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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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.

J Clin Oncol 40:3952-3964. © 2022 by American Society of Clinical Oncology

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.
Rucaparib as First-Line Maintenance Treatment for Ovarian Cancer

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).

ATHENA is an international, multicenter, randomized, double-blind, phase III trial consisting of four treatment arms (rucaparib, nivolumab, rucaparib + nivolumab, and placebo). 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) 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
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 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
### TABLE 1. Baseline Patient and Disease Characteristics (N = 538)

| Characteristic                                      | 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)          | 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 surgeryc                           | 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)        |

(continued on following page)
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)
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 settings13-15 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)

| Group     | Median | 95% CI     |
|-----------|--------|------------|
| Rucaparib | 25.9   | 16.8 to NR |
| Placebo   | 9.1    | 6.4 to 9.7 |

**FIG 2.** (Continued).
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

| Subgroup | Rucaparib (events/patients in subgroup) | Placebo (events/patients in subgroup) | Investigator-Assessed PFS |
|----------|----------------------------------------|--------------------------------------|--------------------------|
| 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 | Rucaparib (events/patients in subgroup) | Placebo (events/patients in subgroup) | HR (95% CI) |
|----------------|----------------------------------------|--------------------------------------|-------------|
| 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 | 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 | 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.

*Excludes patients with unknown race. *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.
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

| Response | HRD Population | ITT Population |
|----------|----------------|----------------|
| Response | Rucaparib (n = 17) | Placebo (n = 5) | Rucaparib (n = 41) | Placebo (n = 11) |
| 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

| TEAE | Any Grade | Grade ≥ 3 | Any Grade | Grade ≥ 3 |
|------|-----------|-----------|-----------|-----------|
| Rucaparib (n = 425) | Placebo (n = 110) |
| 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,1,2 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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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)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/ficw or ascopubs.org/coauthors/author-center.

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This author is a member of the Journal of Clinical Oncology Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.

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This author is a Social Media Editor for Journal of Clinical Oncology. Journal policy recused the author from having any role in the peer review of this manuscript.
Consulting or Advisory Role: Roche, AstraZeneca, Genentech, Medscape, Clovis Oncology, Gerson Lehman Group, Vaniam Group, Merck, BioAscent, Curio Science, OncLive, Targeted Oncology, Curio Science, GlaxoSmithKline, Eisai, Zentatis, Agensys, EQRX, Lilly, Vincerx Pharma, Mereo BioPharma, Immunogen, Mersana
Research Funding: AstraZeneca (Inst), Novartis (Inst), Bayer (Inst), Cotinga Pharmaceuticals (Inst), Clovis Oncology (Inst), Roche/Genentech (Inst), QOG Foundation (Inst), Mereo BioPharma (Inst), Bio-Path Holdings, Inc (Inst), GlaxoSmithKline (Inst), OncXerna Therapeutics (Inst), Zentatis (Inst)

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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:

1. Had signed an IRB/IEC-approved ICF before any study-specific evaluation
2. 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)
3. Had newly diagnosed, histologically confirmed, advanced (FIGO stage III-IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
4. Completed cytoreductive surgery, including at least a bilateral salpingo-oophorectomy and partial omentectomy, either before chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking)
5. 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
6. 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/RO 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)
7. 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
8. Patient must have been randomly assigned within 8 weeks of the first day of the last cycle of chemotherapy
9. 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
10. 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
    - Renal function
      - Serum creatinine ≥ 30 g/L (3.0 g/dL)
      - Serum albumin ≥ 30 g/L (3.0 g/dL)
    - GFR ≥ 30 mL/min using the Cockcroft-Gault formula
11. Had an ECOG PS of 0-1

Patients were excluded from participation if any of the following criteria applied:

- Non epithelial 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.
| 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.
| Cohort                        | Month | Investigator-Assessed PFS | BICR-Assessed PFS |
|------------------------------|-------|---------------------------|-------------------|
|                              |       | 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 |
|-----------------------------------------------|------------------------|---------------|
|                                               | 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.
| 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.
| 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)*            | 0                 |
| Multiple organ dysfunction syndrome       | 1 (0.2)             | 0                 |
| Pulmonary embolism                        | 1 (0.2)*            | 0                 |

Abbreviation: TEAE, treatment-emergent adverse event.

*Experienced by the same patient.