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Postprogression outcomes and updated safety data for patients with platinum-sensitive recurrent ovarian carcinoma treated with rucaparib in the phase 3 ARIEL3 study

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Abstract:	Background In ARIEL3, rucaparib maintenance treatment significantly improved progression-free survival (PFS) versus placebo. Here we report prespecified, investigator-assessed, exploratory postprogression endpoints and updated safety data. Methods In this ongoing (enrolment complete) phase 3, randomised, placebo-controlled trial (NCT01968213), patients with platinum-sensitive, recurrent ovarian carcinoma who had received at least two previous platinum-based chemotherapy regimens and responded to their last platinum-based regimen were randomised 2:1 to

	oral rucaparib (600 mg twice daily) or placebo in 28-day cycles using a computer generated sequence (block size of six with stratification based on homologous recombination repair gene mutation status, progression-free interval following penultimate platinum-based regimen, and best response to most recent platinum-based regimen). Patients, investigators, site staff, assessors and the funder were masked to assignments. The primary endpoint of investigator-assessed progression-free survival has been previously reported. Prespecified, exploratory outcomes of chemotherapy-free interval (CFI), time to start of first subsequent therapy (TFST), time to disease progression on subsequent therapy or death (PFS2), and time to start of second subsequent therapy (TSST) and updated safety were analysed (31 Dec 2017 visit cutoff). Efficacy analyses were conducted in all patients randomised to three nested cohorts: patients with BRCA mutations, homologous recombination deficiencies, and the intention-to-treat population. Findings Between 7 April 2014 and 19 July 2016, 564 patients were enrolled; median (interquartile range) follow-up was 28 · 1 (22 ·0 –33 ·6) months. In the intention-to-treat population (n=375 rucaparib vs n=189 placebo), median (95% CI) CFI was 14·3 (13·0–17·4) versus 8·8 (8·0–10·3) months (hazard ratio 0·43 [95% CI 0·35–0·53]; p<0·0001), median (95% CI) TFST was 12·4 (11·1–15·2) versus 7·2 (6·4–8·6) months (0·43 [0·35–0·52]; p<0·0001), median (95% CI) PFS2 was 21·0 (18·9–23·6) versus 16·5 (15·2–18·4) months (0·66 [0·53–0·82]; p=0·0002), and median TSST was 22·4 (19·1–24·5) versus 17·3 (14·9–19·4) months (0·68 [0·54–0·85]; p=0·0007). CFI, TFST, PFS2, and TSST were also significantly longer with rucaparib than placebo in the BRCA -mutant and homologous recombination-deficient cohorts. The most frequent treatment-emergent adverse events (TEAEs) of any grade were nausea (76% vs 37%) and asthenia or fatigue (71% vs 44%). The most frequent grade 3 or greater TEAE was anaemia or decreased haemoglobin (22% vs 1%). Serious TEAEs were reported in 22% and 11% of patients in the rucaparib and placebo groups, respectively. TEAEs leading to death were reported in 2% and 1% of patients, respectively. Interpretation In these exploratory analyses over a median follow-up duration of more than 2 years, rucaparib maintenance treatment led to a clinically meaningful delay in starting subsequent therapy and provided lasting clinical benefits versus placebo in all three analysis cohorts. Updated safety data were consistent with prior reports.

Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): postprogression outcomes and updated safety from a randomised, placebo-controlled, phase 3 trial

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ABSTRACT

Background In ARIEL3, rucaparib maintenance treatment significantly improved progression-free survival (PFS) versus placebo. Here we report prespecified, investigator-assessed, exploratory postprogression endpoints and updated safety data.

Methods In this ongoing (enrolment complete) phase 3, randomised, placebo-controlled trial (NCT01968213), patients with platinum-sensitive, recurrent ovarian carcinoma who had received at least two previous platinum-based chemotherapy regimens and

responded to their last platinum-based regimen were randomised 2:1 to oral rucaparib (600 mg twice daily) or placebo in 28-day cycles using a computer generated sequence (block size of six with stratification based on homologous recombination repair gene mutation status, progression-free interval following penultimate platinum-based regimen, and best response to most recent platinum-based regimen). Patients, investigators, site staff, assessors and the funder were masked to assignments. The primary endpoint of investigator-assessed progression-free survival has been previously reported. Prespecified, exploratory outcomes of chemotherapy-free interval (CFI), time to start of first subsequent therapy (TFST), time to disease progression on subsequent therapy or death (PFS2), and time to start of second subsequent therapy (TSST) and updated safety were analysed (31 Dec 2017 visit cutoff). Efficacy analyses were conducted in all patients randomised to three nested cohorts: patients with *BRCA* mutations, homologous recombination deficiencies, and the intention-to-treat population.

Findings Between 7 April 2014 and 19 July 2016, 564 patients were enrolled; median (interquartile range) follow-up was 28·1 (22·0–33·6) months. In the intention-to-treat population (n=375 rucaparib *vs* n=189 placebo), median (95% CI) CFI was 14·3 (13·0–17·4) versus 8·8 (8·0–10·3) months (hazard ratio 0·43 [95% CI 0·35–0·53]; p<0·0001), median (95% CI) TFST was 12·4 (11·1–15·2) versus 7·2 (6·4–8·6) months (0·43 [0·35–0·52]; p<0·0001), median (95% CI) PFS2 was 21·0 (18·9–23·6) versus 16·5 (15·2–18·4) months (0·66 [0·53–0·82]; p=0·0002), and median TSST was 22·4 (19·1–24·5) versus 17·3 (14·9–19·4) months (0·68 [0·54–0·85]; p=0·0007). CFI, TFST, PFS2, and TSST were also significantly longer with rucaparib than placebo in the *BRCA*-mutant and homologous recombination-deficient cohorts. The most frequent treatment-emergent adverse events (TEAEs) of any grade were nausea (76% *vs* 37%) and asthenia or fatigue (71% *vs* 44%). The most frequent grade 3 or greater TEAE was anaemia or decreased haemoglobin (22% *vs* 1%). Serious TEAEs were reported in 22% and 11% of patients in the rucaparib and placebo groups, respectively. TEAEs leading to death were reported in 2% and 1% of patients, respectively.

Interpretation In these exploratory analyses over a median follow-up duration of more than 2 years, rucaparib maintenance treatment led to a clinically meaningful delay in

starting subsequent therapy and provided lasting clinical benefits versus placebo in all three analysis cohorts. Updated safety data were consistent with prior reports.

Funding Clovis Oncology.

RESEARCH IN CONTEXT

Evidence before this study

Data on postprogression outcomes for women with recurrent platinum-sensitive ovarian carcinoma who have received poly(ADP-ribose) polymerase (PARP) inhibitor maintenance treatment are limited. Postprogression outcomes can provide clinically meaningful information. Time to start of first subsequent therapy (TFST) can demonstrate a difference in the time before further therapy is started between patients who receive a PARP inhibitor and those who received placebo. Time to disease progression on the subsequent line of treatment or death (PFS2) can provide a “snapshot” of differences in postprogression outcomes to the time to second progression, which may be of particular use when overall survival data are unavailable due to trial immaturity or confounded by long postprogression survival and/or crossover to other treatments.

A search of all PubMed articles published up to 25 Sept 2019, using the search terms ("PARP inhibitor” OR “rucaparib” OR “olaparib” OR “niraparib” OR “veliparib” OR “talazoparib”) AND (“ovarian” AND [“cancer” OR “carcinoma”]) AND “maintenance” with no language restrictions, identified 13 peer-reviewed publications covering trials of PARP inhibitor monotherapy as second-line maintenance treatment, of which only three provide postprogression outcomes data. Patients who received maintenance olaparib in Study 19 or SOLO2 (ie, those with a *BRCA1 or BRCA2* [*BRCA*] mutation) had significantly longer TFST, time to start of second subsequent therapy (TSST), and/or PFS2 than those in the placebo group. In NOVA, median chemotherapy-free interval (CFI) and TFST were significantly longer with maintenance niraparib than placebo in patients with a germline *BRCA* mutation and patients without a germline *BRCA* mutation (this subgroup included patients with a somatic *BRCA* mutation).

Added value of this study

Our analyses include a comprehensive assessment of CFI, TFST, PFS2, and TSST postprogression outcomes for patients from ARIEL3. To our knowledge, we provide the first report of mature PFS2 data in this setting in an all-comer (ie, intention to treat [ITT]) population that includes patients without a *BRCA* mutation. The significant improvements observed in these postprogression outcomes support the PFS benefit previously reported and the clinical benefit of rucaparib in the second-line maintenance setting.

