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A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45)

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abstract

PURPOSE ATHENA (ClinicalTrials.gov identifier: NCT03522246) was designed to evaluate rucaparib first-line maintenance treatment in a broad patient population, including those without *BRCA1* or *BRCA2* (BRCA) mutations or other evidence of homologous recombination deficiency (HRD), or high-risk clinical characteristics such as residual disease. We report the results from the ATHENA–MONO comparison of rucaparib versus placebo.

METHODS Patients with stage III-IV high-grade ovarian cancer undergoing surgical cytoreduction (R0/complete resection permitted) and responding to first-line platinum-doublet chemotherapy were randomly assigned 4:1 to oral rucaparib 600 mg twice a day or placebo. Stratification factors were HRD test status, residual disease after chemotherapy, and timing of surgery. The primary end point of investigator-assessed progression-free survival was assessed in a step-down procedure, first in the HRD population (BRCA-mutant or BRCA wild-type/loss of heterozygosity high tumor), and then in the intent-to-treat population.

RESULTS As of March 23, 2022 (data cutoff), 427 and 111 patients were randomly assigned to rucaparib or placebo, respectively (HRD population: 185 *v* 49). Median progression-free survival (95% CI) was 28.7 months (23.0 to not reached) with rucaparib versus 11.3 months (9.1 to 22.1) with placebo in the HRD population (log-rank $P = .0004$; hazard ratio [HR], 0.47; 95% CI, 0.31 to 0.72); 20.2 months (15.2 to 24.7) versus 9.2 months (8.3 to 12.2) in the intent-to-treat population (log-rank $P < .0001$; HR, 0.52; 95% CI, 0.40 to 0.68); and 12.1 months (11.1 to 17.7) versus 9.1 months (4.0 to 12.2) in the HRD-negative population (HR, 0.65; 95% CI, 0.45 to 0.95). The most common grade ≥ 3 treatment-emergent adverse events were anemia (rucaparib, 28.7% *v* placebo, 0%) and neutropenia (14.6% *v* 0.9%).

CONCLUSION Rucaparib monotherapy is effective as first-line maintenance, conferring significant benefit versus placebo in patients with advanced ovarian cancer with and without HRD.

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INTRODUCTION

Maintenance treatment may delay disease recurrence or progression for patients with ovarian cancer who have achieved a complete response (CR) or partial response (PR) to first-line chemotherapy.[1-4] Efficacy with the poly(ADP-ribose) polymerase (PARP) inhibitors olaparib and niraparib as maintenance treatment varies on the basis of molecular characteristics,[2-7] with the greatest progression-free survival (PFS) benefit observed in patients with ovarian cancer harboring BRCA mutations (eg, *BRCA1* or *BRCA2*), followed by patients with other homologous recombination deficiency (HRD). Similar findings were observed in the ARIEL3 (ClinicalTrials.gov identifier: NCT01968213) study of maintenance treatment with the PARP inhibitor rucaparib in recurrent ovarian cancer; yet, the overall primary analysis demonstrated significantly improved PFS with rucaparib versus placebo regardless of HRD

ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

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

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CONTEXT

Key Objective

Poly(ADP-ribose) polymerase inhibitors have shown efficacy as first-line maintenance treatment for patients with ovarian cancer. However, questions remain about which patients may benefit from their use. Given the broad efficacy of rucaparib in the recurrent setting, we evaluated the efficacy of rucaparib as maintenance in a diverse patient population with newly diagnosed ovarian cancer.

Knowledge Generated

In the first-line setting, rucaparib monotherapy maintenance treatment significantly improved progression-free survival compared with placebo in the intent-to-treat population and population of patients harboring tumors with evidence of homologous recombination deficiency, as well as the non-nested subgroup of patients with tumors without evidence of homologous recombination deficiency (HRD-negative).

Relevance

ATHENA–MONO demonstrates that rucaparib monotherapy is an effective first-line maintenance option that provides clinical benefit to a broad population of patients with newly diagnosed ovarian cancer.

test status (BRCA mutations and genomic loss heterozygosity [LOH], a molecular feature of HRD).[8] Given this broad efficacy of rucaparib in the recurrent setting, we hypothesized that rucaparib may be effective as first-line maintenance therapy across a diverse patient population with newly diagnosed ovarian cancer.

ATHENA is an international, multicenter, randomized, double-blind, phase III trial consisting of four treatment arms (rucaparib, nivolumab, rucaparib + nivolumab, and placebo).[9] The study has two separate and fully independently powered comparisons evaluating rucaparib monotherapy (ATHENA–MONO) and rucaparib + nivolumab (ATHENA–COMBO) as maintenance treatment for patients with newly diagnosed advanced ovarian cancer. Here, we report the efficacy and safety results from the ATHENA–MONO comparison of rucaparib maintenance treatment versus placebo. The results for ATHENA–COMBO are not yet mature and will be reported separately.

METHODS

Study Design

ATHENA (GOG-3020/ENGOT-ov45; ClinicalTrials.gov identifier: NCT03522246) is led by the GOG Foundation and conducted in partnership with the European Network of Gynecological Oncological Trial Groups (under ENGOT model C[10]) and NRG Oncology–Japan. Patients were enrolled at 200 centers in 24 countries in Asia, Australia/New Zealand, Europe, and North America. The study was approved by national or local institutional review boards and conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice Guidelines. Patients provided informed consent before participation.

Patients

Eligible patients were ≥ 18 years and had newly diagnosed, histologically confirmed, advanced (International Federation of Gynecology and Obstetrics stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients had completed cytoreductive surgery (R0/complete resection was permitted) before chemotherapy or following neoadjuvant chemotherapy; had completed four to eight cycles of first-line platinum-doublet treatment, including a minimum of four cycles of a platinum/taxane combination (bevacizumab was only allowed during the chemotherapy phase), and achieved an investigator-assessed response; had sufficient formalin-fixed paraffin-embedded tumor tissue available for planned analyses and a known BRCA mutation result (either positive or negative) via central testing; had an Eastern Cooperative Oncology Group performance status of 0-1; and had adequate organ function. Full eligibility criteria are provided in Appendix Table A1 (online only).

Random Assignment

Within 8 weeks of day 1 of their last cycle of chemotherapy, patients were randomly assigned 4:1 to oral rucaparib + intravenous (IV) placebo or oral placebo + IV placebo.

Random assignment was computer-generated (block size of 10). Patients were stratified by HRD classification (BRCA mutation, BRCA wild-type/LOH high [LOH ≥ 16%], BRCA wild-type/LOH low [LOH < 16%], and BRCA wild-type/LOH indeterminate), disease status after chemotherapy (no residual disease *v* residual disease), and timing of surgery (primary surgery *v* interval debulking). The study was conducted in a double-blinded manner: patients, investigators, site staff, and the study sponsor were blinded to assignments, and study treatments were manufactured to be identical in appearance.

Procedures

Tumor HRD test status (BRCA mutations and genomic LOH) was determined centrally using the FoundationOne CDx next-generation sequencing assay (Foundation

Medicine Inc, Cambridge, MA; full details in the Data Supplement [online only]).

Patients received rucaparib 600 mg or placebo orally twice a day starting on cycle 1 day 1 and placebo IV every 4 weeks starting on cycle 2 day 1 in 28-day cycles. Rucaparib treatment could continue until 24 months after initiation of placebo IV administration, disease progression, death, or unacceptable toxicity. Additional details of dose modification criteria are available in the Data Supplement.

Disease assessments per RECIST v1.1 were conducted at screening, every 12 weeks relative to cycle 2 day 1 for the first 3 years, and every 24 weeks thereafter until radiologic progressive disease. Safety was assessed from first administration of study drug until 28 days after the last dose of oral drug. After 28 days, only adverse events of special interest (myelodysplastic syndrome [MDS] and acute myeloid leukemia [AML]) and serious adverse events considered as potentially study drug–related were to be reported. Patients who discontinued treatment were followed for subsequent treatments, secondary malignancy, and survival every 12 weeks after the 28-day safety follow-up visit until death, loss to follow-up, consent withdrawal, or study closure.

Outcomes

The primary end point for ATHENA–MONO was investigator-assessed PFS per RECIST. Secondary end points included overall survival (OS); investigator-assessed objective response rate (ORR) in patients with measurable disease at baseline; duration of response (DOR) for patients with investigator-assessed confirmed radiographic CR or PR; and blinded independent central review (BICR)–assessed PFS per RECIST. Key exploratory end points included analysis of PFS in subgroups on the basis of patient characteristics and assessment of patient-reported outcomes using the Functional Assessment of Cancer Therapy—Ovarian questionnaire (see study Protocol, online only).

To assess safety, treatment-emergent adverse events (TEAEs) were classified using the Medical Dictionary for Drug Regulatory Activities v24.0 and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. We also assessed safety via physical examinations, laboratory assessments, electrocardiogram, and vital signs.

Statistical Analysis

The significance level for ATHENA–MONO was set at a two-sided $P = .025$ because of the overall family-wise type I error rate being split equally between ATHENA–MONO and ATHENA–COMBO. Assuming approximately 40% of patients enrolled had BRCA-mutant or BRCA wild-type/LOH high carcinoma (HRD population), a sample size of at least 500 patients was required for ATHENA–MONO to yield $\geq$ 90% power at this significance level to show a statistically significant difference in PFS with a hazard ratio (HR) of 0.45 in the HRD population and 0.60 in the intent-to-treat (ITT) population (all randomly assigned patients).

An ordered step-down multiple comparison procedure was used,[11] testing the primary efficacy end point of investigator-assessed PFS first in the HRD population and then, if statistically significant at the two-sided .025 significance level, testing in the ITT population. Analysis of the key secondary end points of final OS and ORR were to follow in a similar ordered step-down procedure. Once significance was not achieved for one test, significance was not declared for all subsequent analyses. BICR-assessed PFS and DOR were evaluated as standalone, secondary end points.

Investigator- and BICR-assessed PFS were analyzed using a stratified log-rank test between randomized treatment groups; we also used a stratified Cox proportional hazards model to estimate the HR with 95% CI between the groups. The proportional hazards assumption (ie, constant relative hazard) was verified graphically using log-log plots (Appendix Fig A1, online only). Investigator-assessed confirmed ORR was evaluated in the subgroup of patients with RECIST measurable disease at baseline and compared between treatment groups using a chi-square test.

