original reports

Overall Survival Results From the POLO Trial: A Phase III Study of Active Maintenance Olaparib Versus Placebo for Germline BRCA-Mutated Metastatic Pancreatic Cancer

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abstract

PURPOSE The phase III POLO study demonstrated significant progression-free survival (PFS) benefit for active olaparib maintenance therapy versus placebo for patients with metastatic pancreatic adenocarcinoma and a germline BRCA mutation. Here, we report the final analysis of overall survival (OS) and other secondary end points.

PATIENTS AND METHODS Patients with a deleterious or suspected deleterious germline BRCA mutation whose disease had not progressed after ≥ 16 weeks of first-line platinum-based chemotherapy were randomly assigned 3:2 to active maintenance olaparib (300 mg twice daily) or placebo. The primary end point was PFS; secondary end points included OS, time to second disease progression or death, time to first and second subsequent cancer therapies or death, time to discontinuation of study treatment or death, and safety and tolerability.

RESULTS In total, 154 patients were randomly assigned (olaparib, n = 92; placebo, n = 62). No statistically significant OS benefit was observed (median 19.0 v 19.2 months; hazard ratio [HR], 0.83; 95% CI, 0.56 to 1.22; $P = .3487$). Kaplan-Meier OS curves separated at approximately 24 months, and the estimated 3-year survival after random assignment was 33.9% versus 17.8%, respectively. Median time to first subsequent cancer therapy or death (HR, 0.44; 95% CI, 0.30 to 0.66; $P < .0001$), time to second subsequent cancer therapy or death (HR, 0.61; 95% CI, 0.42 to 0.89; $P = .0111$), and time to discontinuation of study treatment or death (HR, 0.43; 95% CI, 0.29 to 0.63; $P < .0001$) significantly favored olaparib. The HR for second disease progression or death favored olaparib without reaching statistical significance (HR, 0.66; 95% CI, 0.43 to 1.02; $P = .0613$). Olaparib was well tolerated with no new safety signals.

CONCLUSION Although no statistically significant OS benefit was observed, the HR numerically favored olaparib, which also conferred clinically meaningful benefits including increased time off chemotherapy and long-term survival in a subset of patients.

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INTRODUCTION

Pancreatic cancer represents the seventh most common cause of cancer-related deaths worldwide, with increasing incidence and a 5-year survival rate of 9%-11%.[1-4] For patients diagnosed with metastatic disease, the 5-year survival rate is 3%.[4] Current first-line chemotherapies are associated with toxicities and have a median progression-free survival (PFS) of only 6 months.[5-10]

In common with breast, ovarian, and prostate cancers,[11,12] the risk of pancreatic cancer is increased in patients with loss-of-function *BRCA1* and *BRCA2* mutations. Estimates of the prevalence of such BRCA mutations among all patients with pancreatic cancer range from 4% to 8%,[13-17] with results from the screening phase of POLO indicating a prevalence of approximately 6%.[16] As a result of the deficiency in DNA double-strand break repair in cells with deleterious BRCA mutations,[18,19] patients with BRCA-mutated cancers are sensitive to platinum-based chemotherapy[20,21] and to inhibitors of the single-strand break repair protein poly(adenosine diphosphate-ribose) polymerase (PARP).[22-24]

The phase III POLO trial investigated the PARP inhibitor olaparib as active maintenance therapy for patients with metastatic pancreatic adenocarcinoma and a germline BRCA mutation (gBRCAm) whose disease had not progressed after at least 16 weeks of first-line platinum-based chemotherapy.[25] Active maintenance therapy after cessation of initial

CONTEXT

Key Objective

To present the final overall survival (OS) results of the POLO study of active maintenance therapy with olaparib relative to placebo in patients with metastatic pancreatic cancer and a germline BRCA mutation. We have previously reported that olaparib confers a significant progression-free survival benefit relative to placebo.

Knowledge Generated

No statistically significant OS benefit for olaparib relative to placebo was observed. Kaplan-Meier OS curves separated from approximately 24 months, and estimated 3-year survival rates were 33.9% for olaparib and 17.8% for placebo. Statistically significant benefits were demonstrated for other key secondary end points, including time to treatment discontinuation and time to first and second subsequent therapies.

Relevance

Active maintenance therapy with olaparib confers a significant benefit for multiple clinically relevant end points relative to placebo, including increasing time free from subsequent chemotherapy use. The results also indicate a durable response to olaparib in a subset of patients.

treatment aims to extend PFS and overall survival (OS) without compromising health-related quality of life (HRQoL).[26-30] A significant PFS benefit was demonstrated in POLO for active maintenance olaparib versus placebo (median PFS by blinded independent central review [BICR]: 7.4 months v 3.8 months; hazard ratio [HR], 0.53; 95% CI, 0.35 to 0.82; $P =$ .004).[25] The incidence of grade 3 or higher adverse events (AEs) was similar to that observed among patients receiving olaparib for the treatment of other tumor types.[31-33] Active maintenance olaparib in patients with gBRCAm metastatic pancreatic cancer has been approved in multiple countries, including Europe and the United States,[34,35] and is recommended in the National Comprehensive Cancer Network clinical guidelines.[8]

At the time of the data cutoff (DCO) for the primary PFS analysis (DCO1, January 15, 2019), an interim OS analysis (OS data maturity: 46.1%) showed no significant OS difference between the olaparib and placebo arms (median OS: 18.9 months v 18.1 months; HR, 0.91; 95% CI, 0.56 to 1.46; $P =$ .68).[25] Here, we report the results of the preplanned final analysis of OS (OS data maturity: 70.1%) and other key secondary end points from POLO at the second DCO (DCO2, July 21, 2020).

PATIENTS AND METHODS

Patients, Trial Design, and Interventions

POLO was a randomized, double-blind, placebo-controlled phase III trial. The full trial Protocol (online only) has been published previously.[25] Eligible patients were age 18 years or older with histologically or cytologically confirmed metastatic pancreatic adenocarcinoma and a documented deleterious or suspected deleterious germline mutation in *BRCA1* or *BRCA2*. Patients had received at least 16 weeks of continuous first-line platinum-based chemotherapy; the

maximum duration was unlimited if no evidence of disease progression was noted by the investigator at random assignment. At any time after the minimum 16-week period, patients were permitted to discontinue the platinum component of first-line therapy while continuing other elements of their treatment regimen. All patients provided written informed consent for participation in the trial.

Patients were randomly assigned in a 3:2 ratio to receive active maintenance olaparib tablets (300 mg twice daily) or matching placebo until objective radiologic disease progression (according to modified RECIST, version 1.1) or unacceptable toxic effects. No stratification factors were used.

Trial intervention was initiated 4-8 weeks after the last dose of first-line chemotherapy. The Protocol did not allow crossover to olaparib, but after discontinuation of study drug, subsequent therapies, which could include PARP inhibitors, were administered at the investigators' discretion. POLO was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca bioethics policy, and the trial Protocol was approved by the institutional review boards at each participating center.[36]

End Points and Assessments

The primary end point was PFS assessed by BICR according to modified RECIST v1.1.[25] BICR assessment was discontinued after the primary PFS analysis at DCO1, and a sensitivity analysis of investigator-assessed PFS was performed at both DCO1 and DCO2. Key secondary end points included OS (time from date of randomization until death from any cause), time to second disease progression (PFS2; investigator-assessed objective radiologic or symptomatic progression, or death), time to first subsequent cancer therapy or death (TFST), time to second

subsequent cancer therapy or death (TSST), time to discontinuation of study treatment or death (TDT), and safety and tolerability. All end points were assessed from random assignment. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analysis

Data on efficacy were analyzed in the intention-to-treat population (all patients who underwent random assignment). Data on safety were summarized in the safety population (patients who received at least one dose of study treatment). To control strongly the overall one-sided type I error rate at 2.5%, a multiple testing plan was used across the primary end point (PFS by BICR) and key secondary end point (OS). PFS was tested first (reported in the study by Golan et al),[25] followed by OS when a significant benefit for PFS was observed. The alpha-spending plan for OS at DCO2 was observed to be two-sided $P < .046$ (on the basis of 106 events). All other secondary end points (PFS2, TFST, TSST, and TDT) were tested at a two-sided significance level of 5% without adjustment for multiplicity. Secondary end points were analyzed using the same methodology as reported previously for the primary analysis of PFS, comprising a log-rank test with the calculation of an HR and accompanying 95% CI.[25]

Data on patients with no incidence of the relevant end point at the time of the analysis were censored at the date of the last tumor assessment for which data could be evaluated. For OS, patients who were not known to have died before DCO2 were censored at the last recorded date on which they were known to be alive. Time-to-event curves were generated using the Kaplan-Meier method, which was also used to calculate medians for each trial group.[37] A sensitivity analysis for OS was conducted to control for subsequent PARP inhibitor use after study treatment discontinuation among patients in the placebo arm, using rank preserving structural failure time models.

