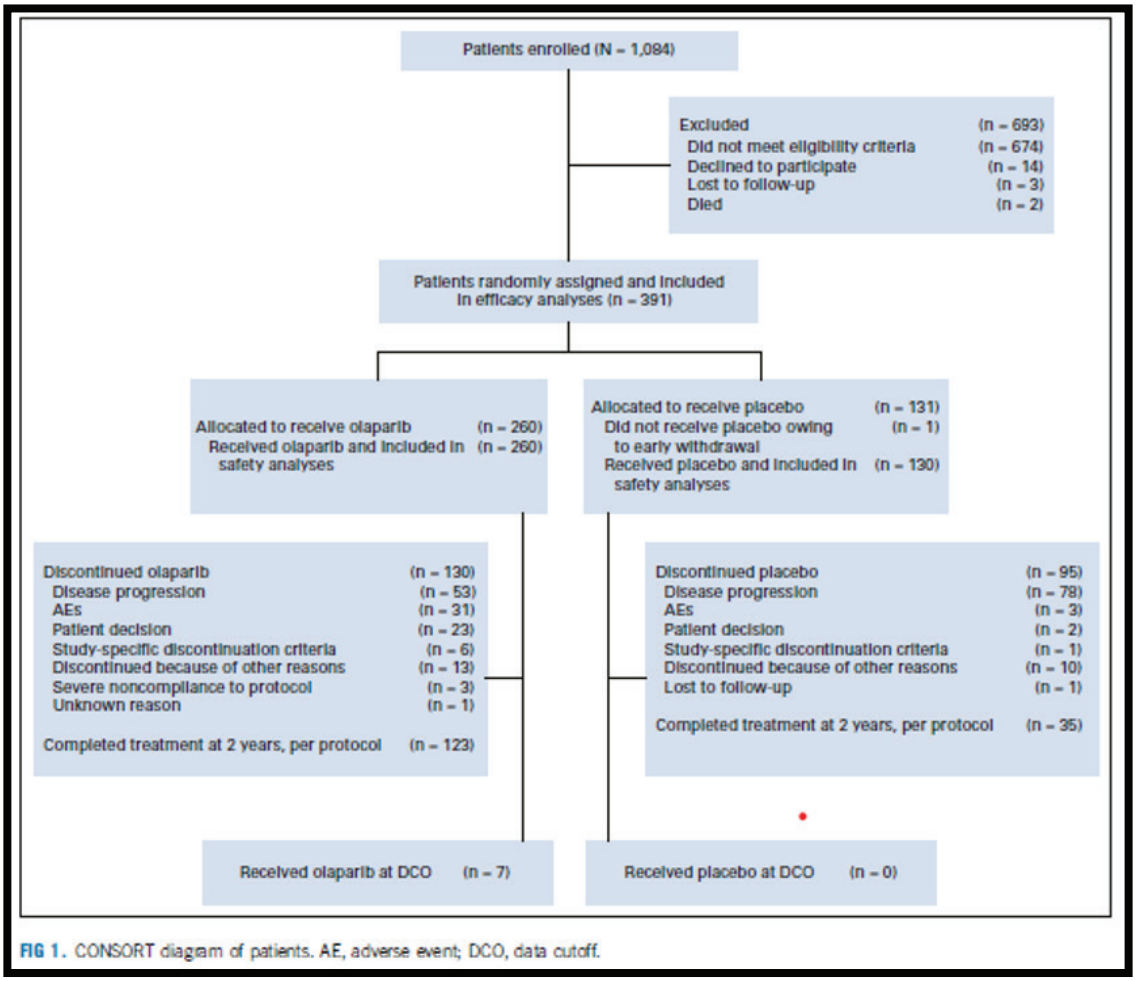

FIG 1. CONSORT diagram of patients. AE, adverse event; DCO, data cutoff.

TABLE 1. Subsequent PARP Inhibitor Therapy

Patients Receiving PARP Inhibitor	Olaparib (n = 260), No. (%)	Placebo (n = 131), No. (%)
Subsequent PARP inhibitor (any line)	38 (14.6)	58 (44.3)
First subsequent therapy	15 (5.8)	32 (24.4)
Second subsequent therapy	14 (5.4)	17 (13.0)
Third subsequent therapy	7 (2.7)	5 (3.8)
Fourth subsequent therapy	0	3 (2.3)
Fifth subsequent therapy	2 (0.8)	1 (0.8)

Abbreviation: PARP, poly(ADP-ribose) polymerase.