Investigator-assessed DOR was analyzed in the subgroup of patients with a confirmed CR or PR. DOR was analyzed using a Cox proportional hazards model and a log-rank test between randomized treatment groups. OS will be considered mature when 70% of death events have been collected. Safety data were summarized descriptively for all patients who received at least one dose of oral study treatment. TEAEs leading to treatment interruption, dose reduction, or discontinuation of oral study drug are reported.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The independent data monitoring committee monitored enrollment and reviewed the safety and efficacy of the trial approximately every 6 months, including maturity of PFS events. Additional details of the statistical analyses can be found in the Data Supplement.

RESULTS

Patients

Between October 1, 2018, and September 30, 2020, 427 patients were randomly allocated to the rucaparib monotherapy group and 111 to the placebo group (Fig 1). Baseline patient, disease, and genomic characteristics are provided in Table 1 and Appendix Table A2 (online only). Most patients did not have a BRCA mutation (rucaparib, 336 [78.7%]; and placebo, 87 [78.4%]).

The study is ongoing, with 53 patients (12.4%) in the rucaparib group and 11 patients (9.9%) in the placebo group still receiving treatment. Median duration of follow-up

was 26.1 months (95% CI, 25.8 to 26.9) for rucaparib versus 26.2 months (95% CI, 24.0 to 27.7) for placebo.

Efficacy

Per the step-down multiple comparison procedure, investigator-assessed PFS was first analyzed in the HRD population (185 [43.3%] patients in the rucaparib group and 49 [44.1%] patients in the placebo group). Median PFS was 28.7 months (95% CI, 23.0 to not reached) in the rucaparib group versus 11.3 months (95% CI, 9.1 to 22.1) in the placebo group (log-rank $P = .0004$; HR, 0.47; 95% CI, 0.31 to 0.72; Fig 2A). In the ITT population, median PFS was 20.2 months (95% CI, 15.2 to 24.7) in the rucaparib group versus 9.2 months (95% CI, 8.3 to 12.2) in the placebo group (log-rank $P < .0001$; HR, 0.52; 95% CI, 0.40 to 0.68; Fig 2B). At 24 months, 45.1% of rucaparib-treated patients in the ITT population were progression-free versus 25.4% with placebo (Appendix Table A3, online only). Exploratory subgroup analyses of investigator-assessed PFS in the ITT population showed that there was greater clinical benefit with rucaparib versus placebo for all subgroups (Fig 3), including by tumor HRD classification: BRCA-mutant (Fig 4A), BRCA wild-type/LOH high (Fig 4B), and BRCA wild-type/LOH low (HRD-negative; Fig 4C).

For the standalone secondary end point of BICR-assessed PFS, the results were consistent with those for investigator-assessed PFS in the HRD population (Fig 2C), ITT population (Fig 2D), and HRD subgroups (Appendix Fig A2, online only). Similarly, sensitivity analyses of investigator-assessed PFS support the statistically significant results of the primary end point, indicating that the time to disease progression was not affected by censoring of patients (Appendix Table A4, online only).

As of the data cutoff, OS results were immature; in the ITT population, 24.7% of death events had occurred. As significance could not be established for this end point, in accordance with the prespecified step-down procedure to adjust for multiplicity, significance could not be claimed for the subsequent ORR analyses at this time.

Confirmed objective responses were observed among rucaparib-treated patients with RECIST measurable disease at baseline (Table 2), including in 10/17 patients (ORR, 58.8% [95% CI, 32.9 to 81.6]) in the HRD population and 20/41 patients (ORR, 48.8% [95% CI, 32.9 to 64.9]) in the ITT population. An objective response was observed in 1/5 placebo-treated patients in the HRD population (ORR, 20.0% [95% CI, 0.5 to 71.6]) and 1/11 patients in the ITT population (ORR, 9.1% [95% CI, 0.2 to 41.3]). Median

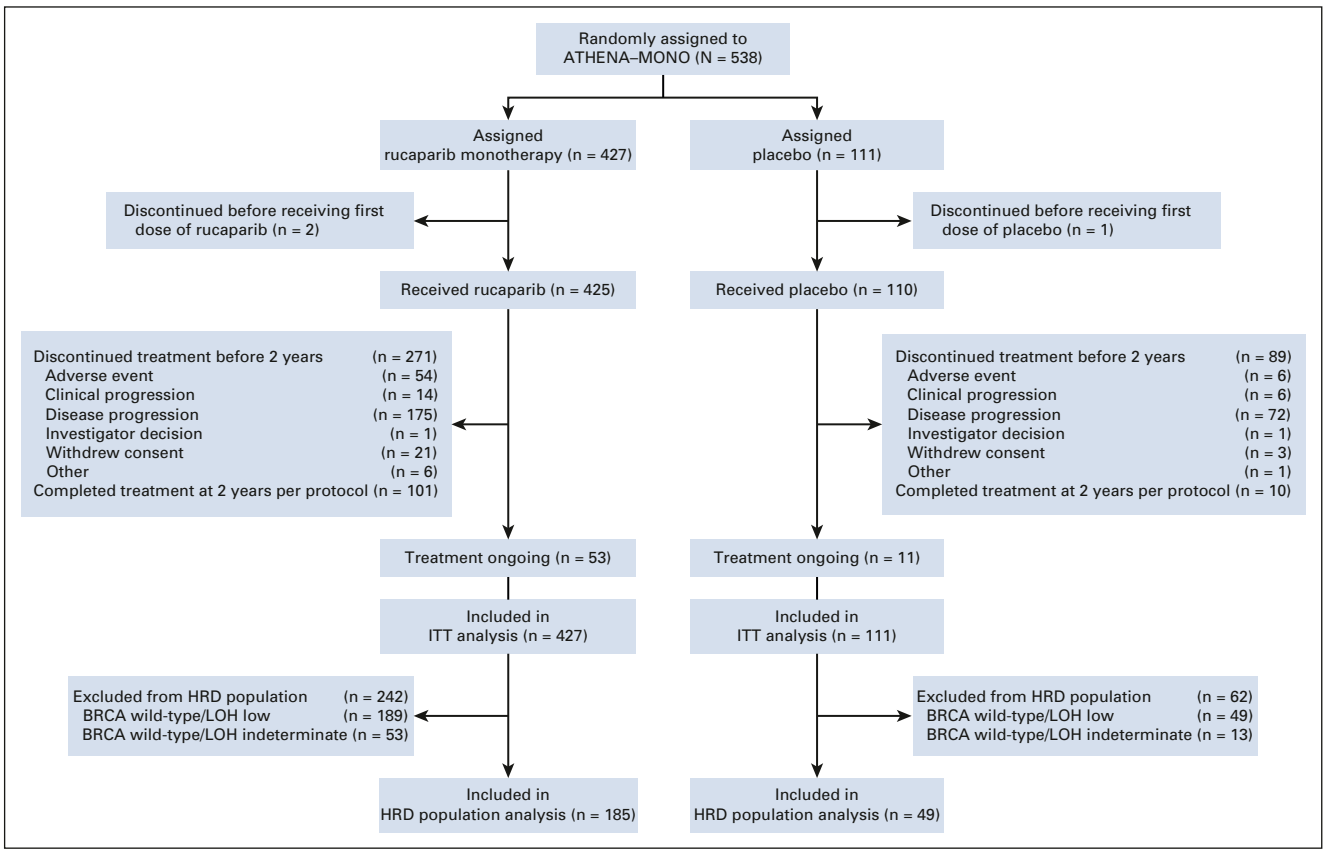

FIG 1. CONSORT diagram of patients. BRCA, *BRCA1* or *BRCA2*; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity.

TABLE 1. Baseline Patient and Disease Characteristics (N = 538)

Characteristic	HRD Population		ITT Population	
	Rucaparib (n = 185)	Placebo (n = 49)	Rucaparib (n = 427)	Placebo (n = 111)
Age, years, median (range)	57.0 (30-81)	59.0 (38-78)	61.0 (30-83)	61.0 (31-80)
Race, No. (%)				
White	137 (74.1)	35 (71.4)	328 (76.8)	87 (78.4)
Asian	41 (22.2)	11 (22.4)	80 (18.7)	16 (14.4)
Other	3 (1.6)	2 (4.1)	11 (2.6)	6 (5.4)
Unknown	4 (2.2)	1 (2.0)	8 (1.9)	2 (1.8)
Geographic region, No. (%)				
North America	52 (28.1)	12 (24.5)	144 (33.7)	38 (34.2)
Europe	87 (47.0)	23 (46.9)	186 (43.6)	52 (46.8)
Asia	35 (18.9)	11 (22.4)	72 (16.9)	14 (12.6)
Australia/New Zealand	11 (5.9)	3 (6.1)	25 (5.9)	7 (6.3)
ECOG PS, No. (%)				
0	132 (71.4)	39 (79.6)	295 (69.1)	76 (68.5)
1	53 (28.6)	10 (20.4)	131 (30.7)[a]	35 (31.5)
FIGO stage, No. (%)				
III	136 (73.5)	31 (63.3)	323 (75.6)	78 (70.3)
IV	49 (26.5)	18 (36.7)	104 (24.4)	33 (29.7)
Type of cancer, No. (%)				
Epithelial ovarian	153 (82.7)	39 (79.6)	336 (78.7)	85 (76.6)
Fallopian tube	21 (11.4)	5 (10.2)	50 (11.7)	18 (16.2)
Primary peritoneal	11 (5.9)	5 (10.2)	41 (9.6)	8 (7.2)
Histology, No. (%)				
Serous	174 (94.1)	47 (95.9)	384 (89.9)	106 (95.5)
Endometrioid	6 (3.2)	0	13 (3.0)	1 (0.9)
Clear cell	0	0	13 (3.0)	2 (1.8)
Mixed	3 (1.6)	1 (2.0)	10 (2.3)	1 (0.9)
Other	2 (1.1)	1 (2.0)	7 (1.6)	1 (0.9)
Surgical outcome, No. (%)[b]				
Complete resection	107 (57.8)	33 (67.3)	263 (61.6)	73 (65.8)
Microscopic residual disease (< 1 cm)	38 (20.5)	5 (10.2)	81 (19.0)	15 (13.5)
Macroscopic residual disease (≥ 1 cm)	40 (21.6)	11 (22.4)	83 (19.4)	23 (20.7)
Radiologic response after first-line platinum-doublet chemotherapy, No. (%)				
No disease after surgery[c]	88 (47.6)	30 (61.2)	224 (52.5)	64 (57.7)
CR	38 (20.5)	4 (8.2)	73 (17.1)	11 (9.9)
PR	33 (17.8)	9 (18.4)	76 (17.8)	22 (19.8)
Inevaluable/other	26 (14.1)	6 (12.2)	54 (12.6)	14 (12.6)
No. of cycles of first-line platinum-doublet chemotherapy, median (range)	6 (4-8)	6 (4-8)	6 (4-8)	6 (4-8)
4 to < 6 cycles, No. (%)	10 (5.4)	4 (8.2)	26 (6.1)	8 (7.2)
6-8 cycles, No. (%)	175 (94.6)	45 (91.8)	401 (93.9)	103 (92.8)
Prior bevacizumab, No. (%)	34 (18.4)	5 (10.2)	84 (19.7)	12 (10.8)
Measurable disease at baseline, No. (%)	17 (9.2)	5 (10.2)	41 (9.6)	11 (9.9)
CA-125 within normal limits at baseline by central or local lab, No. (%)	161 (87.0)	46 (93.9)	371 (86.9)	100 (90.1)