Implications of all the available evidence

Evaluation of overall survival in clinical trials of ovarian cancer can be challenging given the long duration of postprogression survival, and can be confounded by highly effective subsequent treatments. Therefore, assessment of postprogression outcomes is important to demonstrate the clinical benefit of novel therapies, such as whether further anticancer therapies may be delayed and whether patients continue to derive benefit from subsequent therapies. Together, CFI, TFST, PFS2, and TSST provide a complementary and comprehensive assessment of the postprogression outcomes following rucaparib maintenance treatment. Our postprogression outcomes data are consistent with those from other studies, further demonstrating the clinical benefit of PARP inhibitors as second-line maintenance treatment for patients with ovarian cancer.

INTRODUCTION

Although most patients with advanced ovarian cancer respond to initial treatment, typically surgery followed by platinum- and/or taxane-based chemotherapy, the majority will experience disease recurrence and require subsequent therapies.[1] For patients with recurrent ovarian cancer who respond to second-line platinum-based chemotherapy, continuing therapy with bevacizumab as a maintenance therapy or introducing a targeted agent such as a poly(ADP-ribose) polymerase (PARP) inhibitor after chemotherapy has become a standard of care that should be offered to patients.[2-7] Maintenance therapy is intended to delay disease progression without negatively affecting patient quality of life.[8,9]

Rucaparib (formerly known as CO-338, AG-014447, and PF-01367338) is an oral, small molecule inhibitor of PARP1, 2, and 3.[10,11] In the phase 3 ARIEL3 study (CO-338-014; NCT01968213) in patients with advanced, recurrent ovarian cancer, rucaparib maintenance treatment significantly improved investigator-assessed progression-free survival (PFS) versus placebo in all of the study's three molecularly defined, nested cohorts: patients with a *BRCA1* or *BRCA2 (BRCA)*-mutated carcinoma (germline, somatic, or unknown origin); patients with a homologous recombination deficient (HRD) carcinoma (*BRCA* mutation + wild-type *BRCA* and high loss of heterozygosity [LOH]); and the intention-to-treat (ITT) population.[12] The median (95% CI) PFS in patients with a *BRCA*-mutant carcinoma was 16·6 (13·4–22·9) months in the rucaparib group versus 5·4 (3·4–6·7) months in the placebo group (hazard ratio [HR] 0·23 [95% CI 0·16–0·34]; p<0·0001). In patients with an HRD carcinoma, the median (95% CI) PFS was 13·6 (10·9–16·2) months versus 5·4 (5·1–5·6) months, respectively (HR 0·32 [95% CI 0·24–0·42]; p<0·0001). In the ITT population, the median (95% CI) PFS was 10·8 (8·3–11·4) months versus 5·4 (5·3–5·5) months, respectively (HR 0·36 [95% CI 0·30–0·45]; p<0·0001). Based on these results, rucaparib is approved in the United States and European Union as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.[13,14]

As new therapies become available and management of ovarian cancer evolves to incorporate strategies such as maintenance, it is important to understand how such treatments influence the postprogression survival of patients. Although overall survival remains the gold standard in oncology trials, including those for ovarian cancer, evaluation may be confounded by subsequent treatments, a long duration of postprogression survival, and crossover to the trial or similar drug.[15] This can be particularly problematic when numerous effective treatments are available. Thus, additional postprogression assessments are needed to help demonstrate the clinical benefit of an investigative therapy, and organisations such as the Gynecologic Cancer InterGroup (GCIG), Society of Gynecologic Oncology, European Society for Gynaecological Oncology, and European Society for Medical Oncology recommend their incorporation into clinical trials to support observed PFS benefits.[16-19]

Postprogression assessments include time to start of first subsequent therapy (TFST), time to disease progression on subsequent therapy or death (PFS2), and time to start of second subsequent therapy (TSST). Significant improvements in these endpoints demonstrate that clinically meaningful improvements in PFS observed during the study can be maintained beyond the first progression event, can delay the need for subsequent therapy, and can persist throughout the course of subsequent treatments.[15] Examination of PFS2 may also provide insight into the influence of an investigative therapy on the efficacy of subsequent therapies and serve as a surrogate for overall survival.[20] Additionally, trials of targeted therapy may assess the chemotherapy-free interval (CFI), defined as the time from the last dose of prior chemotherapy to initiation of subsequent chemotherapy, inclusive of the time on targeted therapy or placebo. This endpoint can help quantify the duration of time that patients avoid the need for chemotherapy, a treatment that may have a negative impact on patient quality of life; side effects associated with chemotherapy can be more frequent and/or severe than those associated with targeted therapies. Overall, these endpoints give complementary and comprehensive information on the postprogression benefits of an investigative therapy.

Here we present results from the analyses of CFI, TFST, PFS2, and TSST in ARIEL3 to investigate the durability of clinical benefit with rucaparib maintenance treatment following disease progression and the switch to a subsequent therapy. Additional safety data are also reported (31 Dec 2017 visit cutoff), which represents a more extensive analysis of safety with an additional 8 months of follow-up than reported previously (15 Apr 2017).[12]

METHODS

Study design and patients

Full details of this randomised, double-blind, multicentre, international, phase 3 trial have been published previously.[12] This trial was conducted at 87 hospitals and cancer centres in 11 countries. Patients were enrolled between 7 Apr 2014 and 19 July 2016. The redacted protocol for the ARIEL3 clinical study is available on ClinicalTrials.gov: https://clinicaltrials.gov/ProvidedDocs/13/NCT01968213/Prot_000.pdf.

Eligible patients were aged at least 18 years, had platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, had received at least two previous platinum-based chemotherapy regimens, had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and must have achieved either a complete response according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST), a partial response according to RECIST, or a serological response based on GCIG cancer antigen 125 (CA-125) response criteria to their last platinum-based regimen. Patients must have had documented radiological disease progression more than 6 months after the last dose of the penultimate platinum administered. For entry into the study, CA-125 had to be less than the upper limit of normal. Patients with symptomatic or untreated central nervous system metastases or who had received anticancer therapy 14 days or fewer before starting the study or previous treatment with a PARP inhibitor were excluded. Previous treatment with bevacizumab was permitted, with the exception of bevacizumab maintenance therapy after the most recent platinum-based regimen. On 4 Nov 2014,

after 91 patients had been randomised, we made an amendment to the protocol requiring that the most recent platinum-based regimen was to be administered as a chemotherapy doublet and for a minimum of four cycles. Full inclusion and exclusion criteria have been reported previously by Coleman et al (Supplemental Table S1 of that manuscript).[12]

The study was approved by national or local institutional review boards and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. Patients provided written informed consent before participation.

Randomisation and masking

As reported previously,[12] randomisation was computer generated using a block size of six, with stratification factors that included homologous recombination repair gene mutation status (based on gene mutation only; mutation in *BRCA1* or *BRCA2*, mutation in a non-*BRCA* gene associated with homologous recombination, or no mutation in *BRCA* or a homologous recombination gene); progression-free interval following penultimate platinum-based regimen (6 to ≤12 months or >12 months); and best response to most recent platinum-based regimen (complete or partial response). Patients were assigned 2:1 to the rucaparib or placebo group in a masked manner via an interactive web and voice response system. Patients, investigators, site staff, assessors, and the funder were masked to assignments. To ensure masking was maintained, rucaparib and placebo tablets were manufactured to have identical appearances.

Procedures

In the screening phase prior to randomisation, patient medical history and archival tumour tissue were obtained. Central testing of DNA derived from patient archival tumour tissue samples was performed to detect mutations in homologous recombination pathway genes and assess genomic LOH. A cutoff of 16% or greater for ARIEL3 was prespecified as a discriminator for high genomic LOH.[12] Full details of the testing protocol have been reported previously.[12]

In ARIEL3, patients received oral rucaparib 600 mg twice daily or placebo in continuous 28-day cycles until disease progression (as assessed by RECIST), death, or other reason for discontinuation. Dose reductions (in 120 mg decrements to 240 mg twice daily) were permitted if a patient had a Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade 3 or greater or a persistent grade 2 adverse event (AE).

Treatment of study drug was to be withheld for any CTCAE grade 3 or 4 toxicities. At the discretion of the investigator, the dose of study drug may have been held and/or reduced for a CTCAE grade 2 toxicity not adequately controlled using concomitant medications and/or supportive care.