Subgroup analyses were conducted using a Cox proportional hazards model containing the treatment group, subgroups, and treatment-by-factor interaction terms. A global interaction test between subgroups was also performed, comparing the fit of a Cox proportional hazards model including treatment, all prespecified baseline factors, and qualifying covariate-by-treatment interaction terms with a model excluding interaction terms. All reported P values are two-sided and coincide with the reported two-sided CIs.

RESULTS

Patients and Treatment

As previously reported, 3,315 patients were screened for trial entry, of whom 154 underwent random assignment (3:2 ratio; olaparib: n = 92; placebo: n = 62).[16,25] In total, 90 patients who were randomly assigned to olaparib (97.8%)

and 61 who were randomly assigned to placebo (98.4%) received ≥ 1 dose of study treatment and were included in the safety analysis set. At the DCO for the final OS analysis (DCO2), a higher proportion of patients in the olaparib arm (n = 13; 14.1%; treatment duration range: 20.0-57.5 months) than in the placebo arm (n = 2; 3.2%; treatment duration range: 45.8-48.2 months) were still receiving study treatment. Most patients who discontinued study treatment did so as a result of objective or investigator-assessed disease progression (66 [71.7%] and 55 [88.7%] patients in the olaparib and placebo arms, respectively). Full patient disposition is given in Appendix Figure A1 (online only), and a CONSORT flow diagram is given in Appendix Figure A2 (online only).

Baseline characteristics of the included patients have been previously published.[25] The median duration of the complete first-line chemotherapy regimen was 4.6 months in the olaparib arm and 4.8 months in the placebo arm (Appendix Table A1, online only). For patients for whom specific data on the duration of the platinum component of therapy were available (olaparib: n = 42; placebo: n = 28), the median duration of the platinum component was 4.5 months in the olaparib arm and 4.8 months in the placebo arm.

Final OS

The preplanned final OS analysis was performed after 108 of the 154 randomly assigned patients (70.1%) had died. The median duration of follow-up for OS in censored patients (time from random assignment to death or date last known to be alive) was 31.3 months in the olaparib arm (range: 0.3-63.5 months) and 23.9 months in the placebo arm (range: 3.9-50.6 months). The HR for OS numerically favored olaparib but did not reach statistical significance (HR, 0.83; 95% CI, 0.56 to 1.22; $P = .3487$; Fig 1). The median OS was 19.0 months in the olaparib arm and 19.2 months in the placebo arm. At the time of the analysis, 26 patients (28.3%) in the olaparib arm were alive and in follow-up, compared with 11 patients (17.7%) in the placebo arm.

The Kaplan-Meier OS curves separated from approximately 24 months (Fig 1). In total, 34 patients (37.0%) in the olaparib arm and 17 patients (27.4%) in the placebo arm survived for more than 2 years after random assignment (Fig 2). For this subset of patients, the median duration of study treatment was 25.9 months in the olaparib arm and 7.3 months in the placebo arm. The greatest point of separation in the curves was at 36 months, at which point survival rates were 33.9% in the olaparib arm and 17.8% in the placebo arm.

Final OS outcomes for prespecified subgroups were generally consistent with the overall population, and the result of the global interaction test for subgroup factors was not statistically significant ($P = .2947$; Fig 3). Median OS was longer for patients who had received > 6 months of first-line
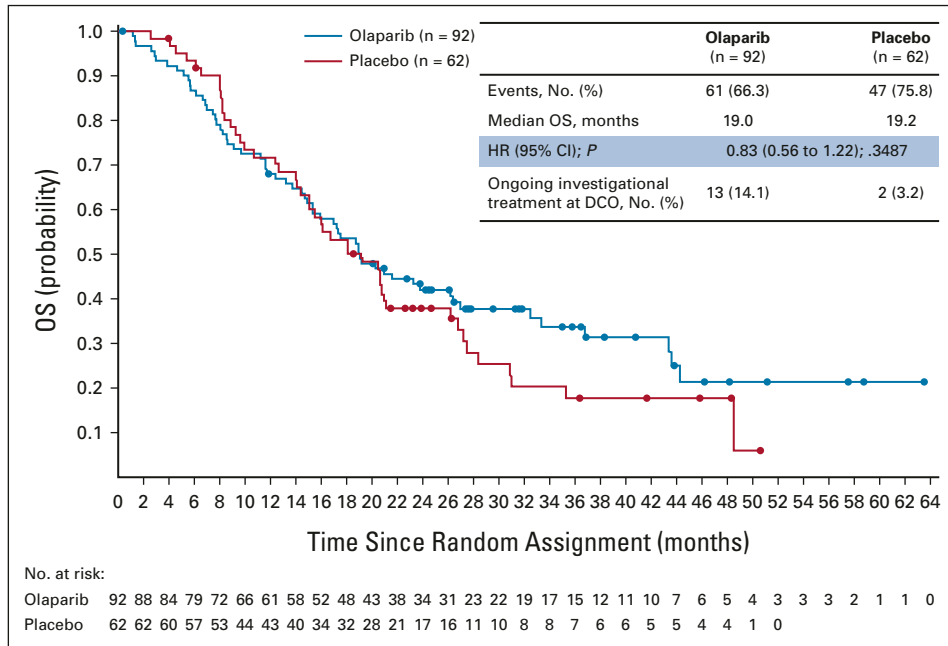
FIG 1. Kaplan-Meier estimates for OS. Circles indicate censored observations. DCO, data cutoff; HR, hazard ratio; OS, overall survival.

chemotherapy (olaparib: 32.5 months; 95% CI, 17.2 to 43.6 months; placebo: 20.6 months; 95% CI, 16.1 to 27.2 months) than for patients who had received ≤ 6 months of first-line chemotherapy (olaparib: 17.0 months; 95% CI, 11.7 to 19.2 months; placebo: 15.0 months; 95% CI, 10.6 to 21.1 months).

Subsequent Therapy After Study Treatment Discontinuation

At DCO2, the majority of patients had discontinued study treatment (77 patients [83.7%] in the olaparib arm and 59 patients [95.2%] in the placebo arm). Patients in both arms received multiple lines of subsequent therapy (range: 2-6 in

FIG 2. Swimmer plot for patients who survived more than 2 years. Each bar represents an individual patient. [a]Patients who received subsequent olaparib and had ongoing olaparib treatment at second data cutoff. OS, overall survival.

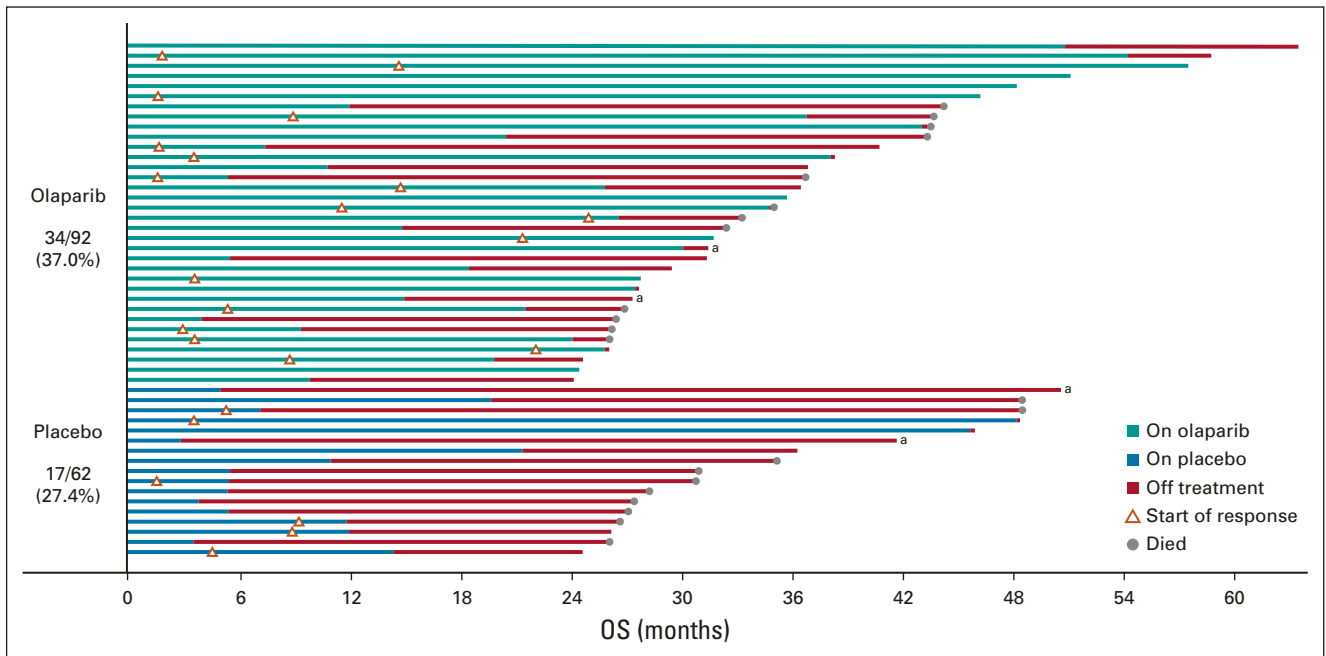| Variable and Subgroup	Olaparib	Placebo		HR (95% CI)
	No. of Patients With Event/Total No. of Patients (%)			
All patients	61/92 (66.3)	47/62 (75.8)		0.83 (0.56 to 1.22)
Previous chemotherapy				
FOLFIRINOX	50/79 (63.3)	37/50 (74.0)		0.79 (0.51 to 1.21)
Others	9/10 (90.0)	7/8 (87.5)		1.19 (0.44 to 3.32)
Presence or absence of biliary stent				
Absence of biliary stent	60/91 (65.9)	43/58 (74.1)		0.83 (0.56 to 1.23)
Type of previous chemotherapy				
Doublets	15/15 (100.0)	9/10 (90.0)		2.00 (0.89 to 4.79)
Triplets	44/73 (60.3)	34/46 (73.9)		0.70 (0.45 to 1.11)
Time on first-line treatment, months				
≤ 6	43/61 (70.5)	32/40 (80.0)		0.87 (0.55 to 1.38)
> 6	18/30 (60.0)	15/21 (71.4)		0.72 (0.36 to 1.44)
Best response on first-line treatment				
PR/CR	28/46 (60.9)	21/30 (70.0)		0.90 (0.51 to 1.60)
SD	33/45 (73.3)	26/31 (83.9)		0.74 (0.44 to 1.25)
Disease status at baseline (BICR)				
Measureable disease	56/78 (71.8)	41/52 (78.8)		0.92 (0.61 to 1.38)
Nonmeasureable disease	5/13 (38.5)	5/6 (83.3)		0.39 (0.11 to 1.42)
gBRCA mutation type				
BRCA1	21/29 (72.4)	12/16 (75.0)		0.82 (0.41 to 1.72)
BRCA2	38/59 (64.4)	34/45 (75.6)		0.86 (0.54 to 1.37)
Age at random assignment , years				
< 65	41/64 (64.1)	37/49 (75.5)		0.68 (0.44 to 1.07)
≥ 65	20/28 (71.4)	10/13 (76.9)		1.43 (0.68 to 3.18)
Sex				
Male	37/53 (69.8)	24/31 (77.4)		0.90 (0.54 to 1.53)
Female	24/39 (61.5)	23/31 (74.2)		0.74 (0.41 to 1.31)
Race				
White	59/82 (72.0)	44/59 (74.6)		0.97 (0.65 to 1.43)
ECOG status at baseline				
(0) Normal activity	41/65 (63.1)	28/38 (73.7)		0.79 (0.49 to 1.29)
(1) Restricted activity	19/25 (76.0)	19/23 (82.6)		0.89 (0.47 to 1.69)