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TABLE 1. Baseline Patient and Disease Characteristics (N = 538) (continued)

Characteristic	HRD Population		ITT Population	
	Rucaparib (n = 185)	Placebo (n = 49)	Rucaparib (n = 427)	Placebo (n = 111)
Randomization stratification factors, No. (%)[d]				
Timing of surgery				
Primary surgery	104 (56.2)	27 (55.1)	209 (48.9)	54 (48.6)
Interval debulking	81 (43.8)	22 (44.9)	218 (51.1)	57 (51.4)
Disease status after chemotherapy				
No residual disease	137 (74.1)	35 (71.4)	322 (75.4)	82 (73.9)
Residual disease	48 (25.9)	14 (28.6)	105 (24.6)	29 (26.1)
HRD test status				
BRCA mutation	91 (49.2)	24 (49.0)	91 (21.3)	24 (21.6)
BRCA wild-type/LOH high	94 (50.8)	25 (51.0)	94 (22.0)	25 (22.5)
BRCA wild-type/LOH low	0	0	189 (44.3)	49 (44.1)
BRCA wild-type/LOH indeterminate	0	0	53 (12.4)	13 (11.7)

Abbreviations: BRCA, *BRCA1* or *BRCA2*; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity; PR, partial response.

[a]One patient (0.2%) not included in the table had an ECOG PS of 1 at screening and 2 at cycle 1 day 1.

[b]As assessed by surgeons.

[c]As assessed by radiographic scans per RECIST.

[d]As entered by investigators at the time of random assignment.

DOR in the HRD and ITT populations for rucaparib-treated responders versus the one placebo-treated responder, respectively, was 16.7 months (95% CI, 5.7 to not reached) versus 5.5 months (95% CI, not evaluable), and 22.1 months (95% CI, 8.4 to not reached) versus 5.5 months (95% CI, not evaluable; Appendix Fig A3, online only).

Safety

The safety population for the ATHENA–MONO comparison included 425 patients and 110 patients who received at least one dose of oral rucaparib or oral placebo, respectively. Median treatment duration was 14.7 (range, 0.1-32.7) months in the rucaparib group and 9.9 (range, 0.9-25.9) months in the placebo group. Median dose intensity was 0.88 (interquartile range, 0.680-0.995) in the rucaparib group and 1.00 (interquartile range, 0.970-1.000) in the placebo group.

A TEAE of any grade occurred in 411 (96.7%) patients in the rucaparib group and 102 (92.7%) in the placebo group (Table 3). The most common TEAEs (reported in ≥ 40% of patients in either group) were nausea, asthenia/fatigue, anemia/decreased hemoglobin, and increased ALT/AST. TEAEs of grade ≥ 3 were reported in 257 (60.5%) patients in the rucaparib group and 25 (22.7%) in the placebo group, with the most common in the rucaparib group being anemia/decreased hemoglobin and neutropenia/neutrophil count decreased. The most common grade ≥ 3 TEAE reported in the placebo group was hypertension, reported in four (3.6%) patients with placebo and seven (1.6%) patients with rucaparib.

The majority of the increased ALT/AST events were grade 1 or 2; ALT and AST levels generally normalized over the course of treatment without other signs of liver injury (Appendix Fig A4, online only). None of the cases of ALT/AST elevation met Hy's law criteria for drug-induced liver injury.

MDS and AML were reported in two patients in the rucaparib group (one MDS during treatment [0.2%] and one AML during long-term follow-up [0.2%]; additional details in the Data Supplement) and no patients in the placebo group.

Treatment interruption of oral study drug because of a TEAE occurred in 258 (60.7%) patients in the rucaparib group and 22 (20.0%) in the placebo group (Appendix Table A5, online only). Dose reduction because of a TEAE occurred in 210 (49.4%) patients in the rucaparib group and nine (8.2%) in the placebo group (Table A5). TEAEs led to discontinuation for 50 (11.8%) and six (5.5%) patients in the rucaparib and placebo groups, respectively (Appendix Table A6, online only); the most common TEAE leading to discontinuation of rucaparib was anemia/decreased hemoglobin.

As of the cutoff date, death due to a TEAE (excluding disease progression) occurred in two (0.5%) patients in the rucaparib group (one because of myocardial infarction and

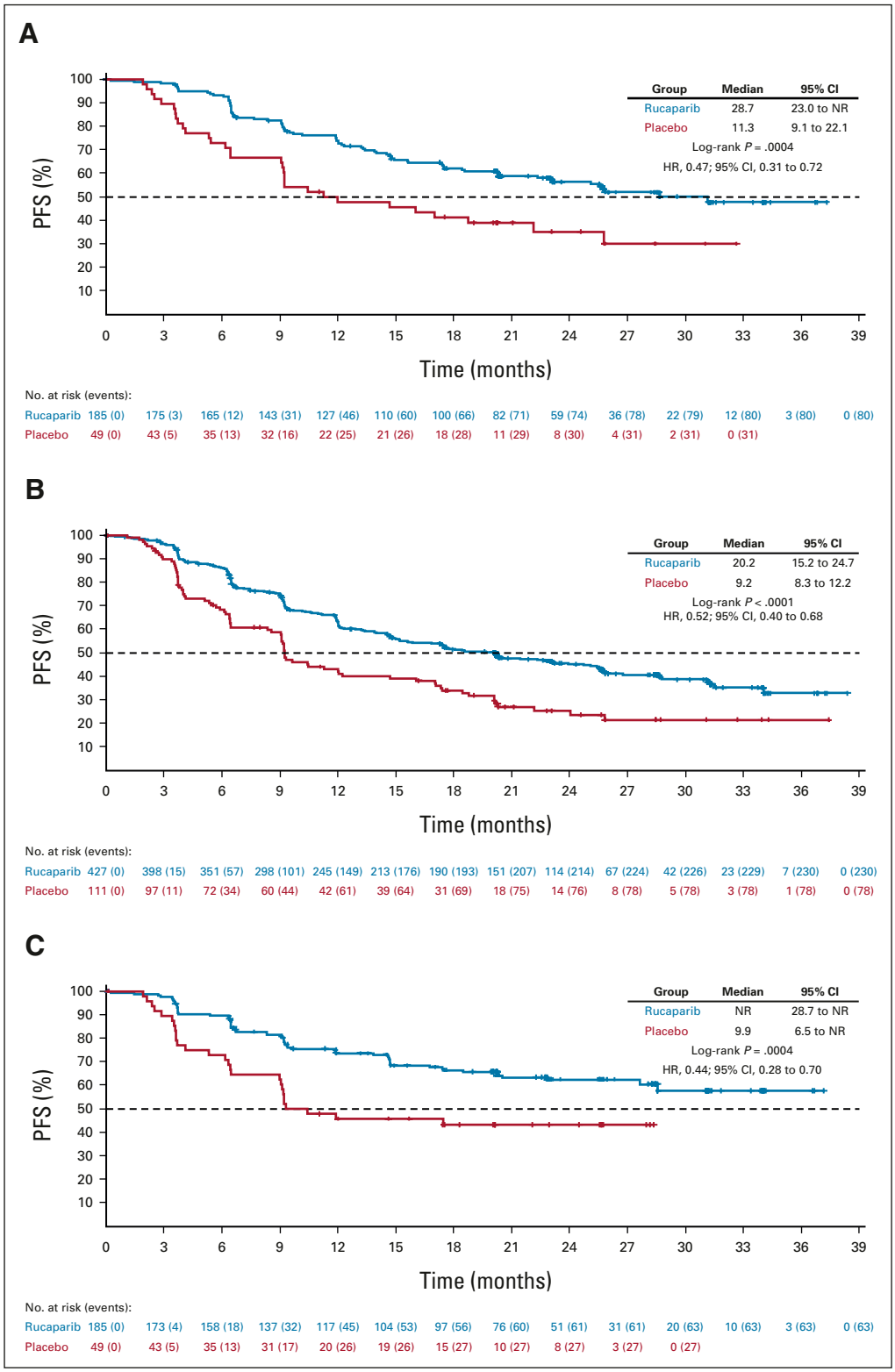

FIG 2. PFS by investigator in the (A) homologous recombination deficiency population and (B) intent-to-treat population and PFS by BICR for the same populations (C and D, respectively). For BICR analyses, nominal *P* values, not adjusted for multiplicity, are shown. BICR, blinded independent central review; HR, hazard ratio; NR, not reached; PFS, progression-free survival. (continued on following page)

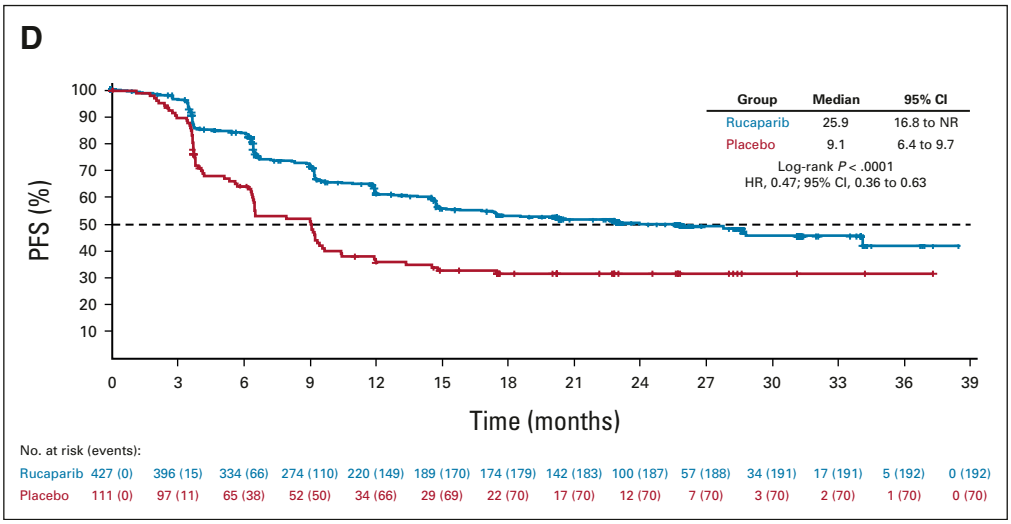

FIG 2. (Continued).

pulmonary embolism and one because of multiple organ dysfunction syndrome; Appendix Table A7, online only); neither was considered related to rucaparib. No patients in the placebo group died because of a TEAE.