Treatment with study drug was to be held until the toxicity resolved to CTCAE grade 2 or less. Twice daily dosing could then be resumed at either the same dose or a lower dose at the discretion of the investigator. If treatment was resumed at the same dose, and the patient experienced the same toxicity, the dose was to be reduced following resolution of the event to CTCAE grade 2 or less. If the patient continued to experience toxicity, additional dose reduction steps were permitted; however, the investigator was expected to consult with the sponsor's medical monitor before reducing to 240 mg twice daily (BID). If a patient continued to experience toxicity despite two dose-reduction steps (ie, to a dose of 360 mg BID rucaparib or placebo), or if dosing with study drug was interrupted for more than 14 consecutive days due to toxicity, treatment was to be discontinued, unless otherwise agreed between the investigator and the sponsor.

We did disease assessments including computed tomography scans, and CA-125 measurements, at screening, every 12 weeks during treatment, following clinical symptoms, and at discontinuation of treatment. Samples were collected for central laboratory investigations of haematological and clinical chemistry parameters every 2 weeks for the first 2 cycles and then on day 1 of every subsequent cycle. Patients were monitored for adverse events during study participation, beginning after the first dose of study drug and until 28 days after the last dose of study drug. Following the 28-day window after treatment discontinuation, only serious adverse events assessed as related to study drug and all adverse events of special interest irrespective of causality,

were reported. After the initial treatment phase, long-term follow-up and overall survival data were collected for all patients. Subsequent treatments, secondary malignancy monitoring, and overall survival information will be collected for all patients every 12 weeks (±14 days) until death, loss to follow-up, withdrawal of consent from study, or closure of the study. For patients who discontinued due to disease progression, the schedule and type of subsequent disease assessments were not prespecified by the protocol and were left to the discretion of the investigator.

Outcomes

The primary efficacy endpoint (investigator-assessed PFS) and secondary endpoints (PFS according to blinded, independent, central radiology review, patient-reported outcomes, and safety) in ARIEL3 have been reported previously using the primary efficacy data after unblinding (15 Apr 2017 visit cutoff).[12] Data for the secondary endpoint of overall survival were not yet mature at the time of the present analyses, and the secondary endpoint of population pharmacokinetic modelling will be reported separately.

Here we report on the prespecified, investigator-assessed exploratory endpoints of CFI, TFST, PFS2, and TSST using a visit cutoff of 31 Dec 2017. CFI was defined as the time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent anticancer therapy after study drug. TFST was defined as the time from randomisation to the date of the first dose of the first subsequent anticancer treatment regimen. PFS2 was defined as the time from randomisation to the second event of disease progression as assessed by the investigator or death due to any cause. This second progression event may have been a documented event as defined in the RECIST guidelines or an event of symptomatic or clinical or CA-125 progression. TSST was defined as the time from randomisation to the date of the first dose of the second subsequent anticancer treatment regimen.

Subsequent treatments are reported up to a visit cutoff date of 31 Dec 2017.

An updated analysis of safety using a visit cutoff date of 31 Dec 2017 is presented. Safety was assessed by monitoring AEs and vital signs, laboratory testing, and physical examination.

Statistical analysis

ARIEL3 was designed to enrol approximately 540 patients and include 180 to 200 patients with a *BRCA* mutation in their carcinoma (limited to 150 with a known deleterious germline *BRCA* mutation) and up to 360 patients without. Subgroup sizes were calculated to result in a 90% power to establish a significant difference between rucaparib and placebo at a one-sided α level of 0·025 given the following assumptions for investigator assessed median PFS for each analysis cohort: *BRCA* mutant (12·0 months in the rucaparib group *vs* 6·0 months in the placebo group; HR 0·5), HRD (10·0 months *vs* 6·0 months; HR 0·6), and the intention-to-treat population (8·5 months *vs* 6·0 months; HR 0·7).[12] Prespecified and post hoc exploratory analyses were performed for the three molecularly defined, nested cohorts: patients with a *BRCA*-mutated carcinoma, patients with an HRD carcinoma, and the ITT population. Post hoc exploratory analyses were performed for subgroups of patients with *BRCA* wild-type carcinomas based on LOH status (high, low, or indeterminate).

Time-to-event variables (CFI, TFST, PFS2, and TSST) were summarised using Kaplan-Meier methodology. A stratified log rank test that included the randomisation strata was used to compare treatments. Additionally, a stratified Cox proportional hazard model was used to calculate the HR between the treatment groups for each endpoint. Proportionality of hazards for the Cox proportional hazard assumption (ie, constant relative hazard) was verified graphically using log-log plots for PFS and PFS2 in the ITT population (appendix p 8). As the assumption was met for these analyses (ie, the plot of the log of the cumulative hazard for the rucaparib and placebo groups resulted in parallel curves), the subgroup analyses were deemed appropriate. Per protocol, all endpoints were exploratory and tested at a one-sided 0·025 significance level, without any multiplicity adjustment.

For CFI, patients without a documented start of a subsequent anticancer therapy after study drug were censored on the date of their last available assessment. For TFST, patients without a documented start of a subsequent anticancer treatment after study drug were censored on the date of their last available assessment. For PFS2, patients without a documented second progression event were censored on the date of their last

available assessment. For TSST, patients without a documented start of a second subsequent anticancer treatment after study drug were censored on the date of their last available assessment.

We also report the post hoc, exploratory endpoint of PFS2–PFS1, defined as the time from investigator-assessed disease progression during ARIEL3 (PFS1) to the second event of investigator-assessed disease progression or death. For this endpoint, patients were censored if they did not experience a second event of progression or death at the last date known to be alive. Duration of PFS2–PFS1 was set to 1 day for patients who were censored for PFS1 and did not have any further follow-up information. The date of the second event of progression or censoring was used to calculate PFS2–PFS1 for patients who were censored for PFS1 but received subsequent anticancer treatment or had other follow-up data.

The safety population included all patients who received at least one dose of study treatment.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). This trial is registered with ClinicalTrials.gov, number NCT01968213.

Role of the funding source

ARIEL3 was designed by JAL, EMS, and RLC in collaboration with the funder. This article was written by the authors, with medical writing and copy editing support paid for by the funder. Data were collected by the investigators, analysed by the funder, and interpreted by all authors. All authors had full access to all trial data and had final responsibility for the decision to submit these data for publication.

RESULTS

Between 7 Apr 2014 and 19 July 2016, 564 patients were randomly allocated to the two groups: 375 (66%) to rucaparib and 189 (34%) to placebo (ie, ITT population); the *BRCA* mutant cohort included 130 and 66 patients, respectively; and the HRD cohort included 236 and 118 patients (figure 1). The majority of patients had an ECOG

Performance Status of 0 (280 [75%] and 136 [72%], respectively) and a *BRCA* wild-type carcinoma (245 [65%] and 123 [65%]) (table 1). Most patients in ARIEL3 had received two previous platinum-based chemotherapy regimens (236 [63%] and 126 [67%]), with the remainder having received three (109 [29%] and 47 [25%]) or more than three (30 [8%] and 16 [8%]) previous platinum-based chemotherapy regimens. Protocol deviations have been reported in full by Coleman et al.[12] As of the 31 Dec 2017 visit cutoff (median [interquartile range] follow-up 28·1 months [22·0–33·6]), 60 (16%) patients in the rucaparib group and five (3%) in the placebo group had not yet progressed and were still receiving treatment.

The CFI was examined in all three nested cohorts. In the *BRCA*-mutant cohort, median (95% CI) CFI was significantly longer in the rucaparib group (20·8 [17·7–27·8] months) than placebo group (8·7 [7·2–10·9] months; HR 0·28 [95% CI 0·19–0·41]; p<0·0001; 75 [58%] events in the rucaparib group *vs* 56 [85%] events in the placebo group; appendix p 9). In the HRD cohort, median (95% CI) CFI was 18·0 (14·3–19·4) months in the rucaparib group, significantly longer than the 9·1 (8·0–10·8) months in the placebo group (HR 0·40 [95% CI 0·31–0·53]; p<0·0001; 152 [64%] *vs* 101 [86%] events; appendix p 11). Median (95% CI) CFI in the ITT population was also significantly longer in the rucaparib group than placebo group (14·3 [13·0–17·4] months *vs* 8·8 [8·0–10·3] months; HR 0·43 [95% CI 0·35–0·53]; p<0·0001; 255 [68%] *vs* 164 [87%] events; figure 2A).