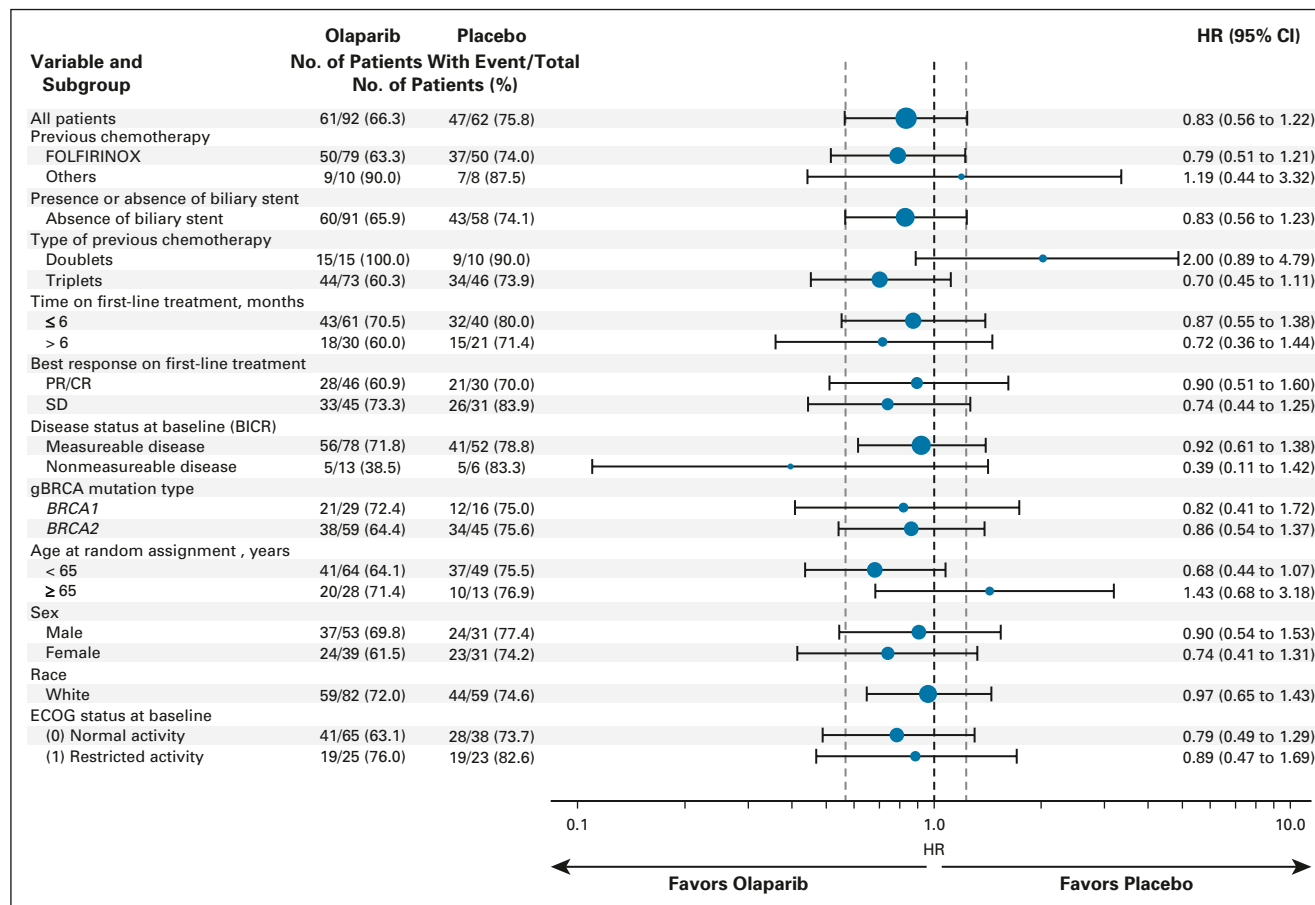Favors Olaparib — Favors Placebo

FIG 3. OS subgroup analyses. The central dashed line indicates an HR of 1 (no treatment effect); outer dashed lines indicate 95% CI result in all patients; the size of circles is proportional to the overall number of events. Subgroups in which fewer than five OS events occurred per group were not included in the analysis. The prespecified gemcitabine-cisplatin subgroup included two patients in the olaparib group and three patients in the placebo group; this subgroup did not meet the threshold for inclusion in the subgroup analysis. Patients who received gemcitabine–cisplatin are not included in the others subcategory of the previous chemotherapy subgroup, but are included in the doublet chemotherapy subgroup. Race was determined from patient records. BICR, blinded independent central review; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, folinic acid–fluorouracil-irinotecan-oxaliplatin; gBRCA, germline BRCA; HR, hazard ratio; OS, overall survival; PR, partial response; SD, stable disease.

the olaparib arm and 2-8 in the placebo arm; Appendix Fig A3, online only and Appendix Table A2, online only); 57 patients (62.0%) in the olaparib arm and 54 patients (87.1%) in the placebo arm received any subsequent therapy. The most common second-line subsequent therapies were platinum-based chemotherapies, most often folinic acid–fluorouracil-irinotecan-oxaliplatin (Appendix Table A3, online only). Of patients who discontinued study treatment, six patients (7.8%) in the olaparib arm and 16 patients (27.1%) in the placebo arm received a subsequent PARP inhibitor. Among the 17 patients in the placebo arm who survived for more than 2 years, four (23.5%) received a subsequent PARP inhibitor (olaparib in all cases) and two (11.8%) had ongoing olaparib treatment at DCO2. The response rate to second-line therapy was 5.3% in the olaparib arm and 5.6% in the placebo arm, and stable disease was observed in 28.1% and 24.1%, respectively. In the OS sensitivity analysis adjusted for subsequent PARP inhibitor use among patients in the placebo arm, the treatment effect was consistent with the unadjusted analysis (rank preserving structural failure time model–adjusted median OS: 19.0 months in the olaparib arm v 18.1 months in the placebo arm; HR, 0.81; 95% CI, 0.56 to 1.24).