Patient-Reported Outcomes

Changes from baseline in Functional Assessment of Cancer Therapy—Ovarian Trial Outcome Index scores were similar between rucaparib and placebo in the ITT population (Appendix Fig A5, online only).

DISCUSSION

In ATHENA–MONO, rucaparib maintenance treatment significantly improved PFS versus placebo for patients with newly diagnosed advanced ovarian cancer regardless of BRCA or HRD status. Analysis of patient populations on the basis of HRD status indicate that the improvement in PFS observed with rucaparib in the ITT population was not driven solely by BRCA or HRD subgroups, with substantial PFS benefit also observed among patients with HRD-negative (ie, BRCA wild-type/LOH low) tumors, commonly considered to be homologous recombination proficient. Together, these data suggest that rucaparib maintenance treatment can provide benefit for a broad set of patients who have responded to first-line chemotherapy. The BICR assessment demonstrated that PFS benefit across subgroups is consistent with that seen by investigator assessment, as evaluated by HRs. The medians for PFS were generally higher with BICR versus investigator assessment, which is a trend previously described in other studies and could reflect bias associated with informative censoring.[12] Approximately 10% of patients in the current analysis had measurable disease at baseline, and approximately half of these patients who received rucaparib maintenance had a deepening of response with confirmed reductions in tumor burden, including in patients with HRD-negative tumors.

The safety profile for rucaparib in ATHENA–MONO is consistent with that of rucaparib in other settings[13-15] and other PARP inhibitors in the first-line maintenance setting.[2,3,5] The most common nonhematologic TEAEs observed with rucaparib were generally low grade, and the majority of grade ≥ 3 events were hematologic TEAEs previously associated with PARP inhibitors. The incidence of MDS/AML in ATHENA–MONO was consistent with other PARP inhibitor studies in the first-line setting.[2,3,5] No clinically meaningful differences in patient-reported outcomes were detected between study groups, suggesting that rucaparib maintenance treatment did not negatively affect patients' health-related quality of life versus placebo.

The SOLO-1 study of olaparib was the first to demonstrate benefit of first-line maintenance treatment of a PARP inhibitor, but the patient population was restricted to women who harbored BRCA mutations.[2] The PRIMA study of niraparib then expanded the assessment of first-line maintenance PARP inhibitor treatment to all molecular subgroups.[3] However, the PRIMA study excluded patients with International Federation of Gynecology and Obstetrics stage III disease who had no visible residual disease after primary debulking surgery, skewing the study population toward those with advanced disease. Notably, PRIMA also implemented an individualized dosing algorithm on the basis of weight and platelet levels late in the study because of high rates of grade ≥ 3 thrombocytopenia reported with niraparib.[16,17] Most patients who enrolled after individualized dosing was adopted received the lower starting dose of niraparib 200 mg once a day, which, when compared with efficacy results with niraparib 300 mg once a day, was found to have less robust PFS benefit versus placebo, particularly in the HRD-negative (homologous recombination proficient)

Subgroup	Rucaparib (events/patients in subgroup)	Placebo (events/patients in subgroup)	HR (95% CI)
ITT population	230/427	78/111	0.52 (0.40 to 0.68)
HRD population	80/185	31/49	0.47 (0.31 to 0.72)
Randomization stratification factors			
HRD test status			
BRCA mutation	30/91	14/24	0.40 (0.21 to 0.75)
BRCA wild-type/LOH high	50/94	17/25	0.58 (0.33 to 1.01)
BRCA wild-type/LOH low	120/189	35/49	0.65 (0.45 to 0.95)
BRCA wild-type/LOH indeterminate	30/53	12/13	0.39 (0.20 to 0.78)
Disease status after chemotherapy			
No residual disease	164/322	56/82	0.59 (0.43 to 0.80)
Residual disease	66/105	22/29	0.44 (0.27 to 0.73)
Timing of surgery			
Primary surgery	94/209	33/54	0.64 (0.43 to 0.95)
Interval debulking	136/218	45/57	0.44 (0.31 to 0.62)
Race			
White	177/328	64/87	0.50 (0.38 to 0.67)
Non-White[a]	47/91	13/22	0.71 (0.39 to 1.32)
ECOG PS			
0	153/295	55/76	0.51 (0.37 to 0.69)
≥ 1[b]	77/132	23/35	0.68 (0.43 to 1.09)
FIGO stage at diagnosis			
III	171/323	51/78	0.64 (0.46 to 0.87)
IV	59/104	27/33	0.40 (0.25 to 0.64)
Disease burden at baseline			
No disease	156/313	52/77	0.57 (0.42 to 0.79)
Nontarget disease	44/73	15/23	0.63 (0.35 to 1.13)
Measurable disease	30/41	11/11	0.31 (0.15 to 0.65)
CA-125 at baseline			
Normal	187/371	68/100	0.55 (0.42 to 0.72)
Above normal	43/56	10/11	0.26 (0.13 to 0.55)
Prior use of bevacizumab			
Yes	48/84	8/12	0.33 (0.15 to 0.69)
No	182/343	70/99	0.58 (0.44 to 0.77)
Best response to chemotherapy			
No disease after surgery	107/224	42/64	0.58 (0.40 to 0.82)
CR	44/73	8/11	0.48 (0.23 to 1.03)
PR	51/76	18/22	0.37 (0.21 to 0.65)
Inevaluable/other	28/54	10/14	0.62 (0.30 to 1.27)
Disease-free with normal CA-125			
Yes	132/270	44/69	0.61 (0.43 to 0.86)
No	98/157	34/42	0.45 (0.30 to 0.67)
Cytoreductive surgery outcome			
Complete resection	127/263	47/73	0.60 (0.43 to 0.84)
Other outcome	103/164	31/38	0.41 (0.27 to 0.62)

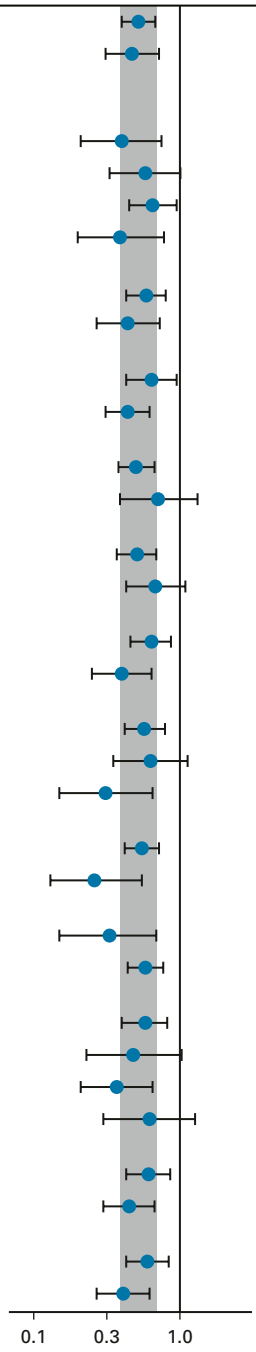

FIG 3. Investigator-assessed PFS in subgroups in the ITT population. The vertical gray band corresponds to the 95% CI of the ITT population. [a]Excludes patients with unknown race. [b]One rucaparib-treated patient had an ECOG PS of 1 at screening and 2 at cycle 1 day 1. BRCA, *BRCA1* or *BRCA2*; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity; PFS, progression-free survival; PR, partial response.

population.[17] ATHENA–MONO enrolled a broad population of women with newly diagnosed ovarian cancer who had responded to first-line treatment, with no restrictions on HRD status or surgical outcome (including R0/complete resection). The results presented here demonstrate clear benefit for rucaparib maintenance across HRD subgroups and in the

