

Olaparib Versus Nonplatinum Chemotherapy in Patients With Platinum-Sensitive Relapsed Ovarian Cancer and a Germline BRCA1/2 Mutation (SOLO3): A Randomized Phase III Trial

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abstract

PURPOSE A phase II study (ClinicalTrials.gov identifier: [NCT00628251](https://clinicaltrials.gov/ct2/show/study/NCT00628251)) showed activity of olaparib capsules versus pegylated liposomal doxorubicin in patients with germline BRCA-mutated platinum-resistant or partially platinum-sensitive relapsed ovarian cancer. We conducted a phase III trial (SOLO3) of olaparib tablets versus nonplatinum chemotherapy in patients with germline BRCA-mutated platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum-based chemotherapy.

PATIENTS AND METHODS In this randomized, open-label trial, patients were randomly assigned 2:1 to olaparib 300 mg twice a day or physician's choice single-agent nonplatinum chemotherapy (pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan). The primary end point was objective response rate (ORR) in the measurable disease analysis set assessed by blinded independent central review (BICR). The key secondary end point was progression-free survival (PFS) assessed by BICR in the intent-to-treat population.

RESULTS Of 266 randomly assigned patients, 178 were assigned to olaparib and 88 to chemotherapy. In patients with measurable disease (olaparib, $n = 151$; chemotherapy, $n = 72$), the BICR-assessed ORR was significantly higher with olaparib than with chemotherapy (72.2% v 51.4%; odds ratio [OR], 2.53 [95% CI, 1.40 to 4.58]; $P = .002$). In the subgroup who had received 2 prior lines of treatment, the ORR was 84.6% with olaparib and 61.5% with chemotherapy (OR, 3.44 [95% CI, 1.42 to 8.54]). BICR-assessed PFS also significantly favored olaparib versus chemotherapy (hazard ratio, 0.62 [95% CI, 0.43 to 0.91]; $P = .013$; median, 13.4 v 9.2 months). Adverse events were consistent with the established safety profiles of olaparib and chemotherapy.

CONCLUSION Olaparib resulted in statistically significant and clinically relevant improvements in ORR and PFS compared with nonplatinum chemotherapy in patients with germline BRCA-mutated platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum-based chemotherapy.

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ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor that traps PARP onto DNA at sites of single-strand breaks, preventing their repair and generating double-strand breaks that cannot be repaired accurately in tumors harboring defects in homologous recombination repair, such as *BRCA1* or *BRCA2* mutations (BRCAm), leading to an accumulation of DNA damage and tumor cell death.¹ In a pooled analysis² of phase I³⁻⁵ and II⁶⁻⁹ trials, a durable response to olaparib capsules 400 mg twice a day administered as treatment, rather than maintenance therapy, occurred in women with heavily pretreated relapsed ovarian cancer and a germline BRCAm. The objective response rate (ORR) was 42% in

the subgroup with platinum-sensitive disease who had received at least 3 prior chemotherapy regimens.² Olaparib gained approval in the United States for treating women with germline BRCAm advanced ovarian cancer who have received 3 or more prior lines of chemotherapy,¹⁰ with a confirmatory trial mandated.

Single-agent nonplatinum chemotherapy is often used in heavily pretreated women with relapsed ovarian cancer, because a survival advantage with platinum-based chemotherapy has been shown only in first- and second-line treatment settings.^{11,12} Study 12 compared olaparib capsules 200 or 400 mg twice a day with pegylated liposomal doxorubicin (PLD) in patients with platinum-resistant or partially platinum-sensitive

relapsed ovarian cancer and a germline BRCAm.⁷ Median progression-free survival (PFS; primary end point) was 8.8 versus 7.1 months with olaparib 400 mg twice a day and PLD (hazard ratio [HR], 0.86 [95% CI, 0.45 to 1.62]; $P = .63$), and the ORR was 31% versus 18% ($P = .11$).⁷ However, higher activity for olaparib versus PLD was observed in the subgroup of patients with partially platinum-sensitive disease ($n = 34$; ORR, 47% v 26%; median PFS, 9.2 v 7.4 months; data on file; Study D0810C00012). PLD seemed to have greater efficacy in Study 12 than previously reported in patients with unknown BRCAm status.¹³

We conducted the confirmatory phase III SOLO3 study to evaluate whether olaparib tablet monotherapy improves outcomes compared with physician's choice single-agent nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCAm who have received at least 2 prior lines of platinum-based chemotherapy.

PATIENTS AND METHODS

Study Design and Participants

SOLO3 is a randomized, controlled, open-label, phase III trial conducted in 13 countries. Eligible patients were ≥ 18 years of age and had relapsed high-grade serous or high-grade endometrioid ovarian cancer, primary peritoneal cancer, and/or fallopian tube cancer, with at least 1 lesion (measurable and/or nonmeasurable) that could be accurately assessed at baseline by computed tomography/magnetic resonance imaging and was suitable for repeated assessment. Patients had a deleterious or suspected deleterious germline BRCAm and an Eastern Cooperative Oncology Group performance status of 0-2. Patients had received at least 2 prior lines of platinum-based chemotherapy for ovarian cancer and were partially platinum sensitive (progression 6-12 months after the end of the last platinum-based regimen) or platinum sensitive (progression > 12 months after the end of the last platinum-based regimen).