Other Secondary End Points

At DCO2, median investigator-assessed PFS, TFST, TSST, and TDT were all significantly longer in the olaparib arm than in the placebo arm, whereas the HR for PFS2 did not reach statistical significance (Fig 4). The median investigator-assessed PFS was 6.7 months in the olaparib arm and 3.7 months in the placebo arm (HR, 0.49; 95% CI, 0.33 to 0.73; P = .0004), with estimated 3-year progression-free rates of 23.1% and 5.4%. The median PFS2 was 16.9 months in the olaparib arm and 9.3 months in the placebo arm (HR, 0.66; 95% CI, 0.43 to 1.02; P = .0613), and estimated 3-year PFS2 rates were 31.2% and 13.1%. The median TFST was 9.0 months in the
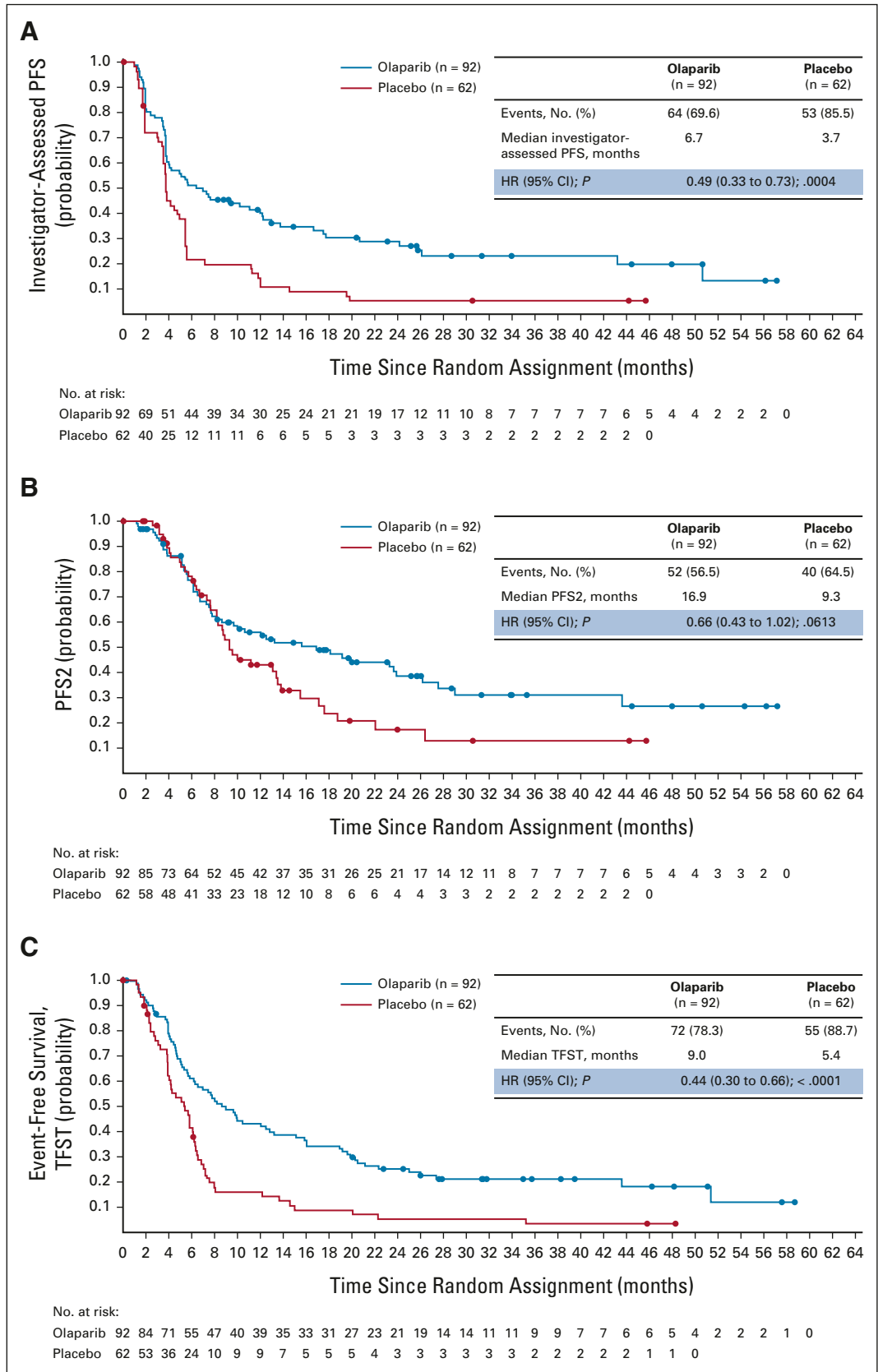
FIG 4. Kaplan-Meier estimates for other secondary end points: (A) investigator-assessed PFS, (B) PFS2, (C) TFST, (D) TSST, and (E) TDT. HR, hazard ratio; PFS, progression-free survival; PFS2, second (continued on following page)
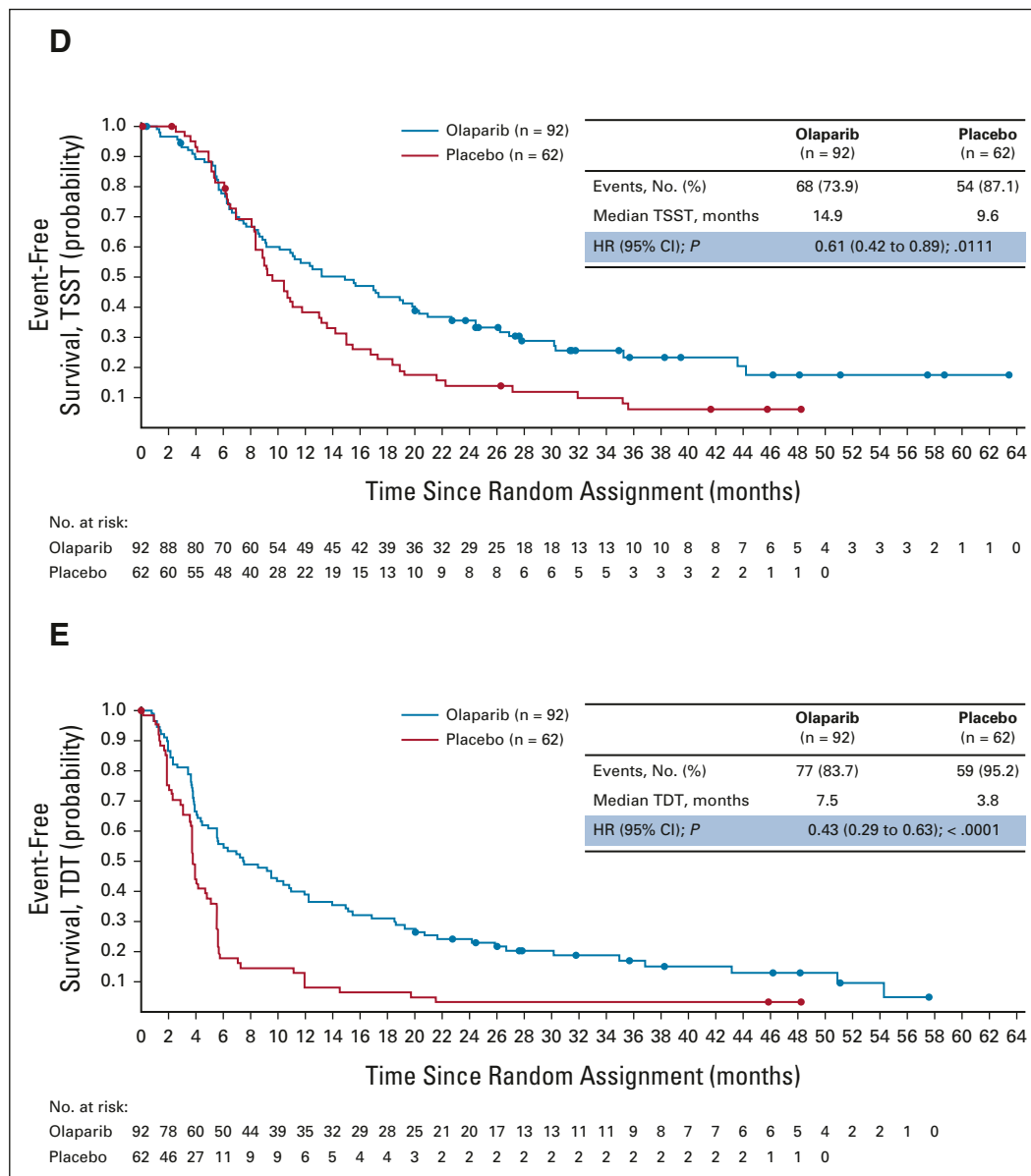
FIG 4. (Continued). progression-free survival; TDT, time to discontinuation of treatment; TFST, time to first subsequent cancer therapy or death; TSST, time to second subsequent cancer therapy or death.