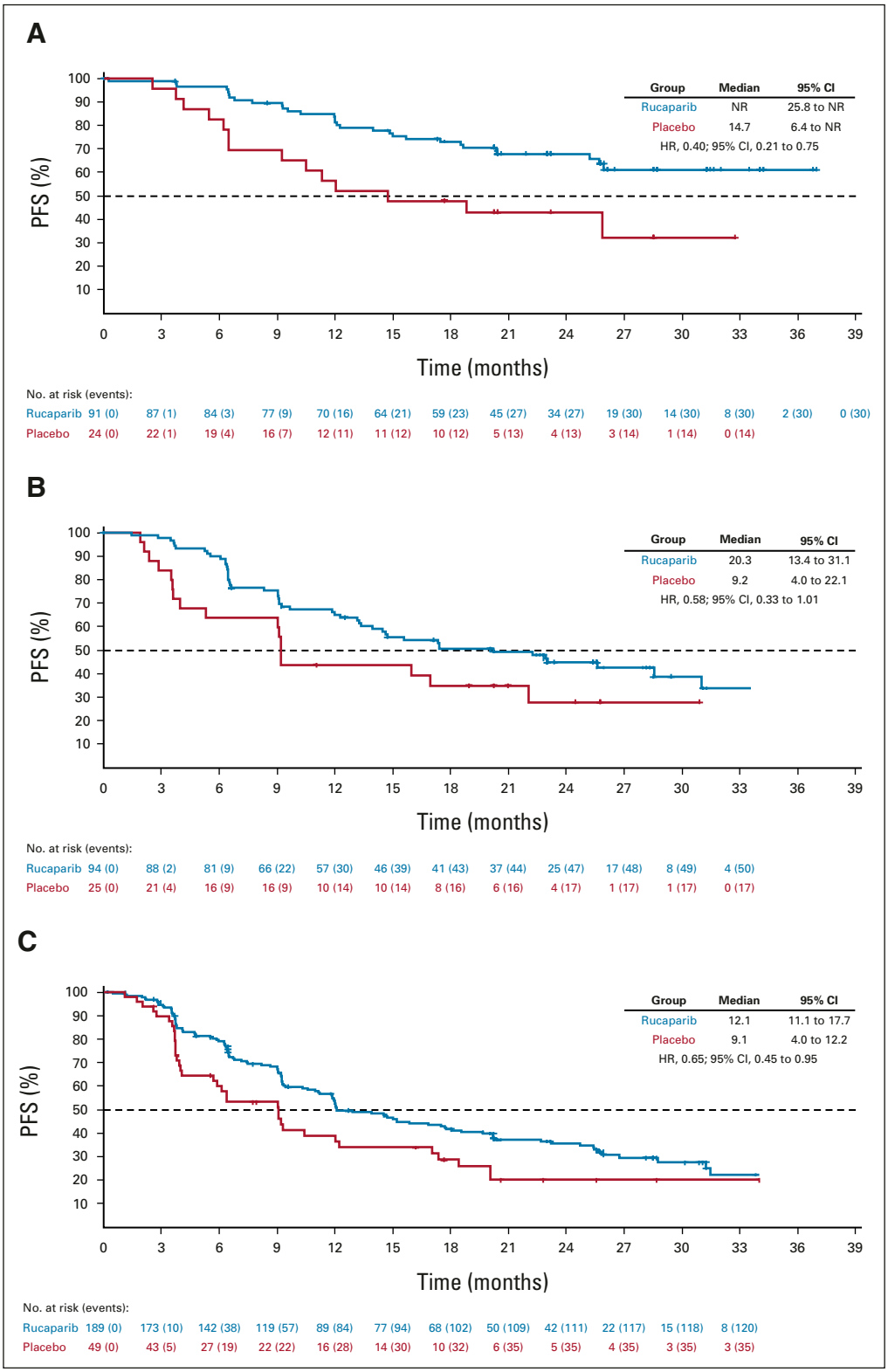

FIG 4. PFS by investigator in (A) patients with BRCA-mutant tumors, (B) patients with BRCA wild-type/LOH high tumors, and (C) patients in the homologous recombination deficiency-negative subgroup (BRCA wild-type/LOH low tumors). BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; LOH, loss of heterozygosity; NR, not reached; PFS, progression-free survival.

TABLE 2. Confirmed ORR by Investigator (in HRD and ITT populations) in Patients With Measurable Disease at Baseline

	HRD Population		ITT Population	
Response	**Rucaparib (n = 17)**	**Placebo (n = 5)**	**Rucaparib (n = 41)**	**Placebo (n = 11)**
Confirmed ORR per RECIST				
No.	10	1	20	1
% (95% CI)	58.8 (32.9 to 81.6)	20.0 (0.5 to 71.6)	48.8 (32.9 to 64.9)	9.1 (0.2 to 41.3)
CR, No. (%)	0	0	1 (2.4)	0
PR, No. (%)	10 (58.8)	1 (20.0)	19 (46.3)	1 (9.1)
Stable disease, No. (%)	6 (35.3)	2 (40.0)	10 (24.4)	4 (36.4)
Progressive disease, No. (%)	1 (5.9)	2 (40.0)	10 (24.4)	6 (54.5)
Not evaluable, No. (%)	0	0	1 (2.4)	0

Abbreviations: CR, complete response; HRD, homologous recombination deficiency; ITT, intent-to-treat; ORR, objective response rate; PR, partial response.

TABLE 3. Most Common TEAEs (≥ 10% any grade, and corresponding grade ≥ 3) in the Safety Population

	Rucaparib (n = 425)		Placebo (n = 110)	
TEAE	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
At least one TEAE, No. (%)	411 (96.7)	257 (60.5)	102 (92.7)	25 (22.7)
Nausea	239 (56.2)	8 (1.9)	33 (30.0)	0
Asthenia/fatigue	237 (55.8)	21 (4.9)	41 (37.3)	1 (0.9)
Anemia/decreased hemoglobin	198 (46.6)	122 (28.7)	10 (9.1)	0
Increased ALT/AST	181 (42.6)	45 (10.6)	9 (8.2)	1 (0.9)
Neutropenia/neutrophil count decreased	118 (27.8)	62 (14.6)	8 (7.3)	1 (0.9)
Abdominal pain	106 (24.9)	2 (0.5)	31 (28.2)	2 (1.8)
Diarrhea	102 (24.0)	6 (1.4)	23 (20.9)	1 (0.9)
Thrombocytopenia/platelet count decreased	101 (23.8)	30 (7.1)	1 (0.9)	0
Vomiting	100 (23.5)	6 (1.4)	13 (11.8)	0
Dysgeusia	90 (21.2)	1 (0.2)	6 (5.5)	0
Arthralgia	86 (20.2)	1 (0.2)	25 (22.7)	0
Headache	85 (20.0)	2 (0.5)	16 (14.5)	0
Constipation	82 (19.3)	0	17 (15.5)	0
Decreased appetite	76 (17.9)	2 (0.5)	16 (14.5)	0
Pruritus	69 (16.2)	1 (0.2)	11 (10.0)	0
Rash	61 (14.4)	1 (0.2)	8 (7.3)	0
Insomnia	59 (13.9)	1 (0.2)	8 (7.3)	0
Dizziness	57 (13.4)	0	9 (8.2)	0
Myalgia	53 (12.5)	1 (0.2)	10 (9.1)	0
Cough	52 (12.2)	0	11 (10.0)	0
Blood creatinine increased	47 (11.1)	1 (0.2)	6 (5.5)	0
Dyspnea	45 (10.6)	6 (1.4)	12 (10.9)	0
Pyrexia	43 (10.1)	0	6 (5.5)	0
Abdominal distension	42 (9.9)	0	14 (12.7)	0
Back pain	42 (9.9)	1 (0.2)	13 (11.8)	0
Edema peripheral	33 (7.8)	0	12 (10.9)	0

NOTE. MedDRA-preferred terms are combined for the following adverse events: anemia or decreased hemoglobin, asthenia or fatigue, increased ALT or AST, neutropenia or decreased neutrophil count, and thrombocytopenia or platelet count decreased.

Abbreviation: TEAE, treatment-emergent adverse event.

ITT population, including those with stage III cancer without residual disease, expanding our knowledge of the populations that may benefit from PARP inhibitor maintenance treatment. Additionally, the safety profile of rucaparib supports a single starting dose of 600 mg twice a day, and the availability of four dose reduction steps in the study offers flexibility for managing side effects.

Strengths of the study include that ATHENA–MONO had the highest proportion of patients with BRCA wild-type (78.6%) and HRD-negative tumors (44.2%) among phase III clinical studies evaluating first-line maintenance with a PARP inhibitor,[1-4] giving further weight to the observed effectiveness of rucaparib maintenance treatment in patients typically thought to be less sensitive to a PARP inhibitor. ATHENA–MONO also enrolled a population that included patients with a complete resection or nonmeasurable disease after surgery but cancer antigen 125 response, a population that could be considered more real-world compared with other studies in its inclusion of patients without certain prognostically high-risk clinical characteristics. A limitation of the ATHENA–MONO analysis was the relatively small number of placebo group patients; although the 4:1 random assignment to rucaparib and placebo was considered advantageous for encouraging participation, the placebo group sample size limits the interpretation of some subgroup analyses. Regardless, despite the smaller number of placebo group patients, analyses of PFS demonstrated a clear trend toward rucaparib benefit versus placebo across subgroups.

In summary, ATHENA–MONO demonstrates that rucaparib monotherapy is effective in the first-line maintenance setting with benefit observed in a broad patient population with advanced ovarian cancer, including those with and without HRD tumors.

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DATA SHARING STATEMENT

Requests for deidentified data sets for the results reported in this publication will be made available to qualified researchers following submission of a methodologically sound proposal to medinfo@clovisoncology.com. Data will be made available for such requests following online publication of this article and for 1 year thereafter in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Data will be provided by Clovis Oncology. Clovis Oncology does not share identified participant data or a data dictionary.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45)

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No other potential conflicts of interest were reported.