Among patients in the ITT population who discontinued and had not withdrawn consent for follow-up, 134 (46%) of 294 patients from the rucaparib group and 66 (38%) of 175 patients from the placebo group received platinum-based chemotherapy as their first subsequent therapy, with 81 (28%) and 52 (30%) patients receiving nonplatinum-based chemotherapy (figure 3). Four (1%) patients from the rucaparib group and 18 (10%) patients from the placebo group received PARP inhibitor treatment as their first subsequent therapy; two (1%) and three (2%), respectively, received PARP inhibitor maintenance as their first subsequent therapy (figure 3). Patients in the rucaparib group had a significantly longer TFST than patients in the placebo group across all the cohorts, with a median (95% CI) TFST of 18·9 (15·9–25·3) versus 7·2 (5·5–9·1) months

in the *BRCA*-mutant cohort (HR 0·28 [95% CI 0·20–0·41]; p<0·0001; 81 [62%] *vs* 58 [88%] events; appendix p 9), 16·4 (12·5–17·9) versus 7·4 (6·5–9·1) months in the HRD cohort (HR 0·39 [95% CI 0·30–0·51]; p<0·0001; 160 [68%] *vs* 106 [90%] events; appendix p 11), and 12·4 (11·1–15·2) versus 7·2 (6·4–8·6) months in the ITT population (HR 0·43 [95% CI 0·35–0·52]; p<0·0001; 273 [73%] *vs* 172 [91%] events; figure 2B).

Median (95% CI) investigator-assessed PFS2 was significantly longer in the rucaparib group than placebo group in the *BRCA*-mutant cohort (26·8 [23·4–41·4] *vs* 18·4 [15·7–23·6] months; HR 0·56 [95% CI 0·38–0·83]; p=0·0040; 64 [49%] *vs* 42 [64%] events; appendix p 10), the HRD cohort (25·3 [21·9–28·5] *vs* 18·4 [15·8–22·1] months; HR 0·66 [95% 0·49–0·87]; p=0·0042; 125 [53%] *vs* 78 [66%] events; appendix p 12), and the ITT population (21·0 [18·9–23·6] *vs* 16·5 [15·2–18·4] months; HR 0·66 [95% CI 0·53–0·82]; p=0·0002; 223 [59%] *vs* 134 [71%] events; figure 2C). In a post hoc analysis, across all three cohorts there was no significant difference in PFS2–PFS1 between the rucaparib and placebo groups (appendix p 13).

In the ITT population, among the 292 and 173 patients in the rucaparib and placebo groups who discontinued and had not withdrawn consent for follow-up, 170 (58%) and 100 (58%), respectively, had received a second subsequent therapy as of the visit cutoff date. The most common second subsequent therapy was nonplatinum-based chemotherapy (87 [30%] and 38 [22%] patients, respectively; figure 3). Of patients who received a second subsequent therapy, the proportion of those receiving a platinum-based chemotherapy (49 [17%] and 36 [21%] patients, respectively) was lower than the proportion of patients who received platinum-based chemotherapy as their first subsequent treatment (figure 3). Four (1%) patients from the rucaparib group and 11 (6%) patients from the placebo group received PARP inhibitor treatment as their second subsequent therapy; three (1%) and eight (5%), respectively, received PARP inhibitor maintenance as their second subsequent therapy (figure 3).

For patients in the *BRCA*-mutant cohort, median (95% CI) TSST was 28·8 (24·4–34·2) months in the rucaparib group versus 17·7 (15·1–21·6) months in the placebo group (HR 0·53 [95% CI 0·36–0·80]; p=0·0022; 65 [50%] *vs* 41 [62%] events; appendix p 10). In the HRD cohort, median (95% CI) TSST was significantly longer in the rucaparib

group than the placebo group (26·2 [22·9–30·6] *vs* 19·0 [15·8–21·7] months; HR 0·67 [95% CI 0·50–0·91]; p=0·010; 123 [52%] *vs* 73 [62%] events; appendix p 12). In the ITT population, there was also a significantly longer median TSST with rucaparib, with a median (95% CI) of 22·4 (19·1–24·5) months in the rucaparib group versus 17·3 (14·9–19·4) months in the placebo group (HR 0·68 [95% CI 0·54–0·85]; p=0·0007; 217 [58%] *vs* 128 [68%] events; figure 2D).

In post hoc analyses of subgroups of patients with *BRCA* wild-type carcinomas, median CFI, TFST, PFS2, and TSST were all longer with rucaparib than placebo regardless of LOH status (appendix p 14), with median CFI and TFST being significantly longer in the rucaparib than placebo group.

The safety population included 372 (99%) patients who received rucaparib (three [1%] patients withdrew before receiving rucaparib), and 189 (100%) patients who received placebo. At the time of the extended visit cutoff date (31 Dec 2017), the median (interquartile range) treatment duration for patients in the safety population was 8·3 (3·4–18·1) months in the rucaparib group and 5·5 (2·8–8·3) months in the placebo group.

Overall, the updated safety profile was comparable to that reported by Coleman et al (2017), with only modest increases in incidences of treatment-emergent AEs (TEAEs) in the rucaparib and placebo groups (table 2; appendix p 4). In the updated safety analysis, a TEAE of any grade occurred in 372 (100%) of the patients in the rucaparib group, and 182 (96%) in the placebo group. The most common TEAEs of any grade (reported in at least 30% of patients in either group) were nausea, asthenia or fatigue, dysgeusia, anaemia or decreased haemoglobin, constipation, vomiting, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increased, diarrhoea, and abdominal pain (table 2). Grade 3 or higher TEAEs were reported in 222 (60%) of the patients in the rucaparib group and 30 (16%) in the placebo group (appendix pp 5-7), the most common of which were anaemia or decreased haemoglobin (80 [22%] patients *vs* 1 [1%] patient) and ALT or AST increased (38 [10%] *vs* none). Serious TEAEs were reported in 83 (22%) of the patients in the rucaparib group and 20 (11%) in the placebo group, most frequently anaemia (16 [4%] in the rucaparib group *vs* 1 [1%] in the placebo

group), vomiting (7 [2%] *vs* 2 [1%]), and pyrexia (6 [2%] *vs* none). Serious TEAEs were considered related to treatment by the investigator for 35 (9%) and 3 (2%) patients in the rucaparib and placebo groups, respectively, the most frequent of which was anaemia (16 [4%] *vs* 1 [1%]). Most TEAEs of anaemia or decreased haemoglobin were managed with dose reduction or treatment interruption and blood transfusions (for grade 2 or 3 events); less than 2% of patients received erythropoietin.

In this updated safety analysis, there were no new TEAEs of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) beyond those previously reported (three [1%] patients in the rucaparib group and none in the placebo group[12]).

Treatment interruption due to a TEAE occurred in 243 (65%) patients in the rucaparib group and 19 (10%) in the placebo group. The most common TEAEs leading to treatment interruption in the rucaparib group were thrombocytopenia or decreased platelets (64 [17%] patients), anaemia or decreased haemoglobin (56 [15%]), ALT or AST increased (38 [10%]), and nausea (38 [10%]), whereas the most common TEAE associated with treatment interruption in the placebo group was asthenia or fatigue (six [3%]).

Dose reduction due to a TEAE occurred in 206 (55%) patients in the rucaparib group and eight (4%) in the placebo group. The most common TEAEs leading to dose reduction in the rucaparib group were anaemia or decreased haemoglobin (47 [13%] patients), ALT or AST increased (41 [11%]), thrombocytopenia or decreased platelets (40 [11%]), and nausea (37 [10%]).

Fifty-seven (15%) patients in the rucaparib group and three (2%) in the placebo group discontinued because of a TEAE (excluding disease progression), of whom 49 (13%) and one (1%) discontinued because of a TEAE that was considered treatment related. The most common TEAEs leading to discontinuation in the rucaparib group were thrombocytopenia or decreased platelets (11 [3%] patients), anaemia or decreased haemoglobin (10 [3%]), and nausea (10 [3%]). These were also the most common treatment-related TEAEs leading to discontinuation in the rucaparib group, with 10 (3%) patients discontinuing due to each TEAE.