olaparib arm and 5.4 months in the placebo arm (HR, 0.44; 95% CI, 0.30 to 0.66; P < .0001), with estimated 3-year first subsequent chemotherapy-free rates of 21.5% and 3.6%. The median TSST was 14.9 months in the olaparib arm and 9.6 months in the placebo arm (HR, 0.61; 95% CI, 0.42 to 0.89; P = .0111), with estimated 3-year second subsequent chemotherapy-free rates of 23.4% and 5.9%. The median TDT was 7.5 months in the olaparib arm and 3.8 months in the placebo arm (HR, 0.43; 95% CI, 0.29 to 0.63; P < .0001), with estimated 3-year study treatment discontinuation–free rates of 17.2% and 3.3%. Appendix Table A4 (online only) summarizes the data for key primary and secondary end points tested at DCO1 and DCO2.[25]

Safety

In the 151 patients in the safety population, the median total duration of treatment was 7.5 months (range: 0.8-57.5 months) in the olaparib arm and 3.7 months (range: 0.1-48.2 months) in the placebo arm. Along with fatigue and anemia, gastrointestinal AEs were frequently reported in both arms (Table 1). Serious AEs occurred in 28 patients (31.1%) who received olaparib and in 10 patients (16.4%) who received placebo. Grade ≥ 3 AEs were reported in 44 patients (48.9%) and 15 patients (24.6%) in the olaparib and placebo arms, respectively. One AE that occurred in the olaparib arm during the 30-day follow-up period after study treatment discontinuation resulted in death (reported

TABLE 1. Summary of AEs Occurring in at least 15% of the Study Population

	Olaparib (n = 90)		Placebo (n = 61)	
Event	Any Grade, No. (%)	Grade ≥ 3, No. (%)	Any Grade, No. (%)	Grade ≥ 3, No. (%)
Any AE	89 (98.9)	44 (48.9)	56 (91.8)	15 (24.6)
Nausea	44 (48.9)	1 (1.1)	15 (24.6)	1 (1.6)
Fatigue	42 (46.7)	5 (5.6)	16 (26.2)	0 (0.0)
Diarrhea	34 (37.8)	1 (1.1)	10 (16.4)	0 (0.0)
Abdominal pain	29 (32.2)	3 (3.3)	16 (26.2)	1 (1.6)
Anemia	29 (32.2)	11 (12.2)	10 (16.4)	2 (3.3)
Constipation	25 (27.8)	0 (0.0)	7 (11.5)	0 (0.0)
Decreased appetite	25 (27.8)	3 (3.3)	4 (6.6)	0 (0.0)
Vomiting	23 (25.6)	2 (2.2)	10 (16.4)	1 (1.6)
Back pain	22 (24.4)	0 (0.0)	13 (21.3)	1 (1.6)
Arthralgia	16 (17.8)	1 (1.1)	7 (11.5)	0 (0.0)
Asthenia	16 (17.8)	1 (1.1)	6 (9.8)	1 (1.6)
Pyrexia	16 (17.8)	0 (0.0)	6 (9.8)	0 (0.0)
Causally related to study treatment[a]	75 (83.3)	22 (24.4)	37 (60.7)	2 (3.3)
Serious AE	28 (31.1)	NA	10 (16.4)	NA
Death	1 (1.1)	NA	0 (0.0)	NA
Interruption of intervention because of AE	37 (41.1)	NA	4 (6.6)	NA
Dose reduction because of AE	16 (17.8)	NA	3 (4.9)	NA
Discontinuation of intervention because of AE	8 (8.9)	NA	1 (1.6)	NA

NOTE. AEs of any grade that occurred in at least 15% of the patients in the safety population of either trial arm during the trial intervention or up to 30 days after discontinuation of the trial intervention. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Abbreviations: AE, adverse event; NA, not applicable.

[a]As assessed by the investigator.

previously and not causally related to study treatment).[25] AEs leading to treatment discontinuation were reported in eight patients (8.9%) and one patient (1.6%) in the olaparib and placebo arms, respectively. There were no reports of myelodysplastic syndrome or acute myeloid leukemia in either treatment arm. No new primary malignancies were reported since DCO1, and there was one new case of grade 1 pneumonitis in the olaparib arm.[25] No new safety signals were observed in the time between DCO1 and DCO2 (Appendix Table A5, online only).[25] AEs were commonly managed through dose reduction or interruption (Table 1 and Appendix Table A6, online only).

DISCUSSION

POLO is the first randomized phase III study to investigate active maintenance therapy in patients with gBRCAm pancreatic cancer who had previously received first-line platinum-based chemotherapy.[25] In this final OS analysis, a higher proportion of olaparib-treated than placebo-treated patients remained alive and in follow-up (28.3% v 17.7%, respectively). No statistically significant difference in OS between the two trial arms was demonstrated although the HR estimate did move in favor of olaparib with a slight tightening of the CI between DCO1 (HR, 0.91; 95% CI, 0.56 to 1.46; $P = .68$) and DCO2 (HR, 0.83; 95% CI, 0.56 to 1.22; $P = .35$).

The Kaplan-Meier OS curves separate at approximately 24 months, indicative of a subset of long-term survivors in the olaparib arm (37.0% of olaparib-treated patients survived for more than 2 years after random assignment v 27.4% in the placebo arm). Among those who survived for more than 2 years, patients in the olaparib arm remained on study treatment more than 3 times longer than patients in the placebo arm (25.9 months v 7.3 months). The tail on the curve may reflect a distinct biologic subgroup of patients who have a unique deficiency in homologous recombination, and further research is required to explore this interesting hypothesis.[20,38]

The Kaplan-Meier OS curves cross at approximately 12 months, indicating that the HR decreases over time, with the reported HR representing an average over the observed extent of follow-up. The greatest point of separation of the Kaplan-Meier OS curves is at 3 years, when nearly twice as many patients in the olaparib arm than in the placebo arm were alive (33.9% v 17.8%). Although comparing studies is challenging, the POLO OS data are comparable with those from prospective phase II studies of patients with BRCA-mutated or PALB2-mutated pancreatic cancer who have previously been treated with platinum-based chemotherapy or PARP inhibitors.[38,39]

Our results do not suggest an effect of the duration of prior platinum therapy on olaparib efficacy. Results of the subgroup analyses of PFS[25] and OS comparing patients who had received ≤ 6 or > 6 months of first-line chemotherapy were comparable, with a trend toward increased benefits of olaparib for patients who had received > 6 months of first-line chemotherapy. Although several possible PARP inhibitor resistance mechanisms have been detected in the laboratory, only BRCA reversions have been observed in the clinical setting, mostly in ovarian cancer where platinum is often rechallenged over multiple lines.[40] Patients in the POLO trial received only first-line platinum-based chemotherapy, during which their disease did not progress, and it is therefore unlikely that these patients had developed resistance to olaparib therapy. It should be noted that the study was not powered to detect differences between the subgroups, so definitive conclusions cannot be drawn.

Significant differences in favor of the olaparib arm were observed for multiple secondary end points, including the significantly longer duration of study treatment and median time to first and second subsequent cancer therapies

relative to the placebo arm. Substantially more patients in the olaparib arm than in the placebo arm remained free of subsequent cancer therapy at 3 years. This is unique to a phase III trial in the active maintenance setting and is clinically meaningful for patients because it extends time free from the potentially toxic effects of subsequent chemotherapy. This is also particularly relevant in the subset of the study population with an extended OS. Patients in the olaparib arm also had a numerically longer PFS2, with an HR that favored olaparib, although the result did not reach statistical significance. Increasing PFS2 is also clinically meaningful, suggesting preservation of treatment benefits.[41] The strength of the association between olaparib and each of the end points appears to decrease in a logical order (TDT, TFST, PFS, TSST, PFS2, OS), suggesting internal validity of the results.

Although OS is considered to be the most compelling end point for demonstrating the clinical benefit of anticancer therapies, it is likely that the POLO trial was not adequately powered to detect a statistically significant OS benefit. OS is longer among patients with gBRCAm pancreatic cancer exposed to platinum-based chemotherapy than the overall population of patients with pancreatic cancer,[20,21] and when the trial was designed, no information was available about patient survival on active maintenance therapy after stopping platinum-based chemotherapy. Patients with gBRCAm pancreatic cancer are rare, representing only approximately 6% of all patients with pancreatic cancer.[16] Random assignment of 2,200 patients would have been needed to show a 3-month improvement in OS relative to placebo with 80% power (18 months v 21 months), which would require the screening of 37,000 patients assuming a gBRCAm prevalence of 6%. PFS is a direct measure of the biologic effect of a drug on tumor growth, and extended PFS delays the time to starting a subsequent cytotoxic chemotherapy and therefore preserves HRQoL. For these reasons, PFS was considered a more practical and clinically relevant end point than OS to measure benefits in this biomarker-selected subset of patients with pancreatic cancer. PFS is generally accepted as a surrogate end point for OS in other tumors, especially in diseases that have extended OS and for which patients receive multiple subsequent additional lines of treatment, although there remains an incomplete understanding of how PFS reliably predicts OS in gBRCAm pancreatic cancer.[42] The data from POLO will be useful in the design of future trials in biomarker-selected patient populations.