Secondary to challenges in patient recruitment resulting from the entry of PARP inhibitors to routine clinical practice, the target number of randomly assigned patients was amended from 411 to 250, and the primary end point was amended from PFS to ORR on September 29, 2017. The trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and the AstraZeneca policy of bioethics,¹⁴ under the auspices of an independent data-monitoring committee. AstraZeneca was responsible for overseeing the collection, analysis, and interpretation of the data. All patients provided written informed consent. Full eligibility criteria and the protocol are provided in the Data Supplement (online only).

Random Assignment and Procedures

Patients were randomly assigned 2:1 to olaparib tablets 300 mg twice a day or to physician's choice of single-agent chemotherapy: PLD 50 mg/m² on day 1 every 4 weeks; paclitaxel 80 mg/m² on days 1, 8, 15, and 22 every 4 weeks;

gemcitabine 1,000 mg/m² on days 1, 8, and 15 every 4 weeks; or topotecan 4 mg/m² on days 1, 8, and 15 every 4 weeks. The investigator made his/her chemotherapy choice before random assignment. Random assignment was performed using an interactive voice and Web response system, and it used a block design with stratification according to the selected chemotherapy (PLD v paclitaxel v gemcitabine v topotecan), the number of prior lines of chemotherapy for ovarian cancer (2 or 3 v ≥ 4), and the time to disease progression after the end of the last platinum-based chemotherapy regimen (6-12 months v > 12 months).

Study treatment continued until objective radiologic disease progression (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 criteria) or until the patient experienced unacceptable toxicity or met other discontinuation criteria (Data Supplement). After study treatment discontinuation, patients could receive the most appropriate anticancer treatment (as defined by the investigator; Data Supplement). Computed tomography or magnetic resonance imaging was performed at baseline, then at 8-week intervals for 48 weeks and then every 12 weeks. Health-related quality of life (HRQoL) was assessed using the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy–Ovarian Cancer questionnaire. These questionnaires were completed at baseline and at day 29 and then every 8 weeks up to week 48.

Outcomes

The primary end point was ORR as assessed by blinded independent central review (BICR) in the measurable disease analysis set (MDAS) using RECIST version 1.1. Sensitivity analysis of ORR used investigator assessment. Secondary end points were PFS as assessed by BICR; investigator-assessed PFS; time from random assignment to second progression or death (PFS2); overall survival (OS); time from random assignment to first subsequent therapy or death (TFST); time to earliest progression by RECIST or cancer antigen-125 (CA-125) or death (Data Supplement); and time from random assignment to study treatment discontinuation or death (TDT). The HRQoL analysis evaluated the change from baseline in the TOI score for the first 48 weeks. TOI scores range from 0 to 100, with higher scores indicating better HRQoL; a difference of 10 points indicates a clinically significant difference.^{15,16} (Data Supplement). Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

A minimum of 250 patients was needed, given the anticipation that approximately 90% of patients would have measurable disease at baseline according to BICR. At least 223 patients would give the trial $> 80\%$ power at a 2-sided significance level of 5% to show a statistically significant difference in ORR, assuming a response rate of 25% with chemotherapy and at least 45% with olaparib in patients with BICR-confirmed measurable disease at

baseline. The primary ORR analysis occurred 6 months after the last patient received the treatment.

ORR was analyzed in patients with measurable disease at baseline (MDAS). PFS and all other efficacy and HRQoL data were summarized and analyzed in the intent-to-treat population (all randomly assigned patients), and safety data were summarized in the safety analysis set (all patients receiving at least 1 dose of randomly assigned treatment).

A multiple testing procedure was used to control the type I error, with ORR tested first, PFS tested if the null hypothesis for ORR was rejected, PFS2 tested if the null hypothesis for both ORR and PFS was rejected, and OS tested if the null hypothesis for ORR, PFS, and PFS2 was rejected (Data Supplement). The ORR analysis used stratified logistic regression, with the odds ratio (OR), accompanying 95% CI, and 2-sided *P* value calculated. The PFS, PFS2, OS, TFST, time to earliest progression by RECIST or CA-125 or death, and TDT analyses used a stratified log-rank test, with the HR, accompanying 95% CI, and 2-sided *P* value calculated. A linear mixed-effect model was used to calculate the change from baseline in TOI score (Data Supplement).

RESULTS

From February 24, 2015, to May 15, 2018, 266 patients underwent random assignment (Fig 1 and Data Supplement). Of the 178 patients randomly assigned to olaparib and 88 to chemotherapy (PLD, *n* = 47; paclitaxel, *n* = 20; gemcitabine, *n* = 13; topotecan, *n* = 8; intent-to-treat population), all 178 patients in the olaparib group and 76 in the chemotherapy group received treatment (safety analysis set). Twelve women (13.6%) withdrew consent before receiving chemotherapy. The primary analysis population was composed of 151 patients (84.8%) in the olaparib group and 72 (81.8%) in the chemotherapy group with measurable disease by BICR at baseline. At primary analysis data cutoff (October 10, 2018), 43 patients in the olaparib group and 1 patient in the chemotherapy group were still receiving treatment.

Baseline characteristics were generally well balanced between treatment arms (Table 1). At least one half of the patients had received only 2 prior lines of chemotherapy, approximately two thirds were partially platinum sensitive, and PLD was the preferred chemotherapy regimen.