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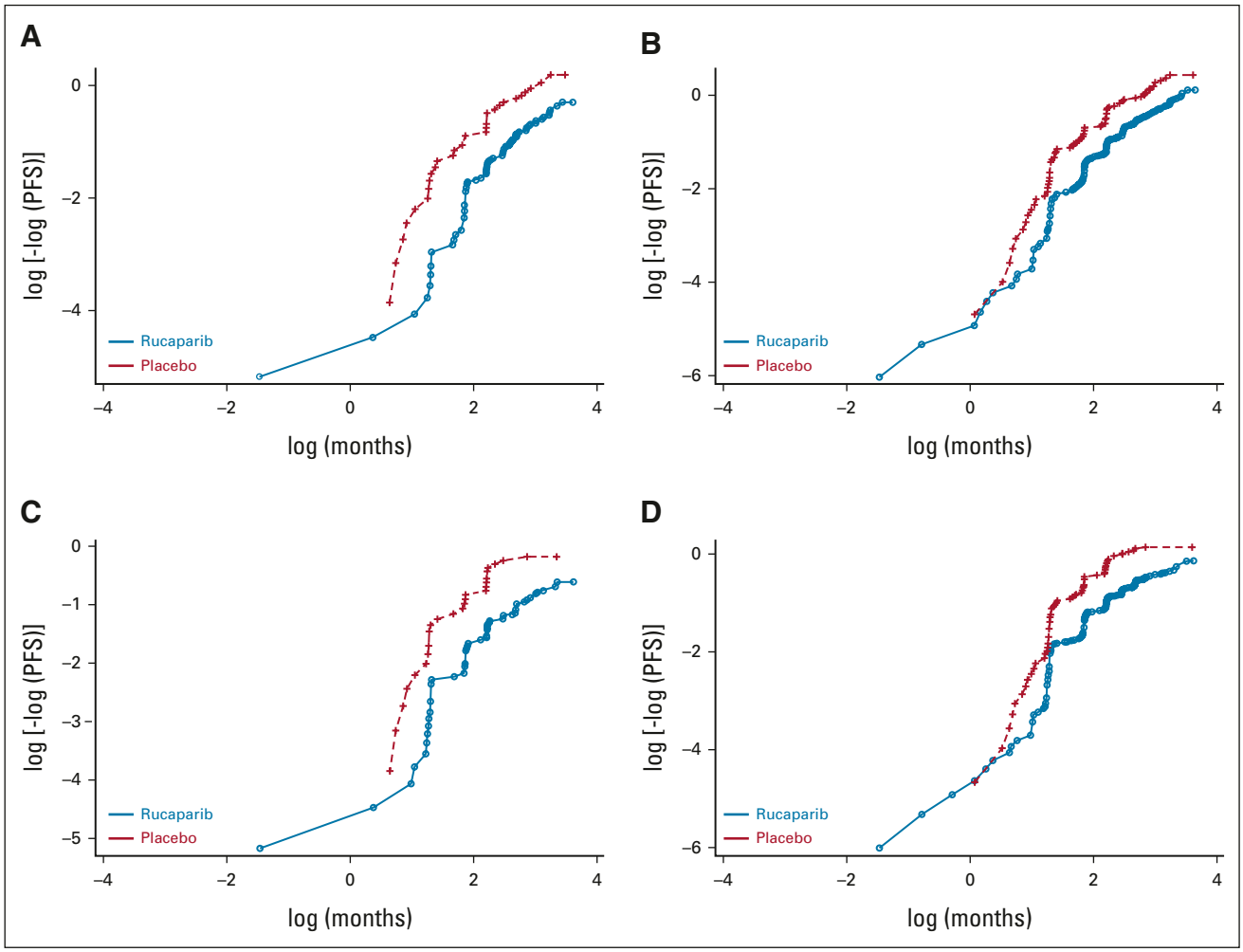

FIG A1. Plots of the log of the cumulative hazard for PFS by investigator in (A) the homologous recombination-deficiency population and (B) the intent-to-treat population and PFS by blinded independent central review for the same populations (C and D, respectively). PFS, progression-free survival.

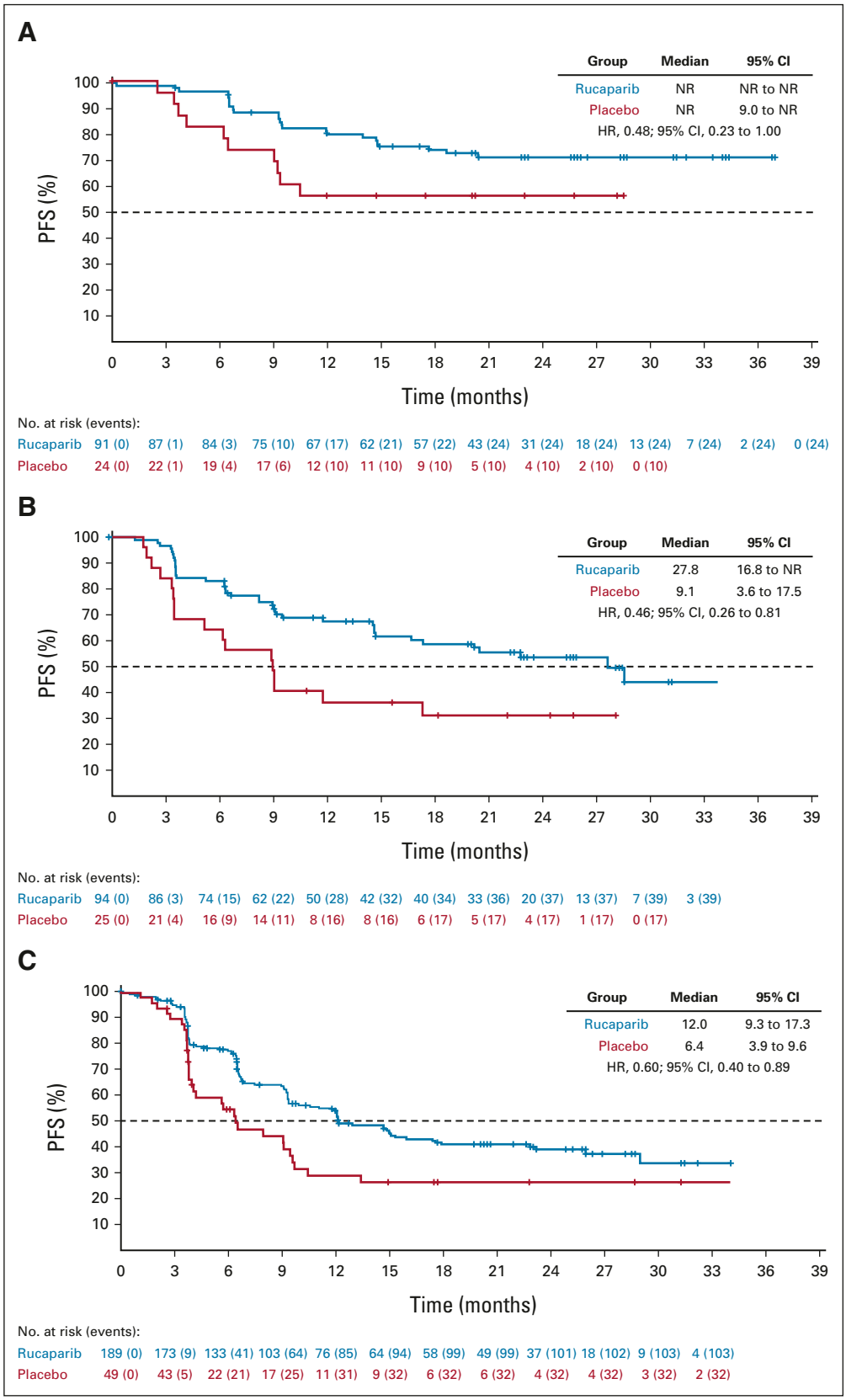

FIG A2. PFS by blinded independent central review in (A) patients with BRCA-mutant tumors, (B) patients with BRCA wild-type/LOH high tumors, and (C) patients in the homologous recombination deficiency-negative subgroup (BRCA wild-type/LOH low tumors). BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; LOH, loss of heterozygosity; NR, not reached; PFS, progression-free survival.

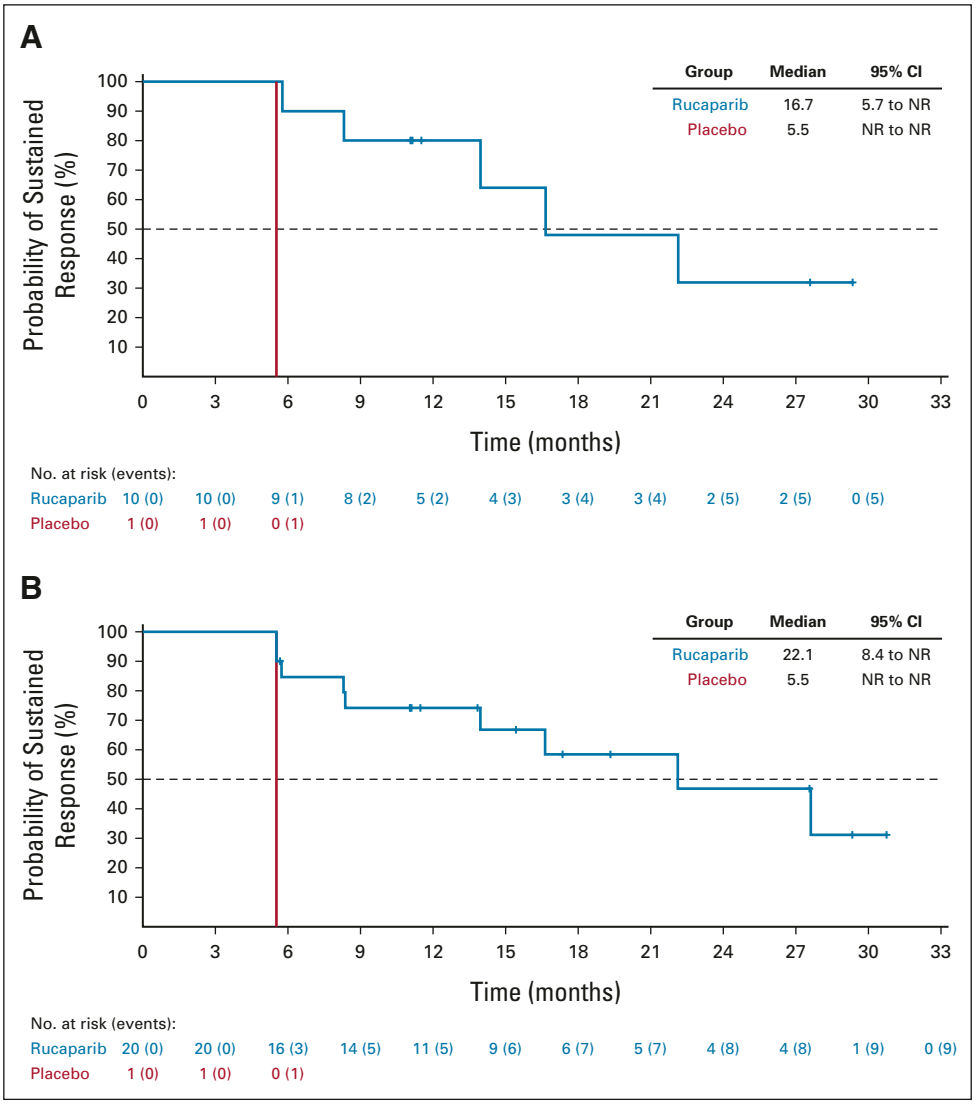

FIG A3. Duration of RECIST response in the (A) homologous recombination deficiency population and (B) intent-to-treat population. NR, not reached.

