

# Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial

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**PURPOSE** In SOLO1, maintenance olaparib (300 mg twice daily) significantly improved progression-free survival (PFS) for patients with newly diagnosed *BRCA1*- and/or *BRCA2*-mutated advanced ovarian cancer compared with placebo (hazard ratio [HR], 0.30; 95% CI, 0.23 to 0.41; median not reached v 13.8 months). We investigated PFS in SOLO1 for subgroups of patients based on preselected baseline factors.

**PATIENTS AND METHODS** Investigator-assessed PFS subgroup analyses of SOLO1 included clinical response after platinum-based chemotherapy (complete [CR] or partial response [PR]), surgery type (upfront or interval surgery), disease status after surgery (residual or no gross residual disease), and BRCA mutation status (*BRCA1* or *BRCA2*). Additionally, we evaluated PFS in patients with stage III disease who underwent upfront surgery and had no gross residual disease. We also report objective response rate.

**RESULTS** The risk of disease progression or death was reduced with olaparib compared with placebo by 69% (HR, 0.31; 95% CI, 0.21 to 0.46) and 63% (HR, 0.37; 95% CI, 0.24 to 0.58) in patients undergoing upfront or interval surgery; 56% (HR, 0.44; 95% CI, 0.25 to 0.77) and 67% (HR, 0.33; 95% CI, 0.23 to 0.46) in patients with residual or no residual disease after surgery; 66% (HR, 0.34; 95% CI, 0.24 to 0.47) and 69% in women with clinical CR or PR at baseline (HR, 0.31; 95% CI, 0.18 to 0.52); and 59% (HR, 0.41; 95% CI, 0.30 to 0.56) and 80% (HR 0.20; 95% CI, 0.10 to 0.37) in patients with a *BRCA1* or *BRCA2* mutation, respectively.

**CONCLUSION** Patients with newly diagnosed advanced ovarian cancer achieve substantial benefit from maintenance olaparib treatment regardless of baseline surgery outcome, response to chemotherapy, or BRCA mutation type.

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## INTRODUCTION

For patients with newly diagnosed advanced ovarian cancer (OC), the standard of care is cytoreductive surgery and platinum-based chemotherapy.<sup>1,2</sup> Most patients have no evidence of disease (NED) after treatment, but approximately 70% will relapse within 3 years of diagnosis.<sup>2</sup> After recurrence, most patients receive multiple additional lines of treatment and will eventually die as a result of the disease.

Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has demonstrated efficacy in several tumor types, including advanced OC, breast, prostate, and pancreatic cancers.<sup>3-7</sup> Olaparib is approved in the United States, the European Union, and other countries as maintenance treatment for women with germline or somatic BRCA-mutated advanced OC who

are in response to first-line platinum-based chemotherapy based on the phase III SOLO1 study (ClinicalTrials.gov identifier: [NCT01844986](https://clinicaltrials.gov/ct2/show/study/NCT01844986)).<sup>8,9</sup> SOLO1<sup>10</sup> reported a substantial improvement in progression-free survival (PFS) after maintenance olaparib (tablets) versus placebo in patients with newly diagnosed advanced OC and a *BRCA1* or *BRCA2* mutation (Kaplan-Meier estimate of rate of freedom from disease progression or death at 3 years, 60% v 27%, respectively; hazard ratio [HR], 0.30; 95% CI, 0.23 to 0.41). In contrast to some contemporary trials in this setting (GOG-0218,<sup>11</sup> ENGOT-OV26/GOG-3012/PRIMA,<sup>12</sup> Imagyn050,<sup>13</sup> AGO-OVAR16<sup>14</sup>), SOLO1 recruited patients regardless of prior surgical status; patients could have undergone upfront or interval cytoreductive surgery and have residual or no gross

## ASSOCIATED CONTENT

### Data Supplement

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

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AstraZeneca was involved in the study design, data collection, data analysis, and data interpretation. Merck Sharp & Dohme also provided input in data interpretation.

## CONTEXT

### Key Objective

To explore whether all patients receiving first-line olaparib maintenance (compared with surveillance alone) will benefit from treatment regardless of baseline characteristics (preselected covariates), including those with favorable prognostic features (eg, patients with complete cytoreduction, those with complete response after platinum-based chemotherapy, or those with stage III disease who underwent upfront surgery and had no gross residual disease), or BRCA mutation status and report objective response rate to better understand the olaparib treatment effect in patients with newly diagnosed BRCA-mutated advanced ovarian cancer.

### Knowledge Generated

SOLO1 subgroup analyses of PFS reported here were consistent with those previously reported in the overall study population, demonstrating that olaparib maintenance therapy was of substantial benefit in all reported patient subgroups.

### Relevance

Regardless of patient baseline outcomes from surgery and chemotherapy or BRCA mutation type, patients with newly diagnosed advanced ovarian cancer are at high risk of disease progression and benefit from maintenance olaparib treatment.

residual disease; however, in SOLO1, patients were required to have a BRCA-mutated tumor.