BICR-assessed ORR was significantly higher in the olaparib group than in the chemotherapy group (72.2% v 51.4%; OR 2.53 [95% CI, 1.40 to 4.58]; *P* = .002; Table 2 and Fig 2).

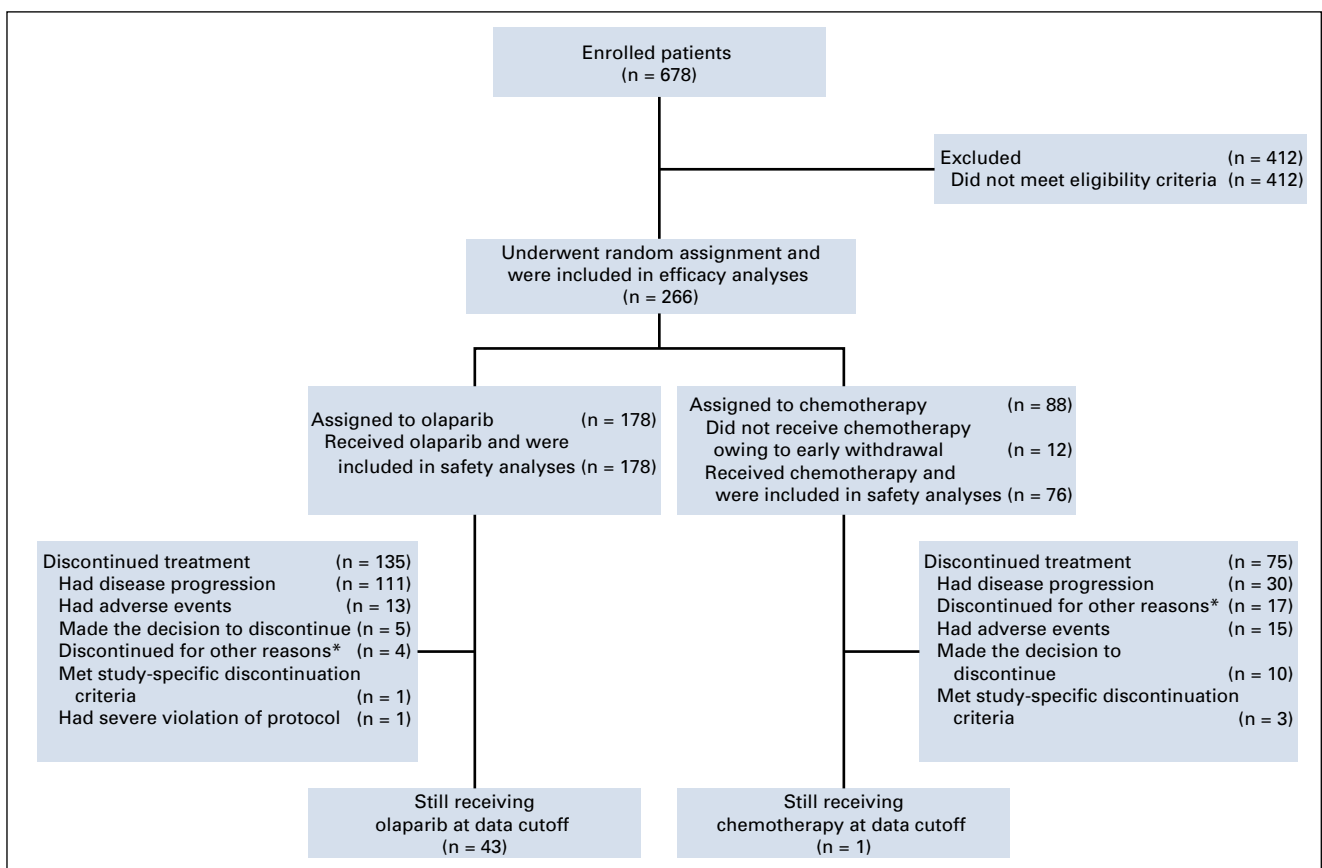


FIG 1. Trial profile. The primary analysis was conducted in the measurable disease analysis set (olaparib, *n* = 151; placebo, *n* = 72). Six of the patients in the chemotherapy group did not receive chemotherapy because of early withdrawal. (*) Other reasons for discontinuation included clinical progression (*n* = 4, olaparib; *n* = 4, chemotherapy), investigator decision (*n* = 6, chemotherapy), and chemotherapy complete (*n* = 7, chemotherapy).