In the previously published analysis (safety visit cutoff 15 Apr 2017), we reported 4 deaths in the rucaparib group considered unrelated to treatment by the investigator (2 [1%] due to progressive disease, 1 [<1%] due to cardiac arrest, and 1 [<1%] due to haematophagic histiocytosis) and 2 considered related to treatment (1 [<1%] due to acute myeloid leukaemia and 1 [<1%] due to myelodysplastic syndrome); 2 deaths occurred in the placebo group considered unrelated to treatment (1 [1%] due to disease progression and 1 [1%] due to pulmonary embolism).[12] At the time of the updated safety visit cutoff date (31 Dec 2017) there was one (<1%) additional death due to a high-grade B-cell lymphoma in the rucaparib group, which was considered unrelated to rucaparib by the investigator, and none in the placebo group.

DISCUSSION

The prespecified, exploratory analyses reported here demonstrate the durable clinical benefit of rucaparib maintenance treatment in the postprogression period for patients with recurrent ovarian cancer. Median CFI, TFST, PFS2, and TSST were all significantly (1·3- to 2·6-times) longer for patients who received rucaparib maintenance treatment than those who received placebo, demonstrating a clinically meaningful improvement in these endpoints for all cohorts regardless of mutational status.

The extension of CFI indicated that patients receiving rucaparib were able to delay initiating additional anticancer therapy, potentially allowing them more time to recover from prior negative impacts of chemotherapy and postpone further side effects associated with anticancer therapy. In particular, the side effects associated with chemotherapy are of specific concern to patients with ovarian cancer.[21,22] The TFST findings were similarly clinically meaningful; in all cohorts, median TFST was approximately 2-times longer in the rucaparib group than the placebo group, and the significant differences in TFST demonstrated that patients who received rucaparib maintenance treatment were able to delay the start of further therapy for longer than patients receiving placebo. Among first subsequent therapies, the use of platinum-based chemotherapy was higher in the rucaparib group than placebo group, indicating that rucaparib-treated patients had tumours that were still considered platinum-sensitive and that these patients remained fit enough to receive additional chemotherapy.

Although a number of patients in the rucaparib group (six [2%]) of the ITT population did receive a different PARP inhibitor as their first subsequent treatment, the proportion of subsequent PARP inhibitor use was higher among patients in the placebo group (21 [12%]), which is consistent with the currently limited understanding regarding the efficacy of PARP inhibitors in patients who have received prior PARP inhibitor therapy. A greater number of patients received a PARP inhibitor as first subsequent therapy in the treatment setting than in the maintenance setting (22 [5%] *vs* five [1%]).

The lasting benefit of rucaparib treatment was further supported by the PFS2 analyses; across cohorts, the median PFS2 was 1·5-times longer in the rucaparib group than the placebo group. The PFS2–PFS1 analyses suggest that rucaparib maintenance treatment did not adversely impact the possibility for patients to benefit from subsequent therapy. This is of particular importance as the duration of PFS following relapse has previously been shown to diminish with each line of chemotherapy in women with ovarian cancer.[23] Such reductions in PFS are likely related to the development of resistance through changes in the tumour, such as mutations or epigenetic modifications, which can accumulate and influence responsiveness to treatment.[24] It is possible that differences in the mechanism of action between rucaparib and other drug classes explain why rucaparib had no apparent impact on the efficacy of subsequent therapies. Furthermore, the benefit in PFS2 for patients who received rucaparib and the similarity in PFS2–PFS1 between rucaparib and placebo groups were seen even though 21 (12%) patients in the placebo group received a PARP inhibitor as the first subsequent therapy. Median TSST was also longer for patients who received rucaparib than those who received placebo across all cohorts, supporting the PFS2 analyses and the benefit of prior rucaparib maintenance treatment. As of the visit cutoff, most patients who had a second subsequent therapy received a nonplatinum-based chemotherapy, suggesting that fewer of these patients had tumours that were considered platinum-sensitive than those who received a first subsequent therapy. More patients received PARP inhibitor maintenance treatment as their second subsequent therapy (11 [2%]) than as a first subsequent therapy (five [1%]).

Rucaparib maintenance treatment provided durable clinical benefit for patients with recurrent, platinum-sensitive ovarian cancer, with 60 (16%) of 375 patients in the rucaparib group still participating in the study as of the 31 Dec 2017 visit cutoff date compared with five (3%) of 189 patients in the placebo group. Our exploratory endpoint analyses suggest that rucaparib maintenance does not negatively affect the efficacy of subsequent treatments and further support the PFS benefit observed in patients receiving rucaparib during the study. For each postprogression endpoint, the difference between medians in the rucaparib and placebo groups were consistent with the difference in medians for PFS on study across all cohorts. Conversely, if rucaparib maintenance treatment had negatively affected postprogression outcomes, differences between the rucaparib and placebo groups would have been substantially shorter than the initial difference in median PFS.

Similar improvements in postprogression outcomes have been reported from clinical trials of other PARP inhibitors used as second-line maintenance treatment for ovarian cancer. In NOVA, maintenance niraparib significantly improved median CFI and median TFST versus placebo in patients with a germline *BRCA* mutation and patients without a germline *BRCA* mutation (this subgroup included patients with a somatic *BRCA* mutation).[4,25] In SOLO2, maintenance olaparib significantly improved median TFST, PFS2, and TSST versus placebo in patients with a *BRCA* mutation.[7] In Study 19, a phase 2 study of maintenance olaparib, median TFST and TSST were significantly longer with olaparib than placebo in patients with and those without a *BRCA* mutation.[26]

Safety results as of 31 Dec 2017 were comparable to those reported earlier by Coleman et al in terms of their incidence, severity, and nature.[12] The safety analysis included an additional 8 months of follow-up, and slight increases in the incidence of TEAEs were not unexpected considering the increased duration of treatment. There was no increase in the incidence of MDS or AML with the additional 8 months of follow-up; patients continue to be followed to monitor for these and other AEs that may develop over time. TEAEs such as gastrointestinal events, haematological toxicities, and fatigue are considered to be class effects, consistent with those of other PARP inhibitors.[3,7,12,27-30] TEAEs and laboratory abnormalities were managed with treatment interruption,

treatment modification, and/or supportive care, such as antiemetic medications for nausea or vomiting or red blood cell transfusions for anaemia. The low incidence of discontinuations due to AEs showed that management with supportive care and dose modifications was effective. The extended safety analysis demonstrated that rucaparib had a tolerable safety profile.

Limitations of the current analysis include the fact that the study is ongoing, and long-term follow-up data continue to be collected. Furthermore, overall survival data are not yet mature; these data will be reported when approximately 70% of the events have occurred. Although efforts were made to maintain treatment blinding for the overall survival analysis, treatment unblinding was permitted upon investigator request if a decision regarding subsequent treatment depended on whether or not a patient had received prior PARP inhibitor therapy (eg, prior PARP inhibitor use was an exclusion criterion for a subsequent study); therefore, the process of unblinding may have influenced the final selection of subsequent therapy.

The significant improvement in the clinically meaningful endpoints of CFI, TFST, PFS2, and TSST observed in patients who received rucaparib maintenance treatment compared with those who received placebo provides additional support to the significant improvement in PFS (the primary endpoint) observed with rucaparib versus placebo in ARIEL3. These significant improvements suggest that when compared with placebo, rucaparib maintenance treatment provided a meaningful delay in starting further therapy and did not impact the possibility of receiving benefit from subsequent therapies after first progression. As with the primary and key secondary efficacy endpoints, improvements in the postprogression endpoints were observed in the *BRCA*-mutant and HRD cohorts as well as in the ITT population. The updated rucaparib safety profile was consistent with prior reports, and no new safety signals were identified.

Contributors

JAL, EMS, and RLC designed the study in collaboration with the funder.

JAL, AMO, DL, CA, AO, AD, NC, JIW, ARC, GS, AL, RWH, MAG, PCF, JCG, DMO, DKA, SB, JG-D, EMS, and RLC treated patients.

JAL, AMO, DL, CA, AO, AD, NC, JIW, ARC, GS, AL, RWH, MAG, PCF, JCG, DMO, DKA, SB, JG-D, EMS, and RLC acquired the data.

All authors interpreted the data.

All authors contributed to the writing of the manuscript, reviewed and amended the drafts, and approved the final version for submission.

Declaration of interests

JAL has received lecture fees from Clovis Oncology, AstraZeneca, Merck/Merck Sharp & Dohme, Pfizer, and Tesaro; served on advisory boards for Clovis Oncology, Artios Pharma, AstraZeneca, Cristal Therapeutics, Merck/Merck Sharp & Dohme, Pfizer, Regeneron, Roche, Seattle Genetics, and Tesaro; and received research grants from AstraZeneca and Merck/Merck Sharp & Dohme.