The use of subsequent therapies after discontinuation of study treatment might have also confounded the OS outcome. Partly because patients with gBRCAm pancreatic cancer treated with platinum-based chemotherapy have a better prognosis than a general population of patients with pancreatic cancer,[20,43] a higher proportion of patients in POLO (more than 70%) received subsequent therapy than in other positive randomized controlled trials of first-line treatment of patients with metastatic pancreatic cancer.[9,10] The most common treatments at second line were platinum-based systemic chemotherapies, of which approximately two thirds were folinic acid–fluorouracil-irinotecan-oxaliplatin. Because disease had not progressed during first-line platinum-based chemotherapy, these patients were still likely to be sensitive to subsequent platinum-based regimens, as reflected in the proportion of patients in both arms who responded or had stable disease during second-line chemotherapy. The similarity of the response rates to second-line therapy between the trial arms is also reassuring in that it indicates that exposure to olaparib does not reduce subsequent sensitivity to platinum. Although crossover to olaparib was not permitted in the Protocol, 27.1% of patients in the placebo arm received a PARP inhibitor, mostly olaparib, at the investigators' discretion after discontinuation of study treatment. In the sensitivity analysis conducted to control for this, the HR moved slightly in favor of olaparib although the difference was small and the result did not reach statistical significance.

Finally, active maintenance olaparib was generally well tolerated, and no new safety signals were observed between DCO1 and DCO2.[25] The safety profile of active maintenance olaparib remains consistent with previous experience in other tumor types.[31-33] A small group of patients have received olaparib for an extended period of time in the POLO trial; it is therefore reassuring that there were no reports of myelodysplastic syndrome or acute myeloid leukemia in either treatment arm and no new primary malignancies on olaparib. HRQoL has also been demonstrated to be preserved on active maintenance olaparib during the trial.[44]

In conclusion, although no statistically significant OS benefit for active maintenance olaparib compared with placebo was demonstrated, benefits for multiple other key secondary end points were observed. Active maintenance olaparib significantly prolonged TFST, TSST, and TDT, whereas PFS2 was extended with an HR favoring olaparib without reaching statistical significance. With a generally well-tolerated safety profile, active maintenance olaparib conferred clinically meaningful benefit to patients, including increased time without chemotherapy and durable response in a subset of patients.