TABLE 1. Characteristics of Patients at Baseline

Characteristic	Olaparib (n = 178)	Chemotherapy (n = 88)
Age, years		
Median	59.0	60.0
Range	39-79	38-85
Ethnicity		
White	148 (83.1)	75 (85.2)
Asian	24 (13.5)	10 (11.4)
Other	6 (3.4)	3 (3.4)
No. of previous chemotherapy regimens		
2	92 (51.7)	47 (53.4)
3	41 (23.0)	24 (27.3)
≥ 4	45 (25.3)	17 (19.3)
Platinum sensitivity		
Progressed ≤ 6 months after platinum	0	1 (1.1)
Progressed > 6 to ≤ 12 months after platinum	114 (64.0)	50 (56.8)
Progressed > 12 months after platinum	64 (36.0)	37 (42.0)
ECOG performance status		
0	135 (75.8)	63 (71.6)
1	42 (23.6)	25 (28.4)
2	1 (0.6)	0
Primary tumor location		
Ovary	160 (89.9)	74 (84.1)
Fallopian tube	7 (3.9)	8 (9.1)
Primary peritoneal	10 (5.6)	3 (3.4)
Other ^a	1 (0.6)	3 (3.4)
Histology		
Serous	157 (88.2)	80 (90.9)
Endometrioid	15 (8.4)	4 (4.5)
Undifferentiated	3 (1.7)	3 (3.4)
Mixed serous/endometrioid	3 (1.7)	0
Other ^b	0	1 (1.1)
Germline BRCA mutation by Myriad testing		
<i>BRCA1</i>	120 (67.4)	52 (59.1)
<i>BRCA2</i>	50 (28.1)	32 (36.4)
Negative on Myriad testing	2 ^c (1.1)	0
Missing	6 ^d (3.4)	4 ^e (4.5)
Prespecified study chemotherapy		
Pegylated liposomal doxorubicin	90 (50.6) ^e	47 (53.4)
Paclitaxel	37 (20.8) ^e	20 (22.7)
Gemcitabine	36 (20.2) ^e	13 (14.8)
Topotecan	15 (8.4) ^e	8 (9.1)

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

^aOther primary tumor locations were rectal wall in the olaparib arm, and uterus, liver, and pleura in the chemotherapy arm.

^bThe other histology type in the chemotherapy arm was adenocarcinoma, poorly differentiated.

^cPatients did not have a deleterious or suspected deleterious germline BRCA mutation on central Myriad testing but had been shown to have a germline *BRCA1* or *BRCA2* mutation on local testing.

^dCentral Myriad results were not available, but patients had been shown to have a germline *BRCA1* or *BRCA2* mutation on local testing.

^eInvestigators assigned all study patients to a chemotherapy option before the patients were randomly assigned, so the olaparib column shows the chemotherapy option that the patients assigned to olaparib would have received had they been randomly assigned to the chemotherapy arm instead.

TABLE 2. Best Objective Response by BICR

Outcome	Olaparib (n = 151)	Chemotherapy (n = 72)
Objective response	109 (72.2)	37 (51.4)
Complete response	14 (9.3)	2 (2.8)
Partial response	95 (62.9)	35 (48.6)
Stable disease ^a	25 (16.6)	19 (26.4)
Progressive disease	14 (9.3)	9 (12.5)
RECIST progression	12 (7.9)	7 (9.7)
Death ^b	2 (1.3)	2 (2.8)
Not evaluable ^c	3 (2.0)	7 (9.7)
Median time to onset of response, months (IQR)	2.0 (1.8-3.9)	3.5 (1.8-3.7)
Median duration of response, months (IQR)	9.4 (5.6-25.7)	10.2 (5.5-15.3)

NOTE. Best overall response by blinded independent central review (BICR) was assessed in the measurable disease analysis set (olaparib, n = 151; chemotherapy, n = 72). Six of the patients in the chemotherapy group did not receive chemotherapy because of early withdrawal. Data are presented as No. (%) unless indicated otherwise.

Abbreviation: IQR, interquartile range.

^aTo meet the criteria for stable disease, patients must have had stable disease at 8 weeks. Stable disease recorded ≥ 7 weeks after random assignment was considered stable disease at 8 weeks, given that the visit window for RECIST assessments was ± 1 week.

^bPatients who died ≤ 17 weeks after random assignment with no evaluable RECIST assessments were assigned to the progressive disease category.

^cPatients were not evaluable because of incomplete postbaseline assessments.

ORR results were consistent in sensitivity analyses and across predefined subgroups, although patients receiving olaparib as third- or fourth-line therapy had a higher ORR than those receiving fifth-line or later olaparib (Fig 3 and Data Supplement). In a post hoc analysis, an objective response was seen in 66 (84.6%) of 78 olaparib patients and in 24 (61.5%) of 39 chemotherapy patients (OR, 3.44 [95% CI, 1.42 to 8.54]) in patients who had received 2 prior lines of treatment (52.5% of the MDAS), and in 43 (58.9%) of 73 olaparib patients and 13 (39.4%) of 33 chemotherapy

patients (OR 2.21 [95% CI, 0.96 to 5.20]) in patients who had received ≥ 3 prior lines of therapy (47.5% of the MDAS). ORR was 58.5% in the PLD subgroup, 56.3% in the paclitaxel subgroup, 20.0% in the gemcitabine subgroup, and 40.0% in the topotecan subgroup (Fig 3 and Data Supplement).

The risk of disease progression as assessed by BICR or death (proportion of patients with events [data maturity], 59.8%) was significantly reduced by 38% with olaparib versus chemotherapy (HR, 0.62 [95% CI 0.43 to 0.91]; $P = .013$), with a median PFS of 13.4 months for olaparib