Baseline factors that may affect outcomes of patients with newly diagnosed advanced OC include tumor response (complete response [CR] v partial response [PR]) after platinum-based chemotherapy, BRCA mutation status, and timing of cytoreductive surgery (interval v upfront), as well as outcomes after surgery (residual v no gross residual disease).<sup>15,16</sup> Surgical outcome has been reported as 1 of the most important independent prognostic factors for survival,<sup>16</sup> with a significant survival advantage observed in patients with no gross residual disease compared with those with residual tumor burden of 1 to 10 mm or > 10 mm in diameter.<sup>17</sup> We wished to explore whether all patients receiving first-line olaparib maintenance (compared with surveillance alone) benefit from treatment regardless of baseline characteristics, including those with favorable prognostic features (eg, complete cytoreduction or CR after platinum-based chemotherapy). In patients with no evidence of gross residual disease after surgery, it is likely that micrometastatic disease remains in almost all cases, and the risk of recurrence remains high<sup>18</sup>; despite being associated with a better prognosis, most of these patients will experience relapse later. It is possible that these patients may obtain even greater benefit from maintenance olaparib than those who have evidence of disease at baseline, because patients who initiate treatment with NED have longer PFS versus those with evidence of disease at baseline.<sup>19-21</sup>

We report the efficacy of olaparib in SOLO1 in terms of PFS using preselected baseline characteristics of surgical status and response after completion of platinum-based chemotherapy, patients with stage III disease who underwent upfront surgery and had no gross residual disease, and

BRCA mutation status. We also report objective response rate (ORR) evaluated in women with radiologic evidence of disease at baseline to better understand the olaparib treatment effect in patients with newly diagnosed BRCA-mutated advanced OC.

## PATIENTS AND METHODS

### Study Design

SOLO1 was a phase III, multicenter, randomized, double-blind study.<sup>10</sup> Patients had newly diagnosed confirmed advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III or IV) high-grade serous or endometrioid OC, primary peritoneal cancer, and/or fallopian tube cancer, were in clinical CR (defined as no radiologic evidence of disease and normal cancer antigen-125 [CA-125] level) or PR ( $\geq 30\%$  decrease in sum of diameters of target lesions or no radiologic evidence of disease after chemotherapy but abnormal CA-125 level) after platinum-based chemotherapy, and had deleterious or suspected deleterious germline or somatic BRCA mutation (Data Supplement provides testing details). Patients with stage III disease had undergone cytoreductive surgery before chemotherapy (upfront) or after initiation but before completion of chemotherapy (interval), and those with stage IV disease had undergone biopsy and/or upfront or interval cytoreductive surgery. Full inclusion/exclusion criteria have been published previously.<sup>10</sup>

### Study Treatments

After completion of first-line platinum-based chemotherapy, patients were randomly assigned 2:1 to maintenance olaparib tablets (300 mg twice daily) or placebo (Fig 1). Random assignment was stratified according to clinical response after platinum-based chemotherapy (CR or PR). Treatment was continued until investigator-assessed