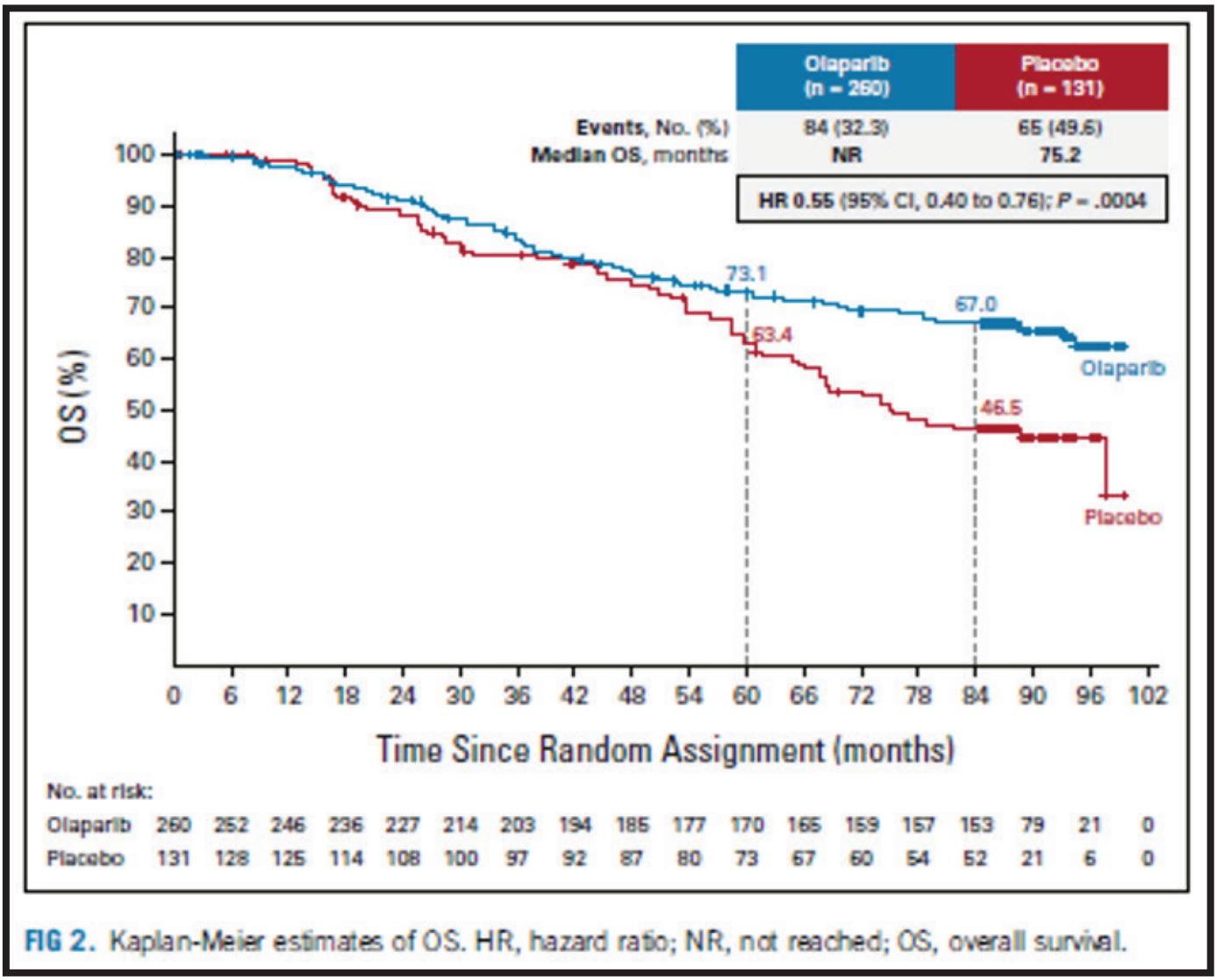

FIG 2. Kaplan-Meier estimates of OS. HR, hazard ratio; NR, not reached; OS, overall survival.