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APPENDIX


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                          Patients assessed
                        for eligibility (N = 3,315)
                                   │
                                   ▼
        Had a gBRCA mutation                      (n = 247)
          Had unknown gBRCA mutation (n = 198)
            status before screening
          Had known gBRCA mutation       (n = 49)
            status before screening
                                   │
                                   │────────────────────►  Excluded                          (n = 80)
                                   │                          Had disease progression or died (n = 43)
                                   │                          Did not meet eligibility criteria  (n = 11)
                                   │                          Not enrolled because of patient  (n = 26)
                                   │                            or physician decision
                                   ▼
                      Provided written consent to
                   undergo random assignment (n = 167)
                                   │
                                   │────────────────────►  Excluded                          (n = 13)
                                   │                          Did not meet eligibility criteria  (n = 11)
                                   │                          Declined to participate          (n = 2)
                                   ▼
                  Underwent random assignment and
               included in the efficacy analyses (n = 154)
                                   │
                    ┌──────────────┴──────────────┐
                    ▼                              ▼
   Assigned to receive olaparib    (n = 92)   Assigned to receive placebo       (n = 62)
     Received olaparib and included  (n = 90)   Received placebo and included    (n = 61)
       in the safety analyses                     in the safety analyses
     Did not receive olaparib         (n = 2)    Did not receive placebo          (n = 1)
       Withdrew consent               (n = 1)      Did not meet eligibility criteria (n = 1)
       Did not meet eligibility criteria (n = 1)
                    │                              │
                    ▼                              ▼
   Discontinued olaparib (n = 77; 83.7%)      Discontinued placebo (n = 59; 95.2%)
     Had objective disease       (n = 50)       Had objective disease       (n = 46)
       progression                                progression
     Had disease progression     (n = 16)       Had disease progression      (n = 9)
       determined by                              determined by
       investigator assessment                    investigator assessment
     Had an AE                     (n = 7)       Had an AE                     (n = 2)
     Withdrew                      (n = 2)       Withdrew                      (n = 1)
     Others^a                      (n = 2)       Others^a                      (n = 1)
                    │                              │
                    ▼                              ▼
          Still receiving                   Still receiving
     olaparib at DCO2 (n = 13; 14.1%)   placebo at DCO2 (n = 2; 3.2%)
```
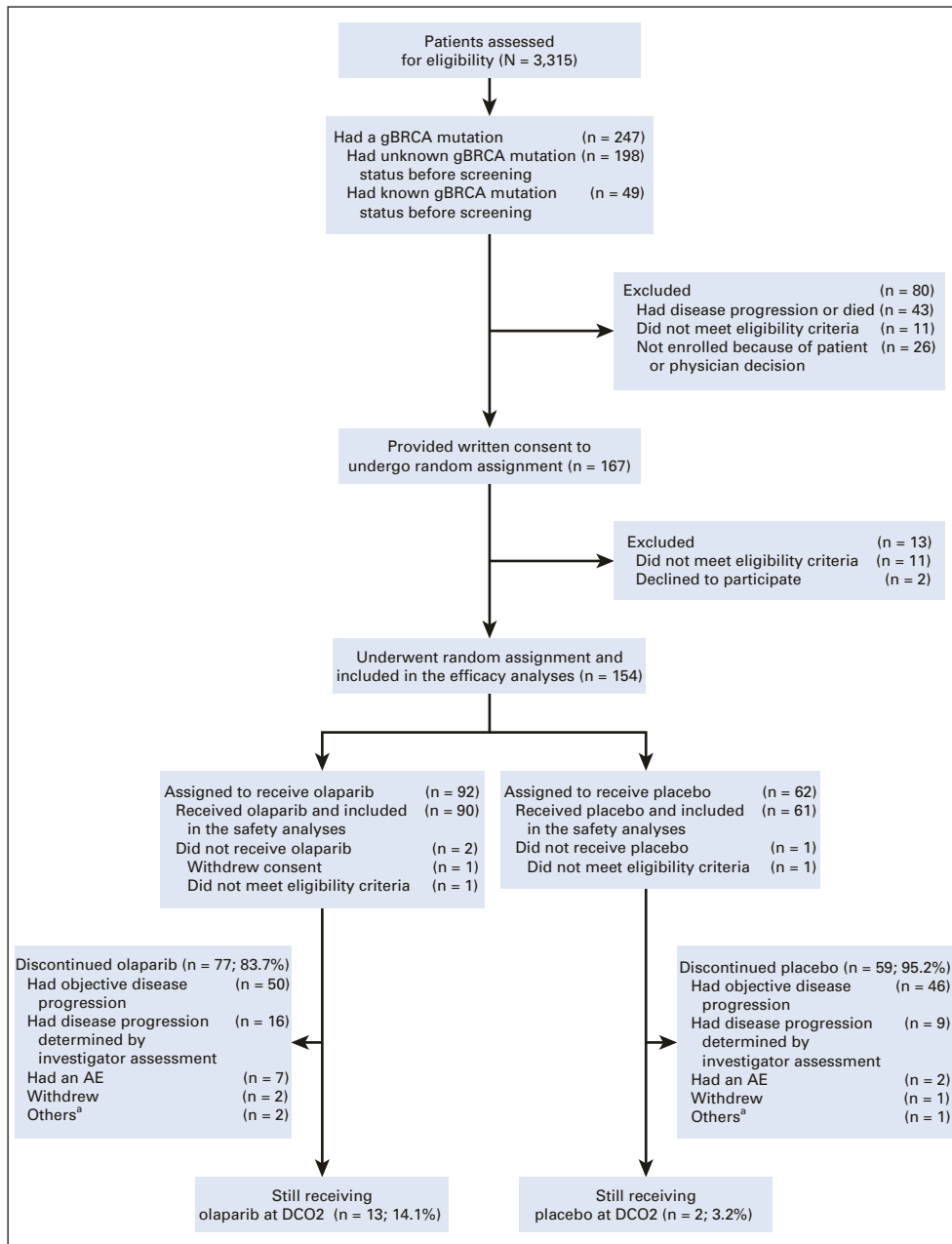
FIG A1. Full patient disposition, showing screening, enrollment, random assignment, and patients still receiving study treatment at DCO2 (July 21, 2020). One patient in the placebo arm was found not to have met the eligibility criteria after initiation of trial intervention, and the intervention was discontinued on day 3. After random assignment, one patient in each trial arm was found not to have met the eligibility criteria and both were included in the intention-to-treat efficacy analyses. Because neither patient received a trial intervention, they were not included in the safety analyses. ^aAny reason not specifically recorded. AE, adverse event; DCO, data cutoff; gBRCA, germline BRCA.
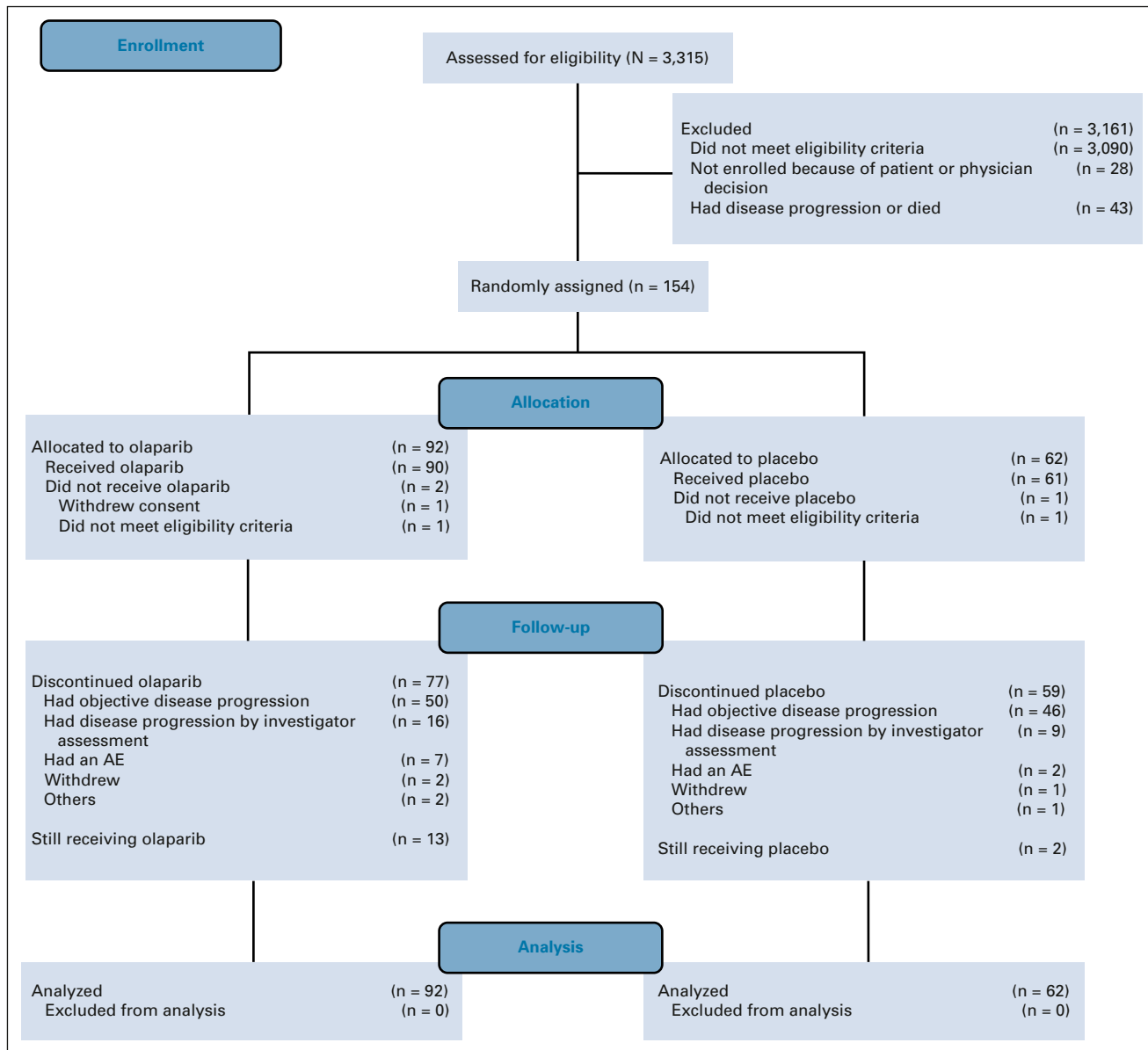
FIG A2. CONSORT flow diagram showing patient disposition through enrollment, allocation, follow-up, and analysis. AE, adverse event.
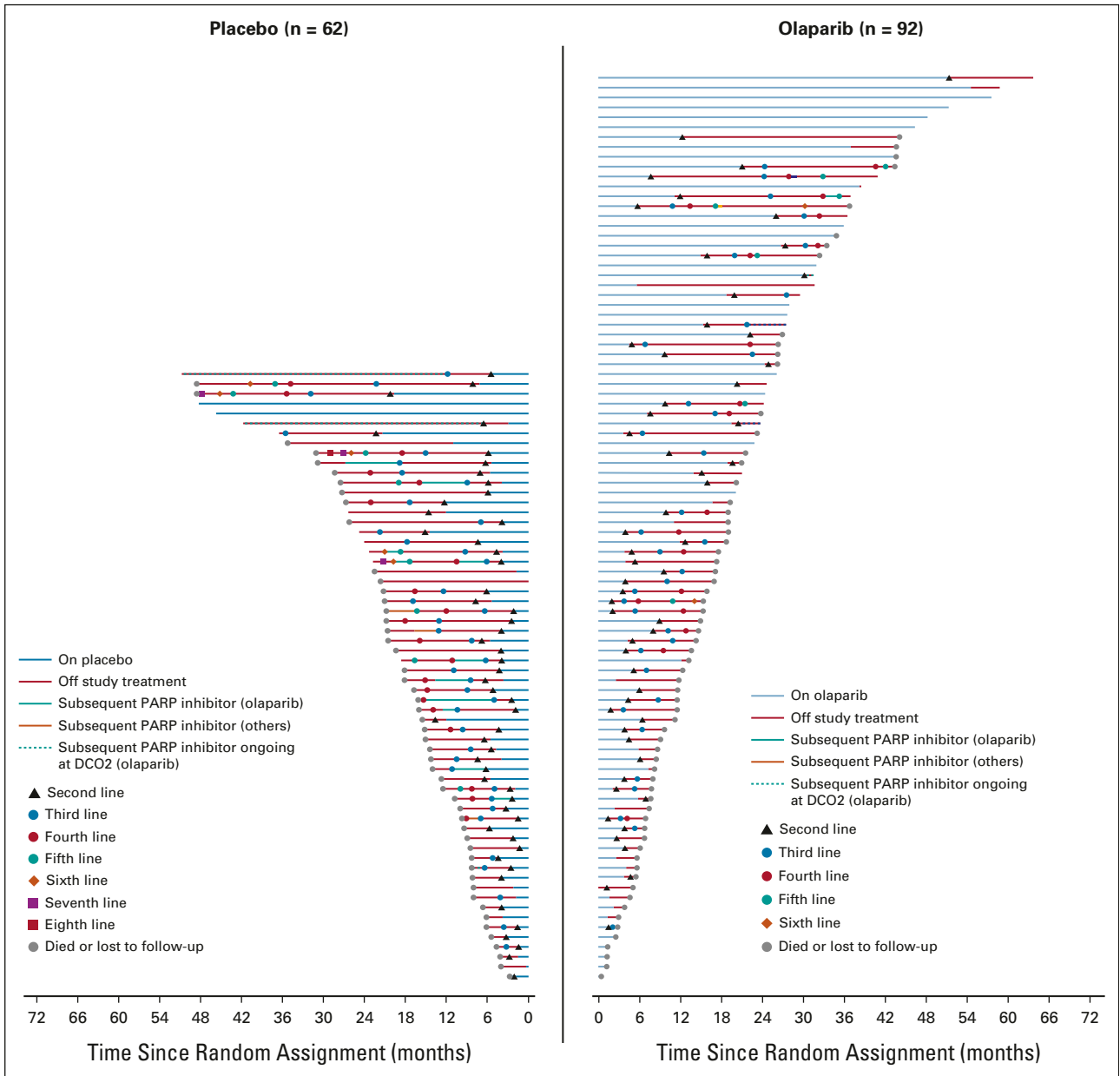
FIG A3. Swimmer plot for all patients, showing the use of subsequent therapy. Each horizontal line represents an individual patient. DCO, data cutoff; PARP, poly(adenosine diphosphate-ribose) polymerase.

TABLE A1. Duration of First-Line Chemotherapy (complete regimen and platinum component)

Duration of First-Line Chemotherapy, months	Complete Regimen			Platinum Component		
	Total (n = 152)[a]	Olaparib (n = 91)	Placebo (n = 61)	Total (n = 70)	Olaparib (n = 42)	Placebo (n = 28)
Mean (SD)	5.6 (3.6)	5.8 (4.0)	5.5 (3.0)	5.7 (4.3)	5.6 (4.5)	5.8 (4.0)
Median (range)	4.7 (2-32)[b]	4.6 (2-32)[b]	4.8 (3-19)	4.6 (2-29)[c]	4.5 (2-29)[b]	4.8 (2-29)[c]

Abbreviation: SD, standard deviation; XELOX, oxaliplatin and capecitabine.

[a]Data not available for two patients after withdrawal of consent.

[b]One patient in the olaparib arm received 70 days (10 weeks) of first-line XELOX chemotherapy; this was listed as an important protocol deviation.

[c]One patient in the placebo arm received 56 days (8 weeks) of first-line XELOX chemotherapy, but received 127 days (18.1 weeks) of the complete regimen.

TABLE A2. Use of Subsequent Therapies

Subsequent Therapy Line	Olaparib (n = 92)				Placebo (n = 62)			
	Any, No. (%)	PARP Inhibitor, No. (%)	Platinum-Based Chemotherapy, No. (%)	Nonplatinum Chemotherapy, No. (%)	Any, No. (%)	PARP Inhibitor,[a] No. (%)	Platinum-Based Chemotherapy, No. (%)	Nonplatinum Chemotherapy, No. (%)