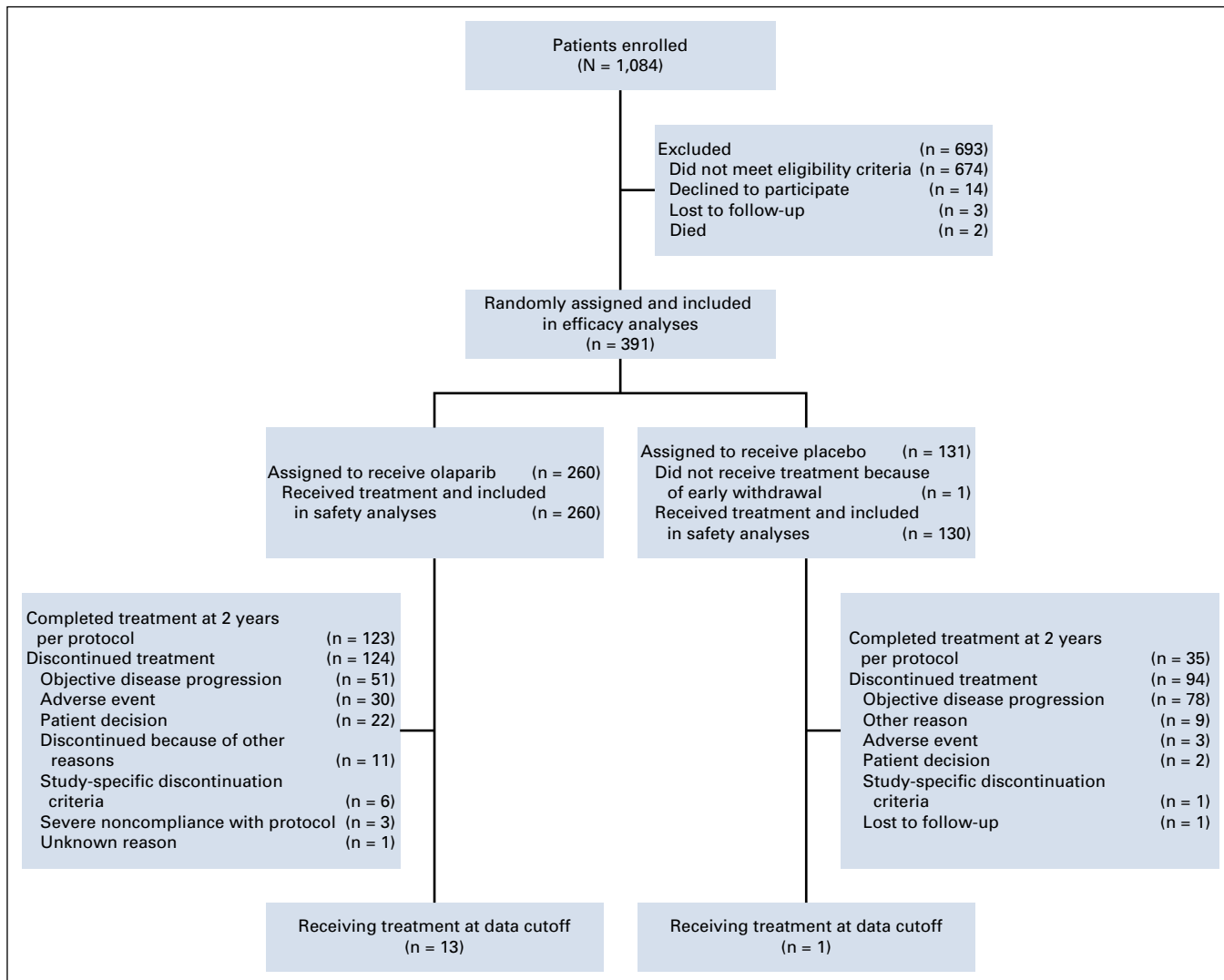


FIG 1. CONSORT diagram.

objective disease progression (modified Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1). After 2 years of treatment, patients with CR or NED discontinued treatment; those with evidence of disease could continue treatment.<sup>10</sup>

### Study Outcome Measures

The primary efficacy analysis data cutoff (DCO) was May 17, 2018.<sup>10</sup> Subgroup analyses reported here evaluated investigator-assessed PFS by modified RECIST (version 1.1) at the primary DCO. We used preselected covariates defined as clinically relevant for study patients. Pre-specified subgroup analyses included clinical response after platinum-based chemotherapy (CR or PR) and BRCA mutation status (*BRCA1/BRCA2*). Subgroup efficacy analyses were also performed based on timing of surgery (upfront/interval; exploratory) and surgery outcome (macroscopic residual or no gross residual disease; pre-specified) reported using data collected by electronic case

report form (eCRF). PFS was also evaluated in patients with stage III disease with no gross residual disease after upfront surgery to determine the value of maintenance olaparib in patients with favorable prognostic features.

ORR (modified RECIST) was a secondary end point evaluated in women with radiologic evidence of disease at baseline. ORR was calculated based on overall visit responses from each postbaseline RECIST assessment (investigator assessed) before detection of progression or initiation of subsequent anticancer therapy.

### Statistical Analysis

For subgroup analyses of PFS, the HRs (olaparib:placebo) and associated 95% CIs were calculated from a Cox proportional hazards model that contained the treatment term, factor (subgroup), and treatment-by-factor interaction term. CIs were calculated using a profile likelihood approach.<sup>22</sup> An HR < 1 favored olaparib. Subgroup analyses of PFS were not powered to detect a statistically significant

**TABLE 1.** Baseline Patient Characteristics for the Overall Study Population and According to Patient BRCA Mutation Status

Characteristic	ITT Population by BRCA Mutation Status						
	ITT Population (n = 391)		BRCA1 Mutation (n = 282)		BRCA2 Mutation (n = 106)		BRCA1 and BRCA2 Mutation <sup>a</sup>
	Olaparib (n = 260)	Placebo (n = 131)	Olaparib (n = 191)	Placebo (n = 91)	Olaparib (n = 66)	Placebo (n = 40)	Olaparib (n = 3)
Age, years							
Median	53	53	52	51	59	58	55
Range	29-82	31-84	29-82	31-74	39-74	39-84	44-59
Response after platinum-based chemotherapy, No. (%)							
Clinical CR <sup>b</sup>	189 (73)	101 (77)	136 (71)	71 (78)	51 (77)	30 (75)	2 (67)
PR <sup>c</sup>	71 (27)	30 (23)	55 (29)	20 (22)	15 (23)	10 (25)	1 (33)
No. of cycles of platinum-based chemotherapy							
Median	6	6	6	6	6	6	6
Range	4-9	5-9	4-9	5-9	4-9	6-9	6-6
ECOG performance status, No. (%)							
0	200 (77)	105 (80)	148 (77)	75 (82)	49 (74)	30 (75)	3 (100)
1	60 (23)	25 (19)	43 (23)	15 (16)	17 (26)	10 (25)	0
Missing	0	1 (1)	0	1 (1)	0	0	0
FIGO stage, No. (%)							
III	220 (85)	105 (80)	160 (84)	75 (82)	58 (88)	30 (75)	2 (67)
IV	40 (15)	26 (20)	31 (16)	16 (18)	8 (12)	10 (25)	1 (33)
BRCA mutation, No. (%) <sup>d</sup>							
BRCA1	191 (73)	91 (69)	—	—	—	—	—
BRCA2	66 (25)	40 (31)	—	—	—	—	—
BRCA1 and BRCA2	3 (1)	0	—	—	—	—	—
BRCA mutation status, No. (%) <sup>e</sup>							
Myriad/BGI-confirmed germline BRCA mutation	253 (97)	130 (99)	191 (100)	91 (100)	66 (100)	40 (100)	3 (100)
FMI-confirmed BRCA mutation	214 (82)	110 (84)	160 (84)	75 (82)	52 (79)	35 (88)	2 (67)
History of cytoreductive surgery, No. (%)							
Upfront surgery	161 (62)	85 (65)	116 (61)	66 (73)	42 (64)	19 (48)	3 (100)
Residual macroscopic disease	37 (23)	22 (26)	26 (22)	15 (23)	10 (24)	7 (37)	1 (33)
No gross residual disease	123 (76)	62 (73)	90 (78)	51 (77)	31 (74)	11 (58)	2 (67)
Unknown	1 (< 1)	1 (1)	0	0	1 (2)	1 (5)	0
Interval cytoreductive surgery	94 (36)	43 (33)	70 (37)	23 (25)	24 (36)	20 (50)	0
Residual macroscopic disease	18 (19)	7 (16)	12 (17)	6 (26)	6 (25)	1 (5)	0
No gross residual disease	76 (81)	36 (84)	58 (83)	17 (74)	18 (75)	19 (95)	0
No surgery before random assignment	4 (1)	3 (2)	4 (2)	2 (2)	0	1 (3)	0