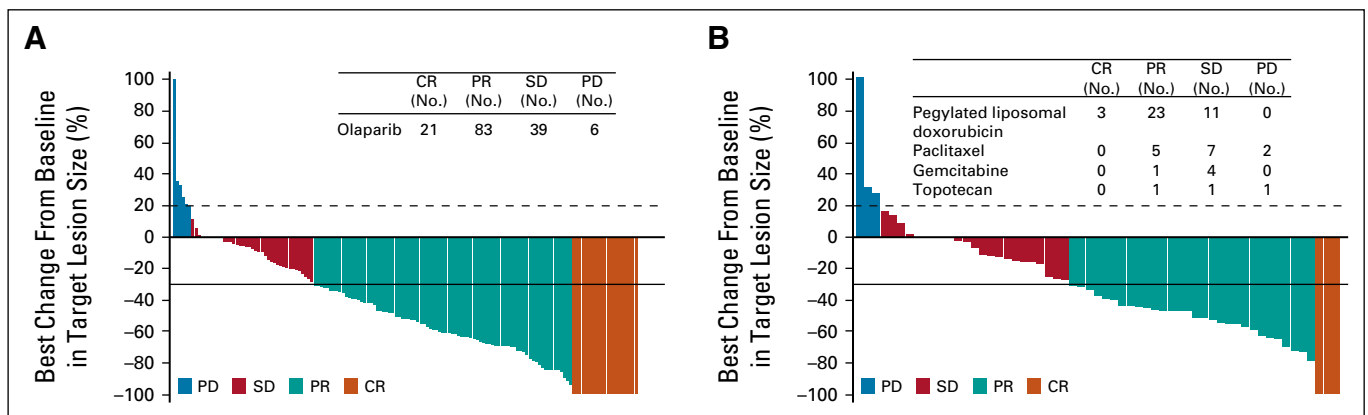


FIG 2. Best response for target lesions by patient in the olaparib and single-agent chemotherapy groups based on investigator assessment. (A) Best change from baseline in target lesion size in the olaparib group. (B) Best change from baseline in target lesion size in the single-agent chemotherapy group, with the accompanying table showing best response by chemotherapy agent. The best change from baseline in target lesion size is based on investigator assessment (RECIST version 1.1) in the measurable disease analysis set (olaparib, n = 160; chemotherapy; n = 78). Eleven patients in the olaparib group and 19 patients in the chemotherapy group were not evaluable. The dashed line represents the threshold for progressive disease (a $\geq 20\%$ increase in the sum of diameters of target lesions), and the solid line represents the threshold for partial response (a $\geq 30\%$ decrease in the sum of diameters of target lesions). CR, complete response; PD, disease progression, PR, partial response; SD, stable disease.

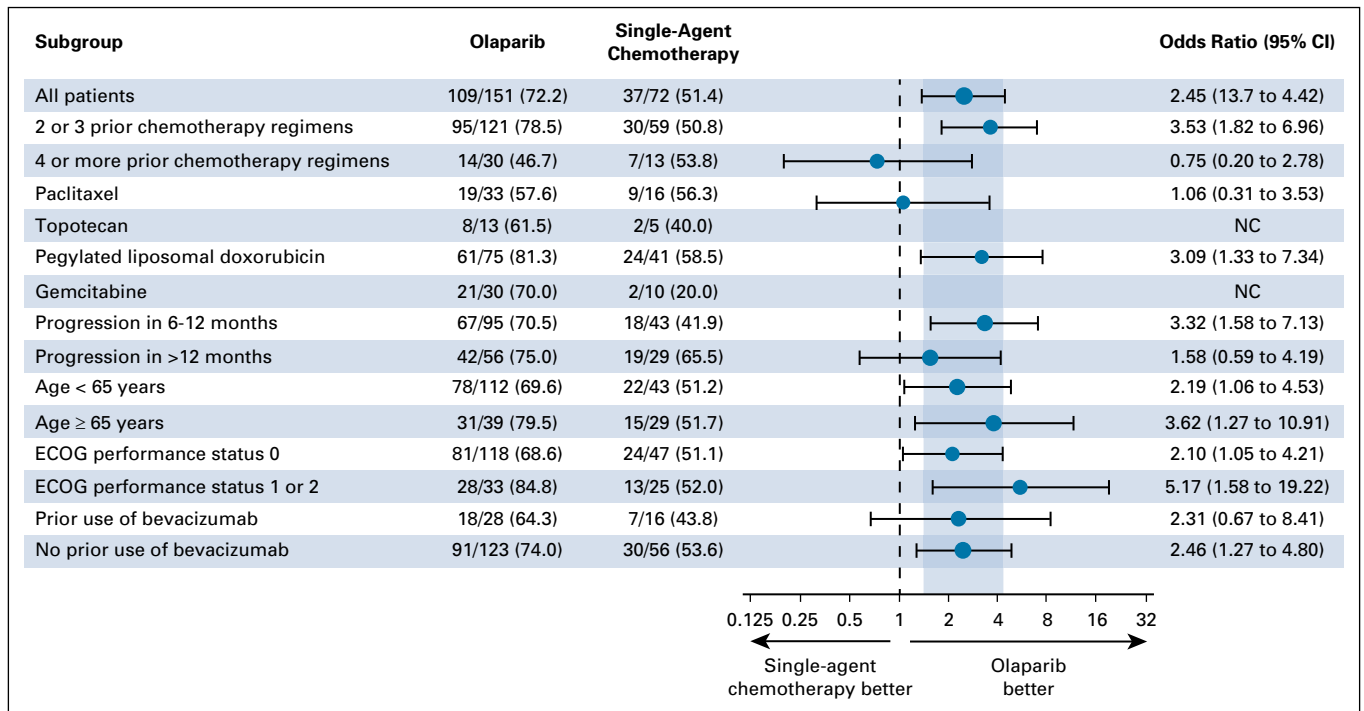


FIG 3. Subgroup analysis of objective response rate. Objective response was assessed in the measurable disease analysis set on the basis of blinded independent central review. The analysis was performed using unadjusted logistic regression, including in all patients. For the odds ratios, the size of the circle is proportional to the number of responses, the vertical gray band represents the 95% CI for all patients, and the dashed line indicates the point of no effect. ECOG, Eastern Cooperative Oncology Group; NC, not calculated.

versus 9.2 months for chemotherapy (Fig 4A). The HR for investigator-assessed disease progression or death (data maturity, 69.9%) was 0.49 (95% CI, 0.35 to 0.70; $P < .001$), with a median PFS of 13.2 months for olaparib versus 8.5 months for chemotherapy (Fig 4B). The HR for PFS on the basis of BICR was 0.69 (95% CI, 0.48 to 1.00) in the prespecified subgroup of patients with measurable disease by BICR (Data Supplement).