Second	57 (62.0)	2 (2.2)	39 (42.4)	16 (17.4)	54 (87.1)	3 (4.8)	34 (54.8)	17 (27.4)
Third	36 (39.1)	1 (1.1)	10 (10.9)	25 (27.2)	40 (64.5)[b]	11 (17.7)	14 (22.6)	16 (25.8)
Fourth	19 (20.7)	2 (2.2)	4 (4.3)	13 (14.1)	21 (33.9)	0	10 (16.1)	11 (17.7)
Fifth	8 (8.7)	1 (1.1)	4 (4.3)	3 (3.3)	9 (14.5)	3 (4.8)	2 (3.2)	4 (6.5)
Sixth	2 (2.2)	0	0	2 (2.2)	5 (8.1)	0	4 (6.5)	1 (1.6)
Seventh	0	0	0	0	3 (4.8)	0	0	3 (4.8)
Eighth	0	0	0	0	1 (1.6)	0	1 (1.6)	0

Abbreviation: PARP, poly(adenosine diphosphate-ribose) polymerase.

[a]One patient received a subsequent PARP inhibitor twice, at third and fifth lines.

[b]One patient received both a PARP inhibitor and a platinum-based chemotherapy at third line.

TABLE A3. Second-Line Therapies

Therapy	Olaparib (n = 57), No. (%)	Placebo (n = 54), No. (%)
Platinum-based chemotherapy	39 (68.4)	34 (63.0)
FOLFIRINOX	26 (45.6)	18 (33.3)
FOLFIRINOX followed by capecitabine maintenance therapy	0 (0.0)	1 (1.9)
FOLFOX	2 (3.6)	4 (7.4)
FU/cisplatin	3 (5.4)	0 (0.0)
FU/carboplatin	2 (3.6)	1 (1.9)
Gemcitabine/cisplatin	3 (5.4)	6 (11.1)
GEMOX	3 (5.4)	1 (1.9)
Gemcitabine/carboplatin	0 (0.0)	1 (1.9)
Gemcitabine/cisplatin/epirubicin/ capecitabine	0 (0.0)	1 (1.9)
Gemcitabine/nab-paclitaxel/ cisplatin	0 (0.0)	1 (1.9)
Nonplatinum-based chemotherapy	16 (25.8)	17 (31.5)
FOLFIRI	7 (12.5)	3 (5.6)
FOLFIRI followed by capecitabine maintenance therapy	1 (1.8)	1 (1.9)
Gemcitabine/nab-paclitaxel	3 (5.4)	7 (13.0)
Gemcitabine	0 (0.0)	3 (5.6)
Capecitabine/irinotecan	0 (0.0)	2 (3.7)
LV5FU2	2 (3.6)	0 (0.0)
Irinotecan	1 (1.8)	0 (0.0)
BL-8040/pembrolizumab	1 (1.8)	0 (0.0)
Investigational drug	1 (1.8)	1 (1.9)
PARP inhibitor	2 (3.6)	3 (5.6)
Olaparib	2 (3.6)	3 (5.6)

Abbreviations: FOLFIRI, folinic acid–fluorouracil-irinotecan; FOLFIRINOX, folinic acid–fluorouracil-irinotecan-oxaliplatin; FOLFOX, folinic acid-5-fluorouracil-oxaliplatin; FU, fluorouracil; GEMOX, gemcitabine-oxaliplatin; LV5FU2, leucovorin plus 5-FU; PARP, poly(adenosine diphosphate-ribose) polymerase.

TABLE A4. Summary of Efficacy Results at Primary PFS (DCO1) and Final OS (DCO2) DCOs

End Point	HR (95% CI)	P
End points at DCO1 (January 15, 2019)		
PFS (BICR)	0.53 (0.35 to 0.82)	.0040
PFS (investigator-assessed)	0.51 (0.34 to 0.78)	.0017
OS	0.91 (0.56 to 1.46)	.6800
Objective response rate (BICR)[a]	18/78 (23.1%) v 6/52 (11.5%)	
Duration of response,[a] months	24.9 v 3.7	
End points at DCO2 (July 21, 2020)		
PFS (investigator-assessed)	0.49 (0.33 to 0.73)	.0004
TDT	0.43 (0.29 to 0.63)	< .0001[b]
TFST	0.44 (0.30 to 0.66)	< .0001[b]
TSST	0.61 (0.42 to 0.89)	.0111[b]
PFS2	0.66 (0.43 to 1.02)	.0613[b]
OS	0.83 (0.56 to 1.22)	.3487

Abbreviations: BICR, blinded independent central review; DCO, data cutoff; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PFS2, second disease progression or death; TDT, time to discontinuation of treatment; TFST, time to first subsequent cancer therapy or death; TSST, time to second subsequent cancer therapy or death.

[a]Among patients with measurable disease at baseline.
[b]Nominal.

TABLE A5. Summary of AEs at Primary Progression-Free Survival (DCO1) and Final Overall Survival (DCO2) DCOs

	DCO1 (January 15, 2019)				DCO2 (July 21, 2020)			
AE Category	Olaparib (n = 91), No. (%)	No. of Events	Placebo (n = 60), No. (%)	No. of Events	Olaparib (n = 90), No. (%)	No. of Events	Placebo (n = 61), No. (%)	No. of Events
Any AE	87 (95.6)	940	56 (93.3)	369	89 (98.9)	1,195	56 (91.8)	395
Any AE causally related to study treatment[a]	73 (80.2)	339	36 (60.0)	110	75 (83.3)	381	37 (60.7)	115
Any AE of NCI CTCAE grade ≥ 3	36 (39.6)	83	14 (23.3)	26	44 (48.9)	103	15 (24.6)	27
Any AE with outcome of death	0 (0.0)	0	0 (0.0)	0	1 (1.1)	1	0 (0.0)	0
Any SAE (including events with outcome of death)	22 (24.2)	46	9 (15.0)	11	28 (31.1)	57	10 (16.4)	12
Any AE leading to discontinuation of treatment	5 (5.5)	8	1 (1.7)	1	8 (8.9)	9	1 (1.6)	1
Any AE leading to dose reduction	15 (16.5)	23	2 (3.3)	2	16 (17.8)	24	3 (4.9)	3
Any AE leading to dose interruption	32 (35.2)	70	3 (5.0)	4	37 (41.1)	80	4 (6.6)	5

NOTE. Includes AEs with an onset date on or after the date of first dose and up to and including 30 days after the date of last dose of study treatment. AEs were graded according to the NCI CTCAE, version 4.03. At DCO1, one patient in the placebo arm was believed to have received 1 month of olaparib and was included in the olaparib arm for safety analysis. However, this patient in fact received placebo as intended and was returned to the placebo arm for the safety analysis at DCO2.

Abbreviations: AE, adverse event; DCO, data cutoff; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event.

[a]As assessed by the investigator.

TABLE A6. Occurrence, Resolution, and Management of Fatigue/Asthenia, Nausea, Anemia, and Vomiting

	Fatigue/Asthenia		Nausea		Anemia		Vomiting	
AEs and Management	Olaparib (n = 90)	Placebo (n = 61)	Olaparib (n = 90)	Placebo (n = 61)	Olaparib (n = 90)	Placebo (n = 61)	Olaparib (n = 90)	Placebo (n = 61)
Patients with AE, No. (%)	57 (63.3)	22 (36.1)	44 (48.9)	15 (24.6)	29 (32.2)	10 (16.4)	23 (25.6)	10 (16.4)
Grade ≥ 3	6 (6.7)	1 (1.6)	1 (1.1)	1 (1.6)	11 (12.2)	2 (3.3)	2 (2.2)	1 (1.6)
Median time to first onset, months	0.49	0.82	0.28	0.92	1.41	1.15	1.84	2.30
AEs with a resolution date, No. (%)	21 (23.3)	9 (14.8)	29 (32.2)	11 (18.0)	21 (23.3)	8 (13.1)	23 (25.6)	9 (14.8)
Median duration of first event, months	4.34	1.13	1.58	0.79	1.91	0.33	0.03	0.07
AE management, No. (%)								
Dose reduction	5 (5.6)	1 (1.6)	0 (0.0)	0 (0.0)	5 (5.6)	0 (0.0)	2 (2.2)	0 (0.0)
Dose interruption	4 (4.4)	1 (1.6)	1 (1.1)	0 (0.0)	11 (12.2)	0 (0.0)	4 (4.4)	1 (1.6)
Discontinuation	2 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)

Abbreviation: AE, adverse event.