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; FMI, Foundation Medicine; ITT, intention to treat; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors.

<sup>a</sup>No patients in the placebo arm had *BRCA1* and *BRCA2* mutations.

<sup>b</sup>Clinical CR was defined as no evidence of (RECIST) measurable or nonmeasurable disease in the posttreatment scan and normal cancer antigen–125 level and was determined by electronic case report form.

<sup>c</sup>PR was defined as  $\geq 30\%$  reduction in the sum of diameters of target lesions (taking baseline sum diameters as reference) from start to end of chemotherapy or no evidence of disease in the posttreatment scan but with a cancer antigen–125 level that had not decreased to within the normal range and was determined by electronic case report form.

<sup>d</sup>Myriad/BGI or locally reported; the 5 patients from China had germline BRCA mutation testing performed in China with the BGI test.

<sup>e</sup>Central germline BRCA testing used the Myriad BRACAnalysis CDx test or, in China, the BGI *BRCA1/2* genetic testing assay. Tumor BRCA mutation status was assessed in evaluable samples using the FMI FoundationOne CDx clinical trial assay. Patients with a tumor BRCA mutation but no detectable germline BRCA mutation were considered to be carrying a somatic BRCA mutation (Data Supplement).

difference between subgroups evaluated. ORR was summarized by the number and percentage of patients with measurable disease at baseline. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC).

## RESULTS

### Patient Characteristics

Patient characteristics were generally well balanced between treatment groups (Table 1).<sup>10</sup> Overall, 282 patients (72%) had a *BRCA1* mutation, 106 (27%) had a *BRCA2* mutation, and 3 (1%) had both. Patient baseline characteristics for *BRCA* mutation (Table 1) and other subgroups (Data Supplement) were generally balanced.

### PFS According to Subgroup Analysis

At DCO, median follow-up was approximately 41 months in both arms. In the olaparib arm, median treatment duration was 24.6 months, consistent with the 2-year prespecified treatment duration; for placebo, this was 13.9 months, consistent with the median PFS reported.

**Surgical status.** In total, 63% and 35% of patients underwent upfront and interval surgery, respectively; 21% and 76% had residual and no gross residual disease, respectively.

The risk of disease progression or death was reduced with olaparib compared with placebo by 69% (median PFS, not reached [NR] v 15.3 months, respectively; HR, 0.31; 95% CI, 0.21 to 0.46) and 63% (33.6 v 9.8 months; HR, 0.37; 95% CI, 0.24 to 0.58) in patients undergoing upfront and interval surgery, respectively (Fig 2A), and by 56% (29.4 v 11.3 months; HR, 0.44; 95% CI, 0.25 to 0.77) and 67% (NR v 15.3 months; HR, 0.33; 95% CI, 0.23 to 0.46) in patients with residual and no gross residual disease after surgery, respectively (Fig 2B). Similar results were observed for patients with or without residual disease after upfront surgery (Table 2).

Kaplan-Meier estimates of the percentage of patients who had undergone upfront surgery, received olaparib, and were progression free at 1, 2, and 3 years were 91%, 78%, and 69% (v 58%, 40%, and 32% receiving placebo), respectively; for those who underwent interval surgery, estimates were 83%, 66%, and 47% (v 43%, 26%, and 19%), respectively (Fig 3A). For patients who had residual macroscopic disease after cytoreductive surgery before entry into the study, 79%, 60%, and 48% of patients who received olaparib were progression free at 1, 2, and 3 years (v 41%, 28%, and 24% who received placebo), respectively; for patients who had no gross residual disease at study entry, the percentages for olaparib-treated patients were 90%, 77%, and 65% (v 57%, 38%, and 29% who received placebo; Fig 3B), respectively.