TFST and TDT were delayed, with a median TFST of 15.1 months for olaparib versus 10.2 months for chemotherapy (HR, 0.48 [95% CI, 0.33 to 0.71]; $P < .001$) and a median TDT of 13.3 months versus 5.1 months (HR, 0.17 [95% CI, 0.11 to 0.25]; $P < .001$; Data Supplement).

The HR for PFS2 (data maturity, 41.0%) was 0.81 (95% CI, 0.52 to 1.26; $P = .35$), and the median PFS2 was 23.6 months for olaparib versus 19.6 months for chemotherapy. OS data are immature.

Median (interquartile range) total treatment durations were 11.3 months (7.3-19.3 months) for olaparib, 6.0 months (4.6-9.5 months) for PLD, 5.1 months (3.7-6.4 months) for paclitaxel, 3.3 months (1.3-7.3 months) for gemcitabine, and 6.2 months (3.5-8.7 months) for topotecan. The most common adverse events were nausea, fatigue/asthenia, anemia, vomiting, and diarrhea in the olaparib group and fatigue/asthenia, palmar-plantar erythrodysesthesia (PPE), nausea, neutropenia, and anemia in the chemotherapy

group, and the most common grade ≥ 3 adverse events were anemia in the olaparib group and PPE and neutropenia in the chemotherapy group (Table 3).

Serious adverse events occurred in 23.6% of patients in the olaparib group (most commonly anemia [2.8% of patients]) versus 18.4% of patients in the chemotherapy group (most commonly vomiting [3.9%]; Data Supplement). Myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) occurred in 4 patients (2.2%) in the olaparib group and in 3 patients (3.9%) in the chemotherapy group, and new primary malignancies occurred in 3 patients (1.7%) in the olaparib group and in no patients in the chemotherapy group (Data Supplement). Fatal adverse events occurred in 4 patients (2.2%) in the olaparib group (MDS; cardiopulmonary decompensation; AML and subarachnoid hemorrhage; and sepsis) versus 1 patient (1.3%) in the chemotherapy group (mesenteric vein thrombosis).

Adverse events were usually managed by dose modification, with fewer discontinuations seen with olaparib than with chemotherapy (Table 3 and Data Supplement). The most common adverse events leading to discontinuation were vomiting, anemia, and thrombocytopenia in the olaparib group and PPE, mucosal inflammation, peripheral neuropathy, and neutropenia in the chemotherapy group (Data Supplement).