AMO has served on advisory boards for Clovis Oncology, Amgen, Immunovaccine, and Verastem; received support for travel or accommodation from AstraZeneca; and received honoraria from WebRx.

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JG-D has received research funding from AstraZeneca, Pierre Fabre, and Pfizer; received personal fees from Clovis Oncology, Astellas, Pierre Fabre, and Pfizer; and received nonfinancial support from Astellas, Pierre Fabre, and Pfizer.

EMS has nothing to disclose.

TC, LM, and SG are employees of Clovis Oncology and may own stock or have stock options in that company.

RLC reports grants from Clovis Oncology, AstraZeneca, Gateway Foundation, Janssen, Judy Reis/Albert Pisani, MD, Ovarian Cancer Research Fund, Merck, National Institutes of Health, Roche/Genentech, and V-Foundation; has served as an advisor to Clovis Oncology, Agenus, AstraZeneca, GamaMabs, Genmab, Janssen, OncoQuest, Pfizer (Medivation), Regeneron, Roche/Genentech, and Tesaro; and has an endowment as the Ann Rife Cox Chair in Gynecology.

Data sharing

Requests for deidentified datasets 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 anonymisation. Data will be provided by Clovis Oncology. The redacted protocol for the ARIEL3 clinical study is available on ClinicalTrials.gov: https://clinicaltrials.gov/ProvidedDocs/13/NCT01968213/Prot_000.pdf. Clovis Oncology does not share identified participant data or a data dictionary.

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Table 1: Patient demographics and baseline characteristics in intention-to-treat population

	Rucaparib (n=375)	Placebo (n=189)
Age, years	61·0 (53·0–67·0)	62·0 (53·0–68·0)
ECOG Performance Status		
0	280 (75%)	136 (72%)
1	95 (25%)	53 (28%)
Diagnosis		
Epithelial ovarian cancer	312 (83%)	159 (84%)
Fallopian tube cancer	32 (9%)	10 (5%)
Primary peritoneal cancer	31 (8%)	19 (10%)
High-grade serous adenocarcinoma	0	1 (1%)*
***BRCA* mutation in carcinoma**		
***BRCA* mutant**	130 (35%)	66 (35%)
BRCA1	80 (21%)	37 (20%)
BRCA2	50 (13%)	29 (15%)
Germline	82 (22%)	48 (25%)
Somatic	40 (11%)	16 (8%)
Unknown†	8 (2%)	2 (1%)
***BRCA* wild type**	245 (65%)	123 (65%)
LOH high	106 (28%)	52 (28%)
LOH low	107 (29%)	54 (29%)
LOH indeterminate‡	32 (9%)	17 (9%)
Number of previous platinum-based regimens		
2	236 (63%)	126 (67%)
≥3	139 (37%)	63 (33%)
Time to progression with penultimate platinum-based regimen		
6 to ≤12 months	151 (40%)	76 (40%)
>12 months	224 (60%)	113 (60%)
Response to last platinum-based regimen		
CR according to RECIST	126 (34%)	64 (34%)
PR according to RECIST or serological response according to GCIG CA-125 criteria	249 (66%)	125 (66%)

Data are median (IQR) or n (%).
*According to the patient records, origin was fallopian tube or ovary.
†Tumour sample was *BRCA* mutant according to Foundation Medicine's T5 next-generation sequencing assay, but a blood sample was not available for central germline testing.
‡Tumour sample was not evaluable for percentage of genomic LOH because of low tumour content or aneuploidy.
CA-125=cancer antigen 125. CR=complete response. ECOG=Eastern Cooperative Oncology Group. GCIG=Gynecologic Cancer InterGroup. IQR=interquartile range. LOH=loss of heterozygosity. PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

Table 2: **Treatment-emergent adverse events in the safety population: comparison of previously reported and updated data**

	Previous report: 15 Apr 2017 visit cutoff date[12]								Updated data*: 31 Dec 2017 visit cutoff date							
	Rucaparib (n=372)				Placebo (n=189)				Rucaparib (n=372)				Placebo (n=189)			
	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4
Nausea	280 (75%)	266 (72%)	14 (4%)	0	69 (37%)	68 (36%)	1 (1%)	0	282 (76%)	268 (72%)	14 (4%)	0	69 (37%)	68 (36%)	1 (1%)	0
Asthenia or fatigue	258 (69%)	233 (63%)	25 (7%)	0	83 (44%)	78 (41%)	5 (3%)	0	263 (71%)	237 (64%)	26 (7%)	0	84 (44%)	79 (42%)	5 (3%)	0
Dysgeusia	146 (39%)	146 (39%)	0	0	13 (7%)	13 (7%)	0	0	148 (40%)	148 (40%)	0	0	13 (7%)	13 (7%)	0	0
Anaemia or haemoglobin decreased	139 (37%)	69 (19%)	67 (18%)	3 (1%)	11 (6%)	10 (5%)	0	1 (1%)	145 (39%)	65 (17%)	77 (21%)	3 (1%)	10 (5%)	9 (5%)	0	1 (1%)
Constipation	136 (37%)	129 (35%)	7 (2%)	0	45 (24%)	43 (23%)	2 (1%)	0	141 (38%)	134 (36%)	7 (2%)	0	46 (24%)	44 (23%)	2 (1%)	0
Vomiting	136 (37%)	121 (33%)	15 (4%)	0	28 (15%)	26 (14%)	2 (1%)	0	138 (37%)	123 (33%)	15 (4%)	0	29 (15%)	27 (14%)	2 (1%)	0
ALT or AST increased	126 (34%)	87 (23%)	39 (10%)	0	7 (4%)	7 (4%)	0	0	129 (35%)	91 (24%)	38 (10%)	0	8 (4%)	8 (4%)	0	0
Diarrhoea	118 (32%)	116 (31%)	2 (1%)	0	41 (22%)	39 (21%)	2 (1%)	0	121 (33%)	119 (32%)	2 (1%)	0	41 (22%)	39 (21%)	2 (1%)	0
Abdominal pain	111 (30%)	102 (27%)	9 (2%)	0	49 (26%)	48 (25%)	1 (1%)	0	112 (30%)	101 (27%)	11 (3%)	0	49 (26%)	48 (25%)	1 (1%)	0
Thrombocytopenia or platelet count decreased	104 (28%)	85 (23%)	13 (3%)	6 (2%)	5 (3%)	5 (3%)	0	0	109 (29%)	89 (24%)	13 (3%)	7 (2%)	5 (3%)	5 (3%)	0	0
Decreased appetite	87 (23%)	85 (23%)	2 (1%)	0	26 (14%)	26 (14%)	0	0	88 (24%)	85 (23%)	3 (1%)	0	26 (14%)	26 (14%)	0	0
Neutropenia or decreased neutrophil count	67 (18%)	42 (11%)	19 (5%)	6 (2%)	9 (5%)	7 (4%)	1 (1%)	1 (1%)	72 (19%)	43 (12%)	22 (6%)	7 (2%)	9 (5%)	7 (4%)	1 (1%)	1 (1%)
Headache	67 (18%)	66 (18%)	1 (<1%)	0	30 (16%)	29 (15%)	1 (1%)	0	71 (19%)	70 (19%)	1 (<1%)	0	31 (16%)	30 (16%)	1 (1%)	0
Photosensitivity reaction	64 (17%)	62 (17%)	2 (1%)	0	1 (1%)	1 (1%)	0	0	68 (18%)	66 (18%)	2 (1%)	0	1 (1%)	1 (1%)	0	0
Blood creatinine increased	57 (15%)	56 (15%)	1 (<1%)	0	3 (2%)	3 (2%)	0	0	61 (16%)	60 (16%)	1 (<1%)	0	3 (2%)	3 (2%)	0	0
Arthralgia	57 (15%)	55 (15%)	2 (1%)	0	24 (13%)	24 (13%)	0	0	59 (16%)	57 (15%)	2 (1%)	0	24 (13%)	24 (13%)	0	0