Forty-four percent of patients with stage III disease (mostly stage IIIC) underwent upfront surgery and had no gross residual macroscopic disease after surgery. For these

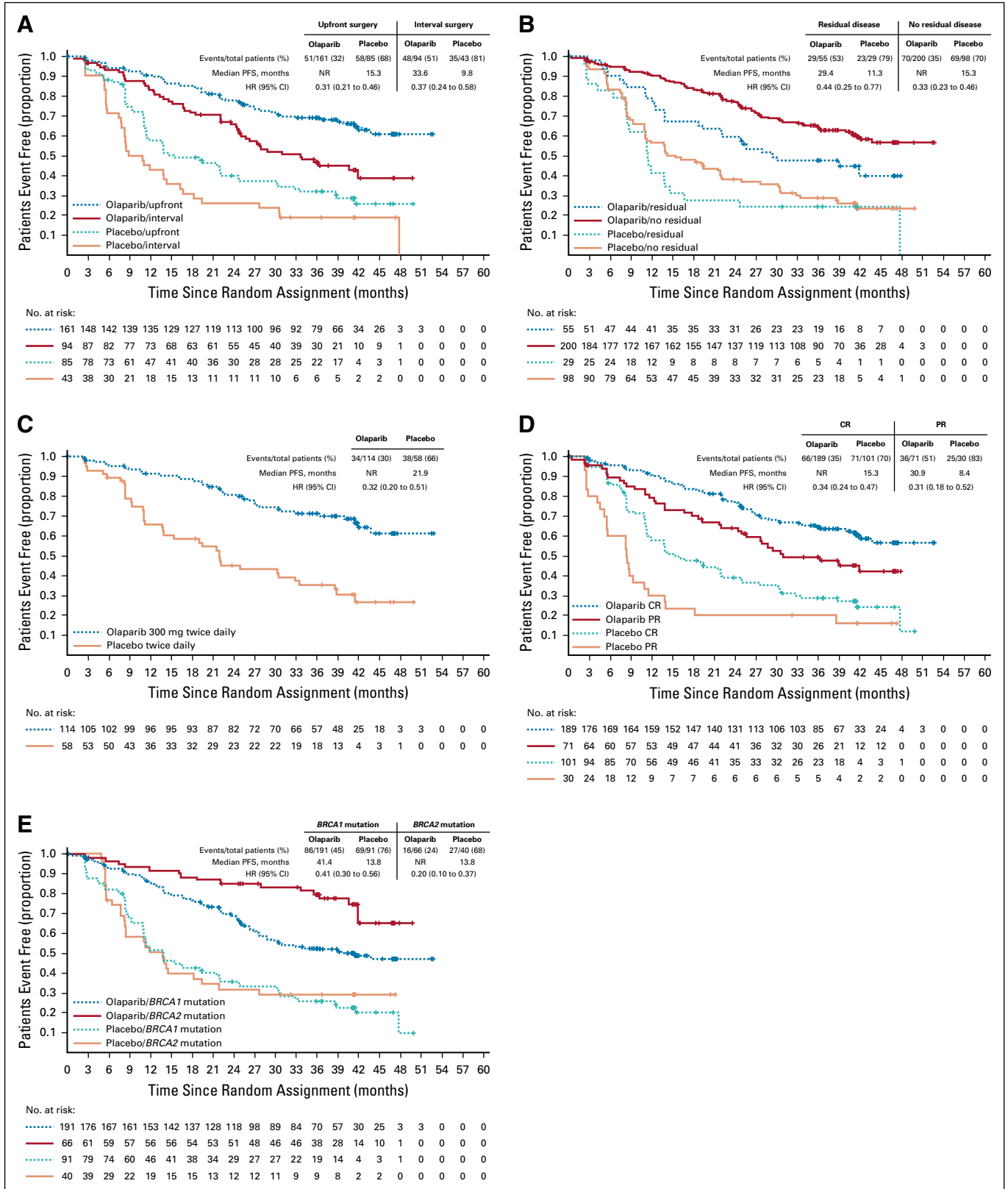
patients, the risk of disease progression or death was reduced by 68% in patients receiving olaparib compared with placebo (median PFS, NR v 21.9 months; HR, 0.32; 95% CI, 0.20 to 0.51; Fig 2C). Of those receiving olaparib, 92%, 81%, and 71% were progression free at 1, 2, and 3 years (v 66%, 45%, and 35% who received placebo), respectively. Additional data for patients with stage III disease are provided in the Data Supplement.