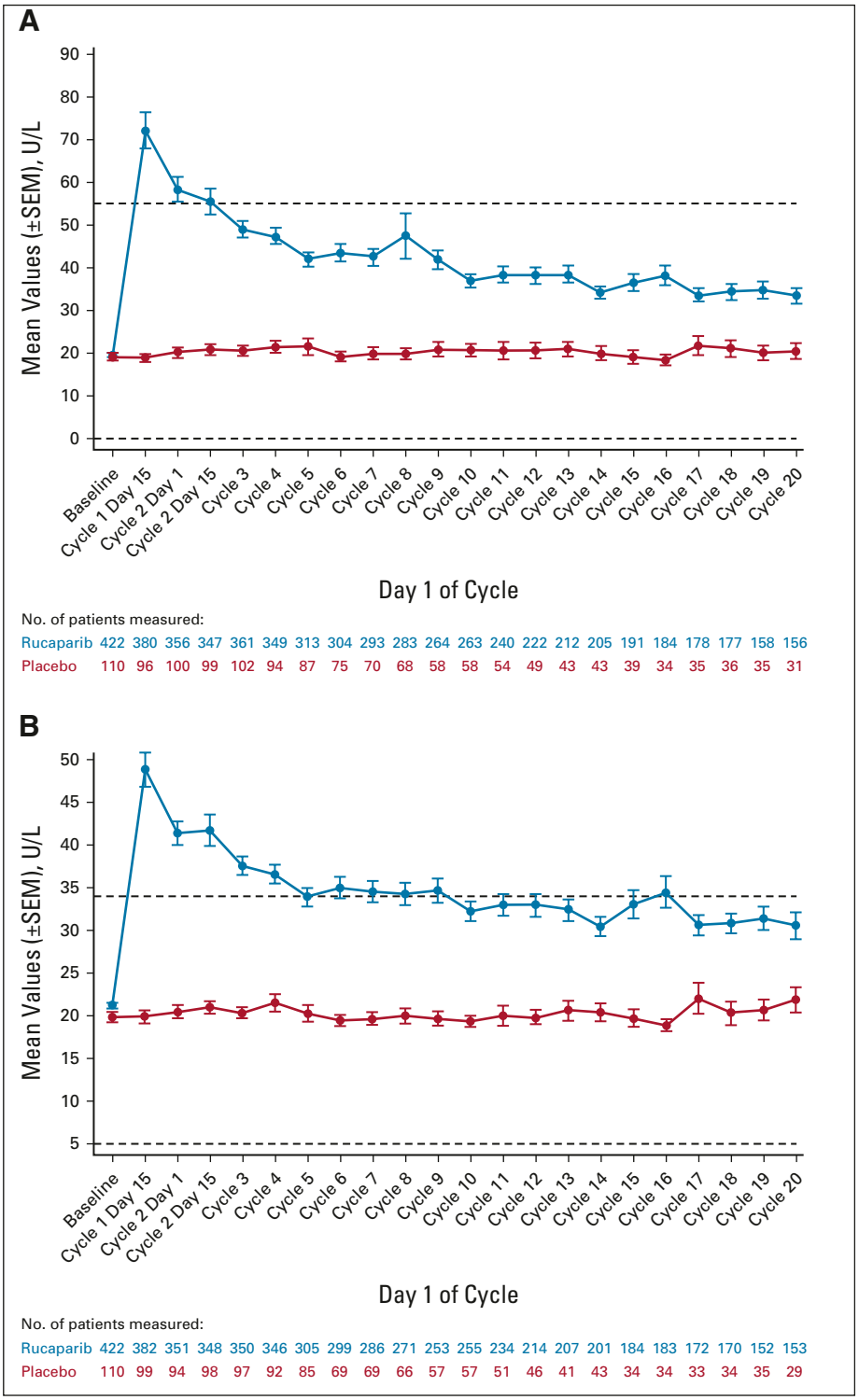

FIG A4. Changes from baseline in (A) ALT and (B) AST. Horizontal dotted lines in graphs represent the upper and lower limits of normal for each laboratory parameter.

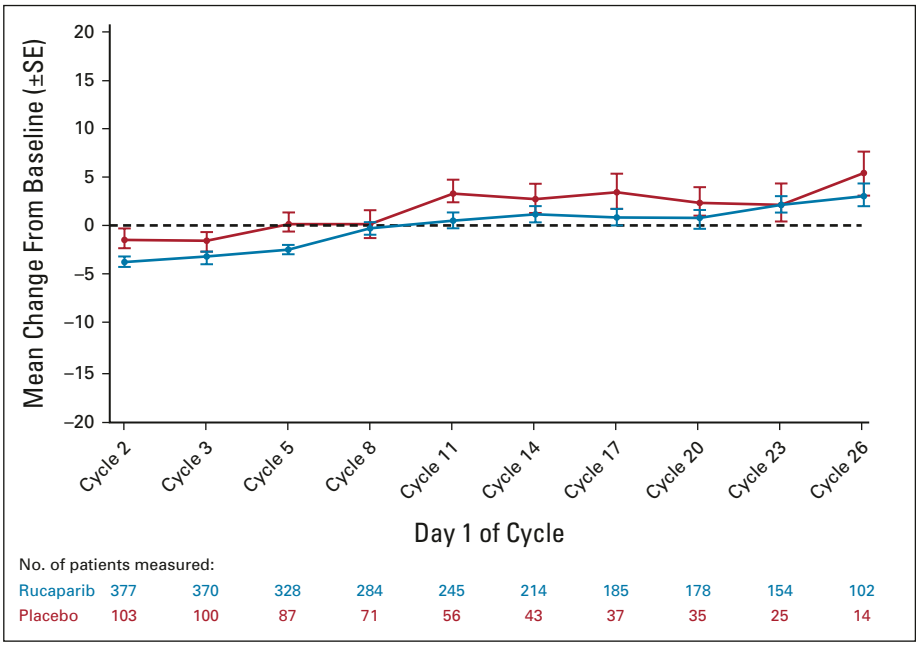

FIG A5. Change from baseline in Functional Assessment of Cancer Therapy—Ovarian Trial Outcome Index score in the intent-to-treat population.

TABLE A1. Inclusion and Exclusion Criteria

Patient Eligibility
All patients enrolled into the study must have met all of the following inclusion criteria
Had signed an IRB/IEC-approved ICF before any study-specific evaluation
Been ≥ 18 years at the time the ICF was signed (patients enrolled in South Korea, Taiwan, and Japan must have been ≥ 20 years at the time the ICF was signed)
Had newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
Completed cytoreductive surgery, including at least a bilateral salpingo-oophorectomy and partial omentectomy, either before chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking)
Had received four to eight cycles of first-line platinum-doublet treatment per standard clinical practice, including a minimum of four cycles of platinum/taxane combination A patient with best response of PR must have received at least six cycles Bevacizumab was allowed during the chemotherapy phase, but not during maintenance, ie, during therapy directed by this protocol
Had completed first-line platinum-based chemotherapy and surgery with a response, in the opinion of the investigator, defined as no evidence of disease progression radiologically or through rising CA-125 (per GCIG guidelines) at any time during first-line treatment; and No evidence of measurable disease by RECIST v1.1 (if complete resection/R0 at primary or interval cytoreductive surgery); or A PR or CR per RECIST v1.1 (if measurable disease was present after surgery and before chemotherapy; see study Protocol); or A GCIG CA-125 response (if only nonmeasurable disease was present after surgery and before chemotherapy; see study Protocol)
Pretreatment CA-125 measurements must have met criteria specified below If the first value was within ULN, the patient was eligible to be randomly assigned and a second sample was not required If the first value was greater than ULN, a second assessment must have been performed at least 7 days after the first. If the second assessment was ≥ 15% than the first value, the patient was not eligible
Patient must have been randomly assigned within 8 weeks of the first day of the last cycle of chemotherapy
Had sufficient FFPE tumor tissue (1 × 4 μm section for HE stain and approximately 8 to 12 × 10 μm sections, or equivalent) available for planned analyses Submission of a tumor block was preferred; if sections were provided, these must all have been from the same tumor sample Tumor tissue from the cytoreductive surgery was required Sample must have been received at the central laboratory at least 3 weeks before planned start of treatment to enable stratification for random assignment
Had adequate organ function confirmed by the following laboratory values obtained within 14 days of random assignment Bone marrow function ANC ≥ 1.5×10^9/L Platelets ≥ 100×10^9/L Hemoglobin ≥ 9 g/dL Hepatic function AST and ALT ≤ 1.5 × ULN Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia was due to Gilbert's syndrome Serum albumin ≥ 30 g/L (3.0 g/dL) Renal function Serum creatinine ≤ 1.5 × ULN unless GFR ≥ 30 mL/min using the Cockcroft-Gault formula
Had an ECOG PS of 0-1
Patients were excluded from participation if any of the following criteria applied
Nonepithelial tumors (pure sarcomas) or ovarian tumors with low malignant potential (ie, borderline tumors) or mucinous tumors. Mixed Mullerian tumors/carcinosarcomas were allowed
Active second malignancy, ie, patient known to have potentially fatal cancer present for which she may have been (but not necessarily) currently receiving treatment Patients with a history of malignancy that had been completely treated, with no evidence of active cancer for 3 years before enrollment, or patients with surgically cured low-risk tumors, such as early-stage cervical or endometrial cancer, were allowed to enroll
Known central nervous system brain metastases
Any prior treatment for ovarian cancer, other than the first-line platinum regimen, including any maintenance treatment between completion of the platinum regimen and initiation of study drug in this study Ongoing hormonal treatment for previously treated breast cancer was permitted. Hormonal maintenance treatment for ovarian cancer was not allowed
Had evidence of interstitial lung disease, active pneumonitis, myocarditis, or a history of myocarditis
Patients with an active, known, or suspected autoimmune disease (eg, autoimmune hepatitis). Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger were permitted to enroll

(continued on following page)

TABLE A1. Inclusion and Exclusion Criteria (continued)

Patient Eligibility
Patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of random assignment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease
Drainage of ascites during the final two cycles of treatment with the platinum regimen
Pre-existing duodenal stent and/or any GI disorder or defect that would have, in the opinion of the investigator, interfered with absorption of study treatment
Known history of a positive test for HIV or known AIDS. NOTE: Testing for HIV must have been performed at all sites where mandated locally
Any positive test result for hepatitis B and/or known history of hepatitis B infection including patients with undetectable HBV DNA and inactive carriers; positive test result for hepatitis C antibody (anti-HCV; except if HCV-RNA–negative)
Pregnant or breastfeeding. All study participants must have avoided pregnancy achieved through assisted reproductive technology for the duration of study treatment and for a minimum of 6 months following the last dose of study drug (oral or IV, whichever was later)
Received chemotherapy within 14 days before first dose of study drug and/or ongoing adverse effects from such treatment > NCI-CTCAE v5.0 grade 1, with the exception of grade 2 nonhematologic toxicity such as alopecia, peripheral neuropathy, grade 2 anemia with hemoglobin ≥ 9 g/dL, and related effects of prior chemotherapy that were unlikely to be exacerbated by treatment with study drug
Non–study-related minor surgical procedure (eg, placement of a central venous access port) ≤ 5 days, or major surgical procedure ≤ 21 days, before first dose of study drug; in all cases, the patient must have been sufficiently recovered and stable before treatment administration
Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study
Hospitalization for bowel obstruction within 12 weeks before enrollment

Abbreviations: ANC, absolute neutrophil count; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed paraffin-embedded; FIGO, International Federation of Gynecology and Obstetrics; GCIG, Gynecologic Cancer InterGroup; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hematoxylin and eosin; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PR, partial response; ULN, upper limit of normal.