Dizziness	54 (15%)	54 (15%)	0	0	15 (8%)	14 (7%)	1 (1%)	0	57 (15%)	57 (15%)	0	0	15 (8%)	14 (7%)	1 (1%)	0
Cough	54 (15%)	54 (15%)	0	0	25 (13%)	25 (13%)	0	0	55 (15%)	55 (15%)	0	0	25 (13%)	25 (13%)	0	0
Abdominal pain upper	52 (14%)	50 (13%)	2 (1%)	0	10 (5%)	10 (5%)	0	0	54 (15%)	52 (14%)	2 (1%)	0	11 (6%)	11 (6%)	0	0
Dyspepsia	54 (15%)	53 (14%)	1 (<1%)	0	9 (5%)	9 (5%)	0	0	54 (15%)	53 (14%)	1 (<1%)	0	9 (5%)	9 (5%)	0	0
Insomnia	53 (14%)	53 (14%)	0	0	15 (8%)	15 (8%)	0	0	54 (15%)	54 (15%)	0	0	15 (8%)	15 (8%)	0	0
Dyspnoea	50 (13%)	50 (13%)	0	0	14 (7%)	14 (7%)	0	0	53 (14%)	53 (14%)	0	0	14 (7%)	14 (7%)	0	0
Pruritus	47 (13%)	47 (13%)	0	0	19 (10%)	19 (10%)	0	0	51 (14%)	51 (14%)	0	0	20 (11%)	20 (11%)	0	0
Back pain	45 (12%)	45 (12%)	0	0	28 (15%)	28 (15%)	0	0	50 (13%)	50 (13%)	0	0	28 (15%)	28 (15%)	0	0
Rash	46 (12%)	45 (12%)	1 (<1%)	0	17 (9%)	17 (9%)	0	0	50 (13%)	49 (13%)	1 (<1%)	0	17 (9%)	17 (9%)	0	0
Pyrexia	44 (12%)	44 (12%)	0	0	8 (4%)	8 (4%)	0	0	45 (12%)	45 (12%)	0	0	9 (5%)	9 (5%)	0	0
Upper respiratory tract infection	41 (11%)	41 (11%)	0	0	6 (3%)	4 (2%)	2 (1%)	0	44 (12%)	44 (12%)	0	0	6 (3%)	4 (2%)	2 (1%)	0
Hypomagnesaemia	40 (11%)	39 (10%)	1 (<1%)	0	11 (6%)	11 (6%)	0	0	43 (12%)	42 (11%)	1 (<1%)	0	11 (6%)	11 (6%)	0	0
Abdominal distension	41 (11%)	41 (11%)	0	0	22 (12%)	22 (12%)	0	0	42 (11%)	42 (11%)	0	0	24 (13%)	24 (13%)	0	0
Oedema peripheral	39 (10%)	38 (10%)	1 (<1%)	0	14 (7%)	14 (7%)	0	0	41 (11%)	40 (11%)	1 (<1%)	0	14 (7%)	14 (7%)	0	0
Hypertension	34 (9%)	26 (7%)	8 (2%)	0	16 (8%)	12 (6%)	4 (2%)	0	36 (10%)	27 (7%)	9 (2%)	0	16 (8%)	12 (6%)	4 (2%)	0

Data are n (%).
*Grade 1–2 TEAEs reported in ≥10% of patients and grade 3–4 TEAEs reported in ≥2% of patients in the updated safety analysis; sorted by decreasing incidence in the rucaparib arm.
ALT=alanine aminotransferase. AST=aspartate aminotransferase. TEAE=treatment-emergent adverse event.

Figure 1

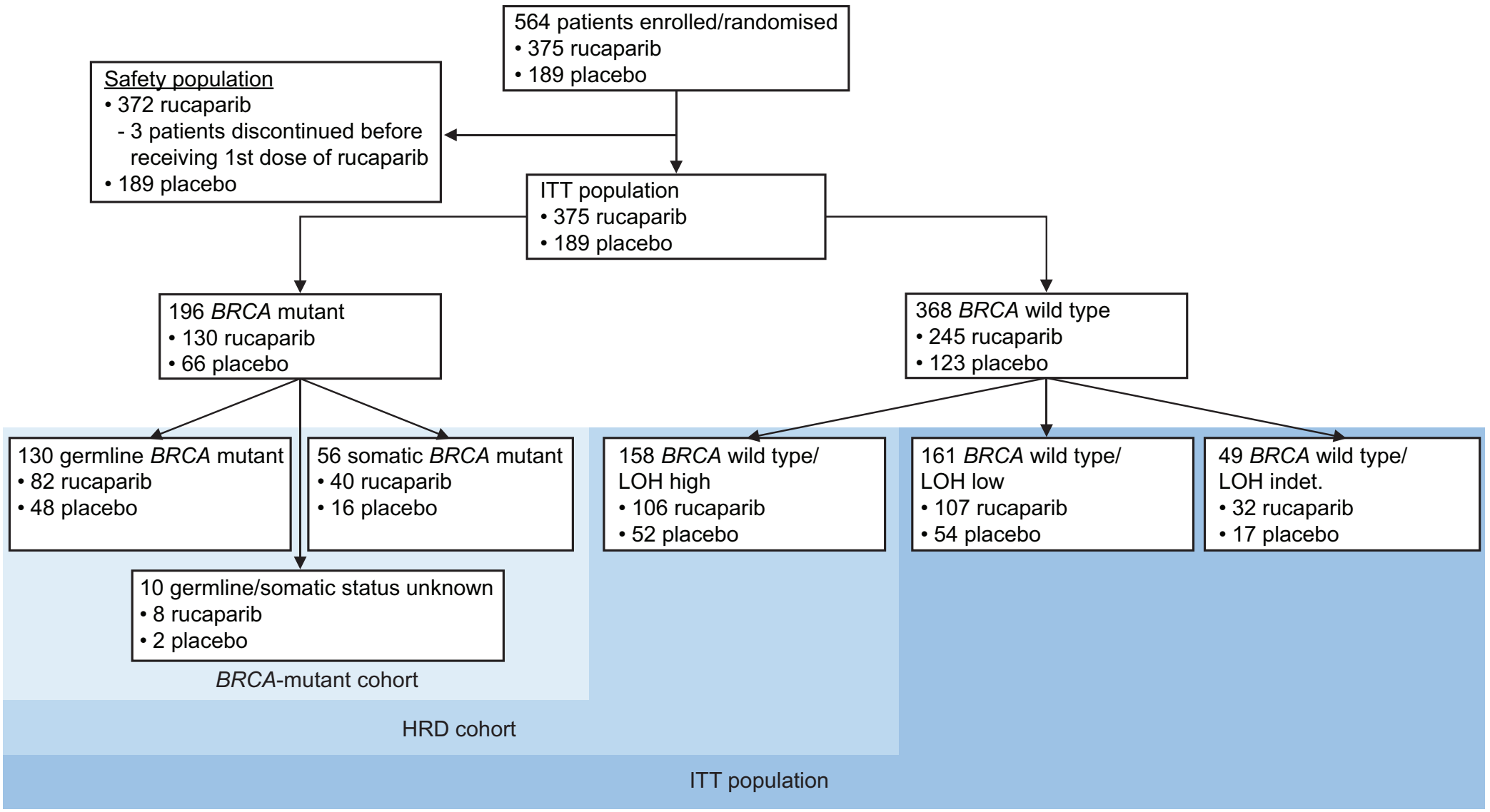
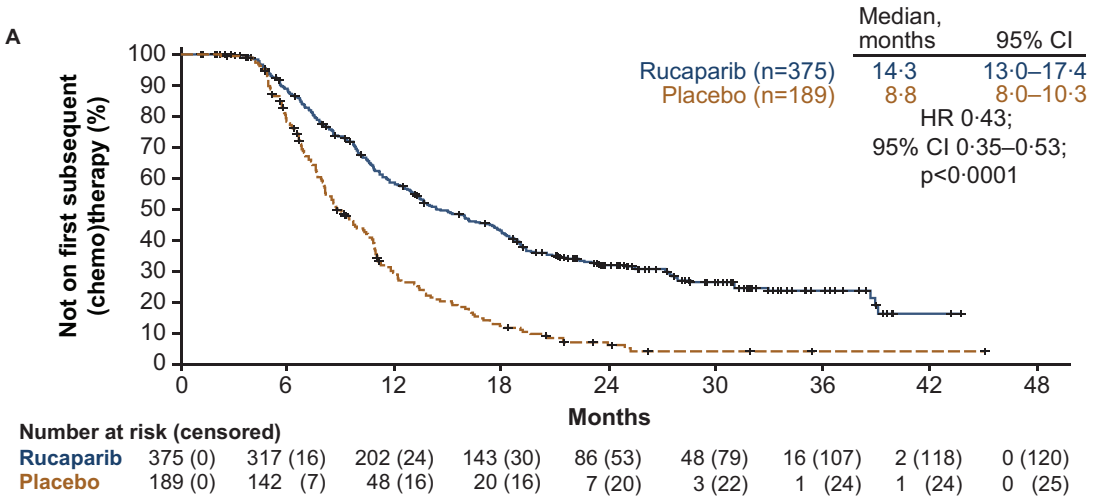
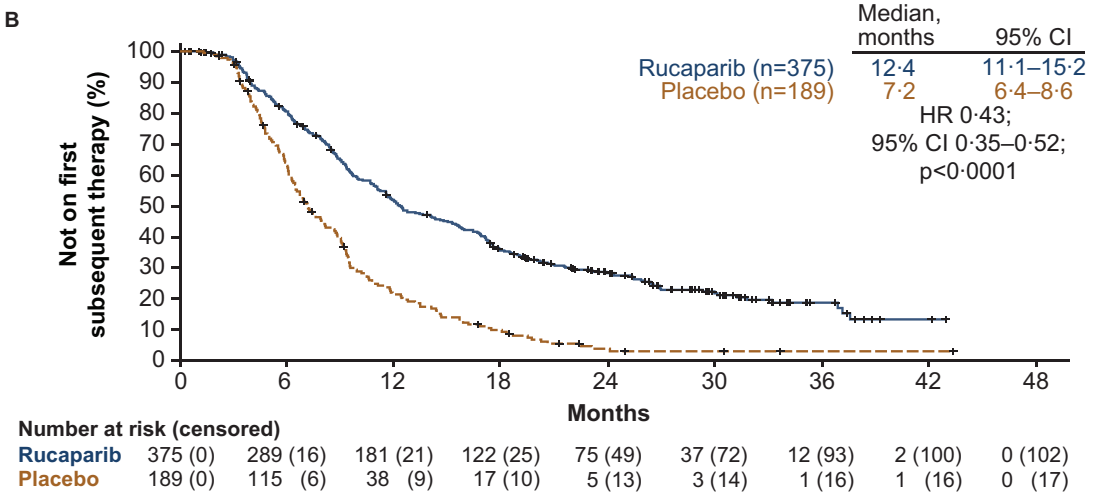
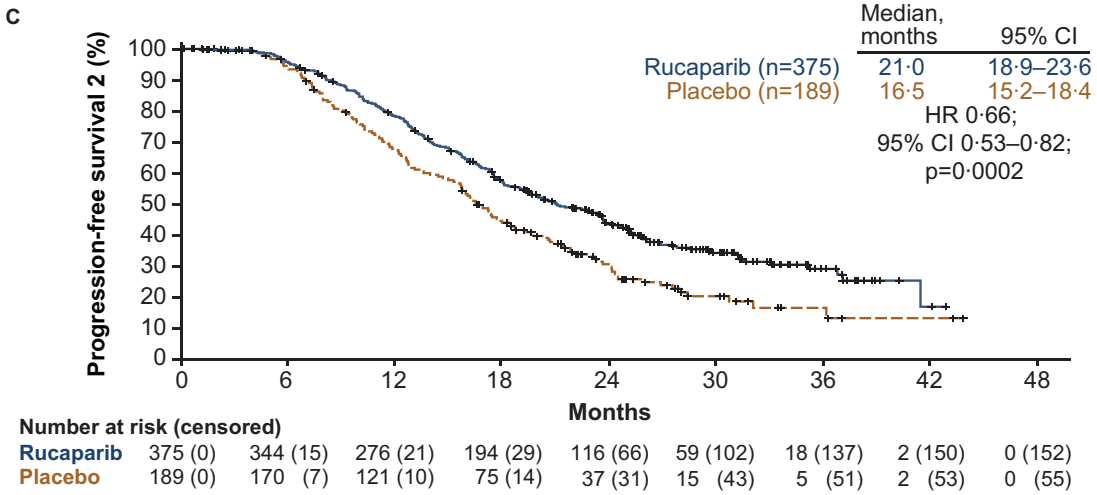