**Response after platinum-based chemotherapy.** On the basis of eCRF data, 74% of women entered the study with no target or nontarget lesions and normal CA-125 (clinical CR), and 26% had a  $\geq 30\%$  reduction in the sum of diameters of target lesions, taking as reference the baseline sum diameters from start to end of chemotherapy, or NED in the posttreatment scan but with a CA-125 level that had not decreased to within the normal range (PR; 35% of patients in PR had status determined by elevated CA-125 level). Risk of disease progression or death was reduced for patients receiving olaparib compared with placebo by 66% in women in clinical CR (median PFS, NR v 15.3 months; HR, 0.34; 95% CI, 0.24 to 0.47) and by 69% in women with a PR at baseline (30.9 v 8.4 months; HR, 0.31; 95% CI, 0.18 to 0.52; Fig 2D). On the basis of Kaplan-Meier estimates, the percentages of patients with a baseline CR who received olaparib and were progression free at 1, 2, and 3 years were 91%, 77%, and 65% (v 58%, 39%, and 29% receiving placebo), respectively, and those of patients with a baseline PR were 79%, 64%, and 50% (v 30%, 20%, and 20% Fig 3C), respectively.

**BRCA mutation status.** At the primary DCO, 155 patients in the *BRCA1*-mutated group (55%), 43 in the *BRCA2*-mutated group (41%), and none in the *BRCA1*- and *BRCA2*-mutated group (n = 3) experienced disease progression. Patients receiving placebo who had a *BRCA1* mutation or *BRCA2* mutation had a median PFS of 13.8 months; this was substantially increased for patients who received olaparib, with a greater PFS benefit observed for those with a *BRCA2* mutation (median PFS, NR) relative to a *BRCA1* mutation (41.4 months; Fig 2E). Kaplan-Meier estimates of the percentage of *BRCA1*-mutated patients who received olaparib and were progression free at 1, 2, and 3 years were 86%, 69%, and 53% (v 52%, 36%, and 26% receiving placebo), respectively, and those of *BRCA2*-mutated patients were 92%, 85%, and 80% (v 50%, 32%, and 29%; Fig 3D), respectively. The risk of disease progression or death was reduced for olaparib-treated patients versus those receiving placebo by 59% (HR, 0.41; 95% CI, 0.30 to 0.56) for *BRCA1*-mutated patients and by 80% (HR, 0.20; 95% CI, 0.10 to 0.37) for *BRCA2*-mutated patients (Fig 2E).

### ORR

Among women with radiologic evidence of disease at baseline (target and nontarget lesions; RECIST), ORR was 43% (n = 23) in the olaparib arm and 23% (n = 6) in the placebo arm (Table 3). CRs were reported for 28% (n = 15)



**FIG 2.** Kaplan-Meier estimates of investigator-assessed progression-free survival (PFS) for subgroup analyses based on (A) surgery timing, (B) residual macroscopic disease status, (C) patients with stage III disease who underwent upfront surgery and had no gross residual disease, (D) response after platinum-based chemotherapy at baseline, and (E) BRCA mutation status. CR, complete response; HR, hazard ratio; NR, not reached; PR, partial response.



**TABLE 2.** Investigator-Assessed PFS After Upfront Surgery Based on Residual Disease Status

Surgery	Olaparib	Placebo
Upfront surgery and no gross residual disease	n = 123	n = 62
Median PFS, months	NR	22.0
HR (95% CI)	0.33 (0.20 to 0.51)	
Upfront surgery and residual disease	n = 37	n = 22
Median PFS, months	NR	11.3
HR (95% CI)	0.29 (0.15 to 0.58)	

Abbreviations: HR, hazard ratio; NR, not reached; PFS, progression-free survival.

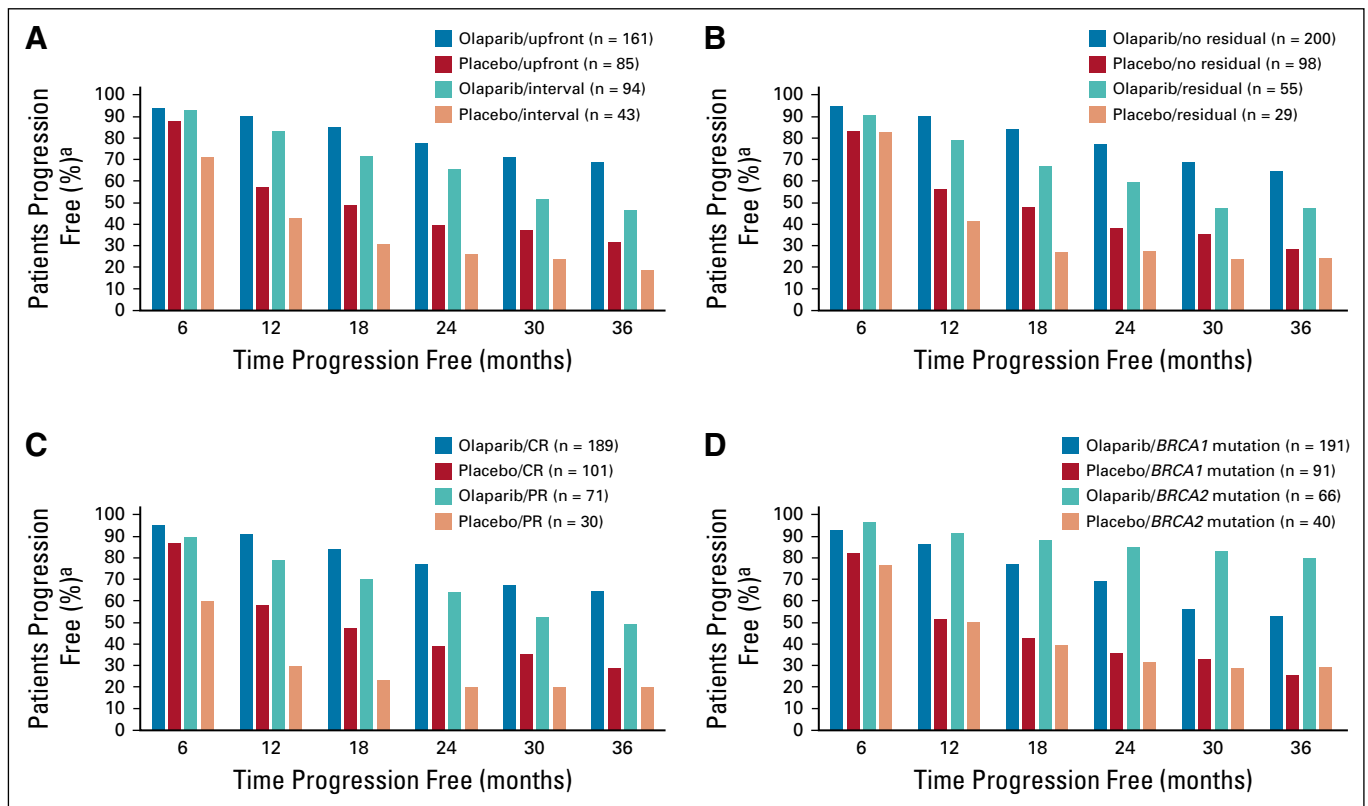
of olaparib-treated patients compared with 12% (n = 3) of patients receiving placebo, and PRs were reported for 15% (n = 8) and 12% (n = 3) olaparib- and placebo-treated patients, respectively. In patients with an objective response, median time from random assignment to onset of response and median duration of response were 10.8 and 28.2 months for olaparib and 5.4 and 8.6 months for placebo, respectively.