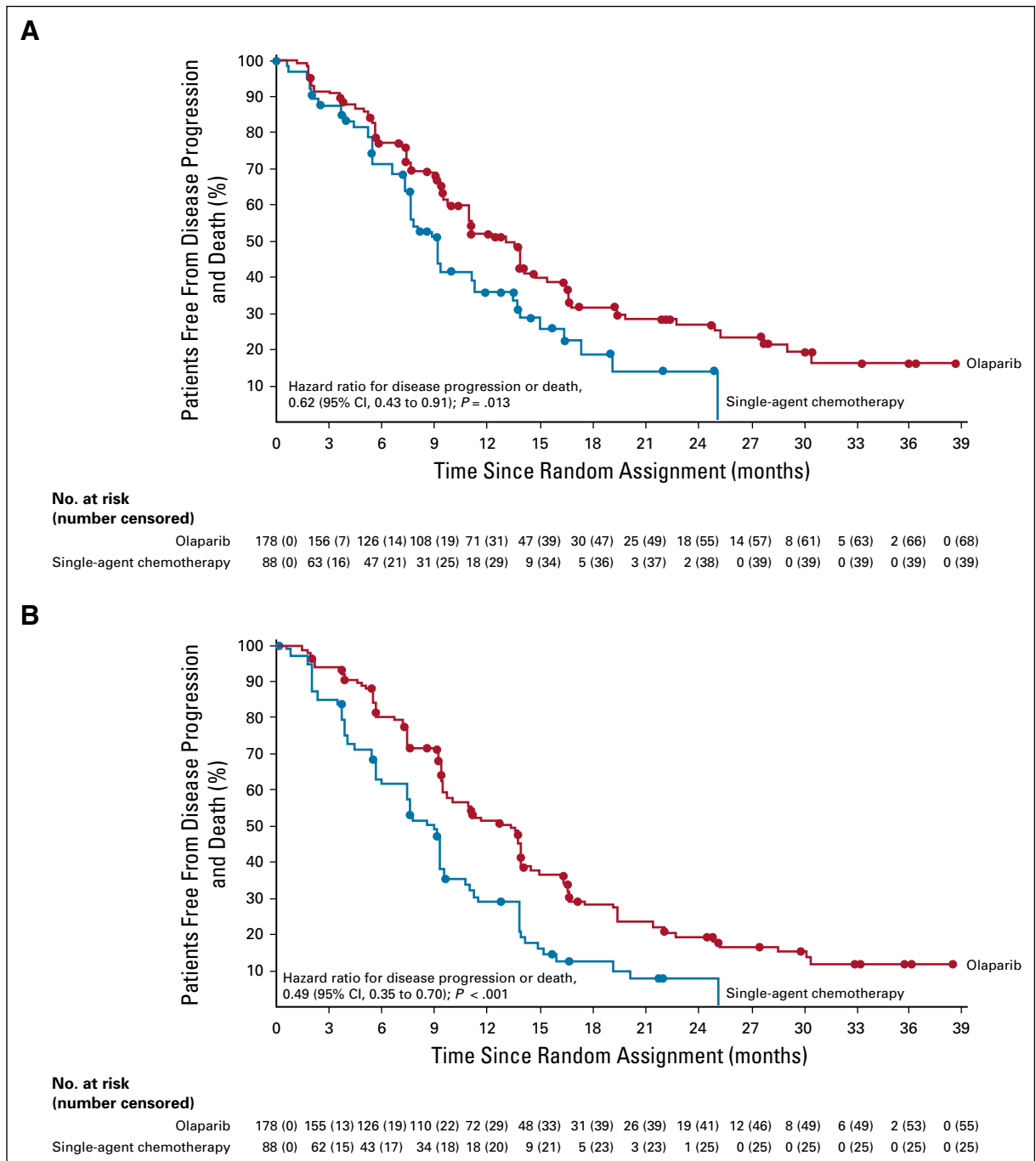


FIG 4. Kaplan-Meier estimates of progression-free survival. (A) Kaplan-Meier estimates of blinded independent central review-assessed disease progression or death in the olaparib group and the chemotherapy group. The median duration of follow-up for censored patients was 13.8 months (interquartile range [IQR], 7.51-22.08 months) in the olaparib group and 3.9 months (IQR, 0.03-12.75 months) in the chemotherapy group. (B) Kaplan-Meier estimates of investigator-assessed disease progression or death in the olaparib group and the chemotherapy group.

Mean TOI scores at baseline were 73.2 in the olaparib group and 71.8 in the chemotherapy group. The overall least-squares mean change from baseline in TOI score was -2.3 with olaparib ($n = 167$) versus -4.8 with chemotherapy ($n = 62$), with a between-group difference of 2.5 (95% CI, -0.5 to 5.5; $P = .108$; Data Supplement).

DISCUSSION

The phase III SOLO3 study provides important prospective data regarding the efficacy of olaparib and nonplatinum chemotherapy agents in patients with heavily pretreated platinum-sensitive relapsed ovarian cancer and a germline BRCAm. Although patients with platinum-sensitive relapsed

TABLE 3. Summary of Adverse Events

Adverse event	Olaparib (n = 178)		Chemotherapy (n = 76)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any	174 (97.8)	89 (50.0)	73 (96.1)	36 (47.4)
Leading to dose interruption/delay	85 (47.8)		32 (42.1)	
Leading to dose reduction	48 (27.0)		25 (32.9)	
Leading to treatment discontinuation	13 (7.3)		15 (19.7)	
Nonhematologic				
Nausea	115 (64.6)	2 (1.1)	26 (34.2)	1 (1.3)
Fatigue/asthenia	93 (52.2)	8 (4.5)	32 (42.1)	1 (1.3)
Vomiting	68 (38.2)	2 (1.1)	17 (22.4)	2 (2.6)
Diarrhea	50 (28.1)	0	13 (17.1)	0
Abdominal pain	38 (21.3)	2 (1.1)	11 (14.5)	0
Headache	28 (15.7)	0	9 (11.8)	0
Constipation	22 (12.4)	0	17 (22.4)	0
Alopecia	11 (6.2)	0	12 (15.8)	1 (1.3)
Stomatitis	7 (3.9)	1 (0.6)	14 (18.4)	3 (3.9)
PPE	1 (0.6)	0	27 (35.5)	9 (11.8)
Hematologic				
Anemia ^a	91 (51.1)	38 (21.3)	19 (25.0)	0
Neutropenia ^b	41 (23.0)	17 (9.6)	32 (42.1)	12 (15.8)
Thrombocytopenia ^c	21 (11.8)	7 (3.9)	8 (10.5)	2 (2.6)

NOTE. Adverse events occurred in at least 15% of patients in either treatment group (except where noted) from the time of informed consent, throughout the study drug treatment period and up to 30 days after the end of treatment (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.) Data are presented as No. (%).

Abbreviation: PPE, palmar-plantar erythrodysesthesia.

^aAnemia includes anemia, decreased hemoglobin level, decreased hematocrit, decreased red blood cell count, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.

^bNeutropenia includes neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, and agranulocytosis.