TABLE A2. BRCA Gene and Mutation Type

Characteristic	HRD Population		ITT Population	
	Rucaparib (n = 185)	Placebo (n = 49)	Rucaparib (n = 427)	Placebo (n = 111)
Gene, No. (%)				
BRCA1	60 (32.4)	15 (30.6)	60 (14.1)	15 (13.5)
BRCA2	31 (16.8)	9 (18.4)	31 (7.3)	9 (8.1)
BRCA wild-type	94 (50.8)	25 (51.0)	336 (78.7)	87 (78.4)
BRCA mutation type, No. (%)				
Germline	56 (30.3)	12 (24.5)	56 (13.1)	12 (10.8)
Somatic	25 (13.5)	8 (16.3)	25 (5.9)	8 (7.2)
Germline/somatic status not available	10 (5.4)	4 (8.2)	10 (2.3)	4 (3.6)

Abbreviations: BRCA, *BRCA1* or *BRCA2*; HRD, homologous recombination deficiency; ITT, intent-to-treat.

TABLE A3. PFS Landmark Analyses at 6, 12, 18, 24, 30, and 36 Months by Investigator and by BICR Assessment

		Investigator-Assessed PFS		BICR-Assessed PFS	
Cohort	**Month**	**Rucaparib**	**Placebo**	**Rucaparib**	**Placebo**
BRCA-mutant	6	0.966	0.826	0.966	0.826
	12	0.815	0.522	0.802	0.565
	18	0.733	0.478	0.741	0.565
	24	0.681	0.430	0.713	0.565
	30	0.614	0.323	0.713	NR
	36	0.614	NR	0.713	NR
HRD	6	0.932	0.729	0.898	0.729
	12	0.738	0.477	0.737	0.457
	18	0.620	0.412	0.666	0.432
	24	0.563	0.350	0.626	0.432
	30	0.499	0.300	0.579	NR
	36	0.477	NR	0.579	NR
ITT	6	0.862	0.684	0.838	0.643
	12	0.630	0.421	0.619	0.361
	18	0.515	0.340	0.531	0.317
	24	0.451	0.254	0.501	0.317
	30	0.387	0.215	0.458	0.317
	36	0.328	0.215	0.420	0.317
BRCA wild-type/LOH high	6	0.900	0.640	0.831	0.640
	12	0.663	0.440	0.674	0.356
	18	0.508	0.352	0.587	0.305
	24	0.451	0.282	0.536	0.305
	30	0.389	0.282	0.440	NR
	36	0.341	NR	0.440	NR
BRCA wild-type/LOH low	6	0.792	0.600	0.773	0.543
	12	0.527	0.388	0.502	0.285
	18	0.418	0.287	0.407	0.259
	24	0.357	0.201	0.388	0.259
	30	0.278	0.201	0.334	0.259
	36	0.224	0.201	0.334	0.259

Abbreviations: BICR, blinded independent central review; BRCA, *BRCA1* or *BRCA2*; HRD, homologous recombination deficiency; ITT, intent-to-treat; LOH, loss of heterozygosity; NR, not reached; PFS, progression-free survival.

TABLE A4. Sensitivity Analyses of Investigator-Assessed PFS

PFS Sensitivity Analysis	No. of Patients		Median PFS (95% CI)		Log-Rank *P* Value	HR (95% CI)
	Rucaparib	Placebo	Rucaparib	Placebo		
Using all scans						
HRD population	185	49	28.7 (22.3 to NR)	11.3 (9.1 to 22.1)	.0005	0.48 (0.31 to 0.73)
ITT population	427	111	20.2 (15.6 to 23.2)	9.2 (8.5 to 12.2)	< .0001	0.52 (0.40 to 0.68)
Including clinical progression and withdrew consent						
HRD population	185	49	25.7 (18.6 to NR)	11.6 (9.1 to 22.1)	.0027	0.54 (0.36 to 0.81)
ITT population	427	111	15.9 (13.2 to 20.2)	9.2 (6.4 to 10.4)	< .0001	0.56 (0.44 to 0.72)

Abbreviations: BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; NR, not reached; PFS, progression-free survival.

TABLE A5. TEAEs Leading to Treatment Interruption and/or Dose Reduction in ≥ 2% of Patients

TEAE	Treatment Interruption		Dose Reduction		Treatment Interruption and/or Dose Reduction	
	Rucaparib (n = 425)	Placebo (n = 110)	Rucaparib (n = 425)	Placebo (n = 110)	Rucaparib (n = 425)	Placebo (n = 110)
Any TEAE leading to treatment interruption and/or dose reduction, No. (%)	258 (60.7)	22 (20.0)	210 (49.4)	9 (8.2)	271 (63.8)	24 (21.8)
Anemia/decreased hemoglobin	115 (27.1)	1 (0.9)	99 (23.3)	0	120 (28.2)	1 (0.9)
Neutropenia/neutrophil count decreased	63 (14.8)	1 (0.9)	40 (9.4)	2 (1.8)	67 (15.8)	2 (1.8)
Asthenia/fatigue	41 (9.6)	4 (3.6)	39 (9.2)	6 (5.5)	56 (13.2)	7 (6.4)
Increased ALT/AST	49 (11.5)	1 (0.9)	32 (7.5)	0	53 (12.5)	1 (0.9)
Thrombocytopenia/platelet count decreased	45 (10.6)	1 (0.9)	29 (6.8)	1 (0.9)	48 (11.3)	1 (0.9)
Nausea	38 (8.9)	1 (0.9)	30 (7.1)	0	47 (11.1)	1 (0.9)
Vomiting	19 (4.5)	2 (1.8)	7 (1.6)	0	20 (4.7)	2 (1.8)
WBC count decreased	16 (3.8)	0	11 (2.6)	0	18 (4.2)	0
Diarrhea	16 (3.8)	4 (3.6)	5 (1.2)	2 (1.8)	17 (4.0)	5 (4.5)
Decreased appetite	7 (1.6)	0	7 (1.6)	1 (0.9)	11 (2.6)	1 (0.9)
Headache	9 (2.1)	0	2 (0.5)	0	10 (2.4)	0
Dysgeusia	6 (1.4)	1 (0.9)	7 (1.6)	0	9 (2.1)	1 (0.9)
Dyspnea	8 (1.9)	1 (0.9)	3 (0.7)	0	9 (2.1)	1 (0.9)
COVID-19	9 (2.1)	0	0	0	9 (2.1)	0

NOTE. MedDRA-preferred terms are combined for the following adverse events: anemia or decreased hemoglobin, asthenia or fatigue, increased ALT or AST, neutropenia or decreased neutrophil count, and thrombocytopenia or platelet count decreased.

Abbreviation: TEAE, treatment-emergent adverse event.

TABLE A6. TEAEs (excluding disease progression) Leading to Treatment Discontinuation

TEAE	Rucaparib (n = 425)	Placebo (n = 110)
Any TEAE leading to treatment discontinuation, No. (%)	50 (11.8)	6 (5.5)
Anemia/decreased hemoglobin	15 (3.5)	0
Asthenia/fatigue	12 (2.8)	3 (2.7)
Nausea	9 (2.1)	0
Vomiting	3 (0.7)	0
Arthralgia	3 (0.7)	0
Dysgeusia	3 (0.7)	0
Dizziness	2 (0.5)	0
Acute kidney injury	2 (0.5)	0
Thrombocytopenia/platelet count decreased	2 (0.5)	0
Neutropenia/decreased neutrophil count	2 (0.5)	0
Abdominal pain upper	1 (0.2)	0
Anxiety	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	0
Chronic kidney disease	1 (0.2)	0
Decreased appetite	1 (0.2)	0
Diarrhea	1 (0.2)	0
Dyspnea	1 (0.2)	0
Edema peripheral	1 (0.2)	0
Increased ALT/AST	1 (0.2)	0
Influenza	1 (0.2)	0
Intestinal obstruction	1 (0.2)	0
Malaise	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.2)	0
MDS	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Oral pain	1 (0.2)	0
Pain in extremity	1 (0.2)	0
Pleural effusion	1 (0.2)	0
Pulmonary embolism	1 (0.2)	0
Pyrexia	1 (0.2)	0
Peripheral neuropathy	0	2 (1.8)
Cough	0	1 (0.9)
Depression	0	1 (0.9)
Sciatica	0	1 (0.9)

NOTE. MedDRA-preferred terms are combined for the following adverse events: anemia or decreased hemoglobin, asthenia or fatigue, increased ALT or AST, neutropenia or decreased neutrophil count, and thrombocytopenia or platelet count decreased.

Abbreviations: MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

TABLE A7. TEAEs (excluding disease progression) Leading to Death

TEAE	Rucaparib (n = 425)	Placebo (n = 110)
Any TEAE leading to death (excluding disease progression), No. (%)	2 (0.5)	0
Myocardial infarction	1 (0.2)[a]	0
Multiple organ dysfunction syndrome	1 (0.2)	0
Pulmonary embolism	1 (0.2)[a]	0

Abbreviation: TEAE, treatment-emergent adverse event.
[a]Experienced by the same patient.