## DISCUSSION

The SOLO1 subgroup analyses of PFS reported here were consistent with those in the overall study population,<sup>10</sup>

demonstrating that olaparib maintenance therapy was substantially beneficial in all reported preselected patient subgroups.

Olaparib demonstrated considerable benefit in the 44% of women in SOLO1 with stage III disease who had undergone upfront surgery and had no gross residual disease, a population ineligible for several recent first-line trials. Despite optimal surgical results, these patients are still at substantial risk of disease recurrence and should be offered olaparib maintenance treatment. In addition, although they had no evidence of gross residual disease, micrometastatic disease probably remains in almost all cases.<sup>18</sup> SOLO1 was designed to reflect clinical practice by including all patients with advanced OC regardless of surgical outcome. Our data demonstrate that all BRCA-mutated patients with advanced OC should be considered at high risk of progression and receive appropriate treatment, such as olaparib maintenance, to provide the best chance of delaying disease progression. Additionally, we found that maintenance olaparib improved outcomes compared with placebo, regardless of whether patients had radiologic evidence of disease at baseline. In these patients, maintenance olaparib induced CR in 28% of women, more than double that observed with placebo (12%).



**FIG 3.** Proportion of patients free of progression or death over time for subgroup analysis—based Kaplan-Meier estimates for (A) surgery timing (8 patients had no surgery or were missing timing data [olaparib arm, n = 5; placebo arm, n = 3]), (B) residual macroscopic disease status, (C) response after platinum-based chemotherapy at baseline, and (D) BRCA mutation status (3 patients [all in olaparib arm] had both *BRCA1* and *BRCA2* mutations and were progression free up to 42 months). CR, complete response; PR, partial response. (a) Based on Kaplan-Meier estimates.

**TABLE 3.** Best Objective Response in Women With Radiologic Evidence of Disease at Baseline

Best Objective Response	No. (%)	
	Olaparib (n = 54)	Placebo (n = 26)
Objective response	23 (42.6)	6 (23.1)
CR	15 (27.8)	3 (11.5)
PR	8 (14.8)	3 (11.5)
SD $\geq$ 12 weeks	26 (48.1)	13 (50.0)
PD	4 (7.4)	7 (26.9)
NE	1 (1.9)	0

NOTE. Based on electronic case report form data.

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

The overall proportion of patients with no gross residual disease after surgery in SOLO1 was slightly higher (77% and 75% of patients in the olaparib and placebo groups, respectively) than may be expected (rate of complete resection in unselected patients with advanced-stage OC ranged between 50% and 70% in surgically specialized gynecologic cancer centers)<sup>23</sup>; our study results may reflect expertise of surgeons at clinical study sites or different characteristics of BRCA mutation versus sporadic high-grade serous cancers<sup>24</sup> rather than patient selection bias. As noted, the SOLO1 population reflects clinical practice and represents 1 of the largest phase III studies in advanced BRCA-mutated OC surgical patients. Furthermore, baseline characteristics were balanced between arms within subgroups analyzed; therefore, outcomes related to timing of surgery or residual disease status after surgery are unlikely to be influenced by baseline differences.