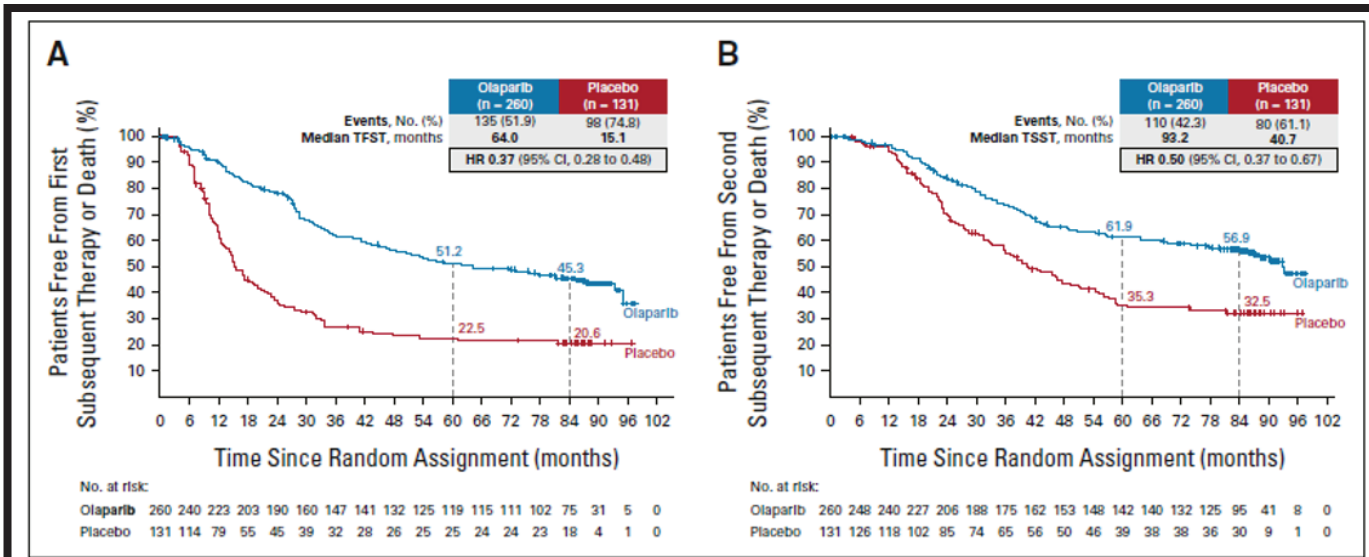

FIG 3. Kaplan-Meier estimates of (A) TFST and (B) TSST. HR, hazard ratio; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

TABLE 2. Summary of AEs[a]

	Olaparib (n = 260), No. (%)		Placebo (n = 130), No. (%)	
Patient With AE	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any	256 (98.5)	103 (39.6)	120 (92.3)	26 (20.0)
Nausea	202 (77.7)	2 (0.8)	49 (37.7)	0.0
Fatigue or asthenia	167 (64.2)	10 (3.8)	54 (41.5)	2 (1.5)
Vomiting	104 (40.0)	1 (0.4)	19 (14.6)	1 (0.8)
Anemia[b]	104 (40.0)	57 (21.9)	13 (10.0)	2 (1.5)
Diarrhea	90 (34.6)	8 (3.1)	32 (24.6)	0.0
Arthralgia	75 (28.8)	0.0	39 (30.0)	0.0
Constipation	72 (27.7)	0.0	25 (19.2)	0.0
Abdominal pain	67 (25.8)	4 (1.5)	25 (19.2)	1 (0.8)
Headache	60 (23.1)	1 (0.4)	31 (23.8)	3 (2.3)
Neutropenia[c]	60 (23.1)	22 (8.5)	15 (11.5)	6 (4.6)
Dysgeusia	56 (21.5)	0.0	5 (3.8)	0.0
Dizziness	53 (20.4)	0.0	20 (15.4)	1 (0.8)
Decreased appetite	53 (20.4)	0.0	13 (10.0)	0.0
Upper abdominal pain	45 (17.3)	0.0	17 (13.1)	0.0
Cough	44 (16.9)	0.0	28 (21.5)	0.0
Dyspepsia	43 (16.5)	0.0	16 (12.3)	0.0
Back pain	42 (16.2)	0.0	16 (12.3)	0.0
Dyspnea	41 (15.8)	0.0	7 (5.4)	0.0
Pyrexia	32 (12.3)	0.0	12 (9.2)	0.0
Urinary tract infection	31 (11.9)	2 (0.8)	8 (6.2)	0.0
Upper respiratory tract infection	30 (11.5)	0.0	12 (9.2)	0.0
Pain in extremity	30 (11.5)	0.0	11 (8.5)	0.0
Thrombocytopenia[d]	29 (11.2)	2 (0.8)	5 (3.8)	2 (1.5)
Nasopharyngitis	28 (10.8)	0.0	17 (13.1)	0.0
Insomnia	27 (10.4)	0.0	16 (12.3)	0.0
Myalgia	26 (10.0)	0.0	13 (10.0)	0.0
Depression	14 (5.4)	1 (0.4)	13 (10.0)	1 (0.8)
Leading to dose interruption	137 (52.7)	—	22 (16.9)	—
Leading to dose reduction	75 (28.8)	—	4 (3.1)	—
Leading to treatment discontinuation	31 (11.9)	—	4 (3.1)	—

Abbreviation: AE, adverse event.

aData are shown for treatment-emergent AEs that occurred in at least 10.0% of patients in either treatment group during study treatment or up to 30 days

after discontinuation of study treatment.

bIncludes patients with anemia or decreased hemoglobin.

cIncludes patients with neutropenia, febrile neutropenia, or decreased neutrophil count.

dIncludes patients with thrombocytopenia or decreased platelet count.

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