^cThrombocytopenia occurred in < 15% of patients in each treatment group, but the data are included to provide a more complete hematologic toxicity profile. Thrombocytopenia includes thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit.

disease are likely to be retreated with platinum-based chemotherapy, benefit diminishes with third-line and later treatment,¹⁷ with no randomized data supporting an OS advantage for platinum-based chemotherapy beyond second line. The greater-than-expected activity shown by PLD in germline BRCA-mutated ovarian cancer⁷ raised the possibility of better treatment outcomes for heavily pretreated patients with a BRCAm. It is not surprising that most patients in SOLO3 had partially platinum-sensitive disease considering the nonplatinum chemotherapy control arm and the concept that using a nonplatinum agent to extend the platinum-free interval and potentially improve outcomes in this population was under investigation when SOLO3 was designed. Although not having a platinum agent in the comparator arm is a limitation, nonplatinum agents are acceptable options in heavily pretreated women, given that platinum agents have not demonstrated an OS benefit beyond the second-line setting.

Making go/no-go decisions during the development of PARP inhibitors has not always been straightforward.¹⁸ The development of olaparib capsules was delayed when patients in the control arm of the phase II Study 12, all of whom had germline BRCAm, responded much better than expected to PLD.⁷ The results of SOLO3, which to our knowledge is the first phase III trial to evaluate PARP inhibitor treatment in this setting, definitively demonstrate the advantage of the established olaparib tablet dose over nonplatinum chemotherapy. SOLO3 met its primary end point, showing a statistically significant and clinically relevant improvement in ORR in favor of olaparib. This was achieved despite the higher-than-predicted ORR seen in the chemotherapy arm.

In terms of secondary end points, PFS significantly favored olaparib versus chemotherapy in these heavily pretreated patients. Although TFST was significantly prolonged with olaparib, interim PFS2 did not significantly differ between

the treatment arms. OS data are currently immature. Additional analysis of PFS2 and OS will be conducted.

Phase II trials investigating other PARP inhibitors in patients with platinum-sensitive relapsed ovarian cancer and a BRCAm demonstrated an ORR of 66% with rucaparib in women who had received at least 2 prior lines of chemotherapy (integrated analysis¹⁹ of Study 10²⁰ and ARIEL2²¹) and 39% with niraparib in women who had received at least 3 prior lines of chemotherapy (QUADRA²²). In patients with relapsed ovarian cancer and a BRCAm, regardless of platinum sensitivity, the ORR was 68% with third-line rucaparib therapy and 45% with fourth-line or later rucaparib therapy.¹⁹

In terms of placing SOLO3 in context with olaparib maintenance therapy trials,^{23,24} the results of SOLO1, a phase III trial in patients with newly diagnosed BRCA-mutated advanced ovarian cancer, indicate that the early introduction of olaparib offers the greatest benefit, including the potential for cure. SOLO1 showed the largest absolute gain in PFS achieved to date with any PARP inhibitor in any ovarian cancer setting: median PFS was approximately 36 months longer with maintenance olaparib than with placebo.²³ Maintenance olaparib also significantly prolonged PFS versus placebo in patients with BRCA-mutated platinum-sensitive relapsed ovarian cancer in the phase III SOLO2 trial,²⁴ with the phase II Study 19 trial showing that the benefit of maintenance olaparib extended to patients with relapsed disease without a BRCAm.^{25,26}

Thus, platinum-based chemotherapy followed by maintenance olaparib remains the first choice of treatment of patients with newly diagnosed BRCA-mutated advanced ovarian cancer and for patients with platinum-sensitive relapsed ovarian cancer regardless of BRCA status. SOLO3 provides an alternative chemotherapy-free treatment option for patients with platinum-sensitive relapsed ovarian cancer and a BRCAm who have received at least 2 prior lines of chemotherapy. In this setting, the population of patients with BRCA-mutated cancer who have not received prior PARP inhibitor therapy is expected to diminish over time as patients are identified and treated with PARP inhibitors earlier in their disease. The role of olaparib in

treating patients with relapsed disease who have received prior PARP inhibitor therapy remains to be established.

The tolerability profiles of olaparib and chemotherapy in SOLO3 were consistent with those in previous studies.^{13,23,24,26-28} The incidence of severe and serious adverse events seemed similar in the olaparib and chemotherapy groups, although women receiving chemotherapy were more than twice as likely than those receiving olaparib to discontinue treatment because of an adverse event; the nature of these adverse events differed between the treatment arms.

There is an established increased risk of MDS/AML in women with ovarian cancer who have received platinum agents.²⁹ The incidence of MDS/AML in the olaparib group was similar to that seen in the chemotherapy group and was consistent with that previously reported with olaparib^{23,24,30} and other PARP inhibitors.^{31,32} Two of the 3 patients in the chemotherapy group who developed MDS/AML had received a PARP inhibitor as a subsequent line of therapy (Data Supplement). There was no clinically meaningful change in HRQoL after olaparib monotherapy, and no clinically or statistically significant difference between olaparib and chemotherapy in HRQoL.

A limitation of SOLO3 is its open-label design. It was not feasible to conduct a blinded study, given the different routes and schedules of administration and tolerability profiles of the study drugs. To ensure this trial was robust, the primary ORR analysis was based on BICR. Other potential limitations are the changes in sample size and primary end point, which reflected increasingly slow patient recruitment because of the exclusion of patients who had received prior PARP inhibitor therapy.

In conclusion, olaparib resulted in statistically significant and clinically relevant improvements in ORR and PFS compared with nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCAm who had received at least 2 prior lines of platinum-based chemotherapy.

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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>

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Olaparib Versus Nonplatinum Chemotherapy in Patients With Platinum-Sensitive Relapsed Ovarian Cancer and a Germline BRCA1/2 Mutation (SOLO3): A Randomized Phase III Trial**

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