Efficacy results observed in the placebo arm of this study demonstrate that all patients with advanced high-grade OC should be considered at high risk of progression. Despite a large proportion of patients having optimal surgical outcomes and being in CR after chemotherapy, outcomes after placebo treatment were poor, further supporting the use of maintenance olaparib for all patients regardless of baseline characteristics. Although the differential effect of PARP inhibitors in maintenance and treatment settings has not been formally evaluated, olaparib reduced risk of disease progression and death for patients with CR or PR at baseline. There may be different prognostic factors for patients who enter the study in CR compared with PR, and we cannot compare the magnitude of benefit between the 2 subgroups based on an exploratory analysis. However, we can conclude that both subgroups of patients derived meaningful benefit from olaparib treatment, with 30% (olaparib, 50% v placebo, 20%) and 36% (olaparib, 65% v placebo, 29%) more patients being progression free at 3 years in the PR and CR groups, respectively. Similar

results were observed in the relapsed setting.<sup>21</sup> For patients who initiate olaparib in CR, the goal of treatment is to delay their disease relapse, and for patients with PR, it is to potentially induce CR and/or delay relapse and the need for subsequent chemotherapy.

Among women with evidence of disease at baseline, nearly twice as many had an objective response while receiving olaparib maintenance (43%) compared with placebo (23%). Reasons for patients receiving placebo (ie, not active treatment) experiencing a response may include a carryover effect from platinum-based chemotherapy, timing of patient scans (baseline followed by scans once every 3 months), or variability in measuring RECIST.<sup>25</sup> Of note, the ORR analysis reported classified patients as being in clinical CR or PR based on eCRF data, whereas the primary analysis used the randomization code.<sup>10</sup>

Consistent with previous prevalence studies, in SOLO1, *BRCA1* mutation was more frequent in patients with newly diagnosed advanced OC than *BRCA2* mutation.<sup>26</sup> A significant PFS benefit with olaparib versus placebo was demonstrated for all patients, regardless of mutation type; medium PFS in the placebo arm was consistent for both *BRCA1*- and *BRCA2*-mutated patients. Statistical tests were not used to compare *BRCA1*- and *BRCA2*-mutated patients; however, those with a *BRCA2* mutation (PFS HR, 0.20) seemed to receive greater benefit from maintenance olaparib than those with a *BRCA1* mutation (HR, 0.41), although the small size of the *BRCA2*-mutated subgroup and potential imbalances in baseline characteristics (ie, more adverse prognostic factors in the placebo v olaparib arm) should be noted (baseline characteristics were generally balanced for *BRCA1*- and *BRCA2*-mutated patients combined). By 2 years, only 12 *BRCA2*-mutated patients remained at risk for progression in the placebo arm. It therefore seems a *BRCA2* mutation may be a marker of response to olaparib rather than a prognostic indicator in SOLO1. This trend for differential benefit between *BRCA1*- and *BRCA2*-mutated patients was not reported with olaparib maintenance therapy for platinum-sensitive relapsed OC in SOLO2<sup>6</sup> (data on file, AstraZeneca, Cambridge, UK; ClinicalTrials.gov identifier: [NCT01874353](https://clinicaltrials.gov/ct2/show/study/NCT01874353)), although enrichment of *BRCA2* mutation was observed among long-term responders to olaparib in Study 19.<sup>27</sup> One explanation for this could be resistance mechanisms associated with *BRCA1*. One mechanism is the production of functional hypomorphic isoforms of *BRCA1* protein from alternative messenger RNA splicing, which has been reported to contribute to resistance to platinum-based chemotherapy and PARP inhibition.<sup>28</sup> In a subanalysis of GOG-0218, PFS was increased in patients with a *BRCA2* versus *BRCA1* mutation (median, 21.6 v 15.7 months) regardless of treatment received.<sup>29</sup> However, in SOLO1, median PFS and Kaplan-Meier estimates at 1, 2, and 3 years were similar for *BRCA1*- and *BRCA2*-mutated patients who received placebo.



A limitation of our analyses is the relatively small patient numbers in some subgroups, including those receiving interval debulking surgery (n = 94 and 43 for olaparib and placebo, respectively), those with residual disease after surgery (n = 55 and 29, respectively), and those in clinical PR after platinum-based chemotherapy (n = 71 and 30, respectively). Although relatively small subgroups, patients receiving olaparib maintenance treatment benefited from treatment.

In conclusion, maintenance therapy with olaparib provided a substantial PFS benefit among women with newly diagnosed advanced OC and a BRCA mutation. This PFS

benefit with olaparib was achieved in all subgroups irrespective of surgery timing, residual disease status after surgery, response after platinum-based chemotherapy (CR or PR), or type of BRCA mutation. Continued follow-up of these patients is important to provide information on which subsets of patients will remain progression free and have NED long-term. These data demonstrate that regardless of patient baseline outcomes from surgery and chemotherapy or BRCA mutation type, patients with newly diagnosed advanced OC are at high risk of disease progression and benefit from maintenance olaparib treatment.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Efficacy of Maintenance Olaparib for Patients With Newly Diagnosed Advanced Ovarian Cancer With a BRCA Mutation: Subgroup Analysis Findings From the SOLO1 Trial**

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