564 patients enrolled/randomised
• 375 rucaparib
• 189 placebo
Safety population
• 372 rucaparib
- 3 patients discontinued before receiving 1st dose of rucaparib
• 189 placebo
ITT population
• 375 rucaparib
• 189 placebo
196 BRCA mutant
• 130 rucaparib
• 66 placebo
368 BRCA wild type
• 245 rucaparib
• 123 placebo
130 germline BRCA mutant
• 82 rucaparib
• 48 placebo
56 somatic BRCA mutant
• 40 rucaparib
• 16 placebo
158 BRCA wild type/ LOH high
• 106 rucaparib
• 52 placebo
161 BRCA wild type/ LOH low
• 107 rucaparib
• 54 placebo
49 BRCA wild type/ LOH indet.
• 32 rucaparib
• 17 placebo
10 germline/somatic status unknown
• 8 rucaparib
• 2 placebo
BRCA-mutant cohort
HRD cohort
ITT population

Figure 2


A
Not on first subsequent (chemo)therapy (%)
Median, months
95% CI
Rucaparib (n=375) 14·3 13·0–17·4
Placebo (n=189) 8·8 8·0–10·3
HR 0·43;
95% CI 0·35–0·53;
p<0·0001
Months
Number at risk (censored)
Rucaparib 375 (0) 317 (16) 202 (24) 143 (30) 86 (53) 48 (79) 16 (107) 2 (118) 0 (120)
Placebo 189 (0) 142 (7) 48 (16) 20 (16) 7 (20) 3 (22) 1 (24) 1 (24) 0 (25)


B
Not on first subsequent therapy (%)
Median, months
95% CI
Rucaparib (n=375) 12·4 11·1–15·2
Placebo (n=189) 7·2 6·4–8·6
HR 0·43;
95% CI 0·35–0·52;
p<0·0001
Months
Number at risk (censored)
Rucaparib 375 (0) 289 (16) 181 (21) 122 (25) 75 (49) 37 (72) 12 (93) 2 (100) 0 (102)
Placebo 189 (0) 115 (6) 38 (9) 17 (10) 5 (13) 3 (14) 1 (16) 1 (16) 0 (17)


C
Progression-free survival 2 (%)
Median, months
95% CI
Rucaparib (n=375) 21·0 18·9–23·6
Placebo (n=189) 16·5 15·2–18·4
HR 0·66;
95% CI 0·53–0·82;
p=0·0002
Months
Number at risk (censored)
Rucaparib 375 (0) 344 (15) 276 (21) 194 (29) 116 (66) 59 (102) 18 (137) 2 (150) 0 (152)
Placebo 189 (0) 170 (7) 121 (10) 75 (14) 37 (31) 15 (43) 5 (51) 2 (53) 0 (55)

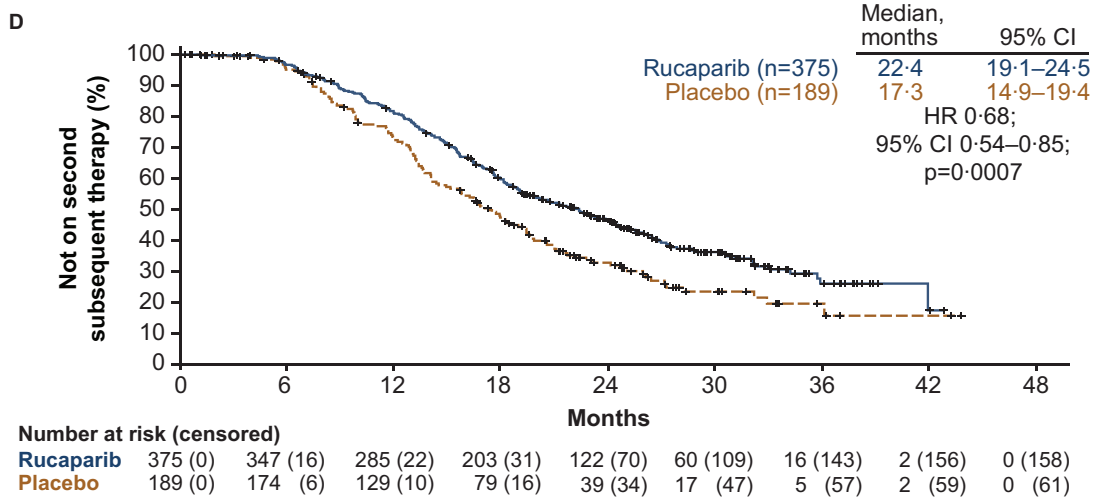
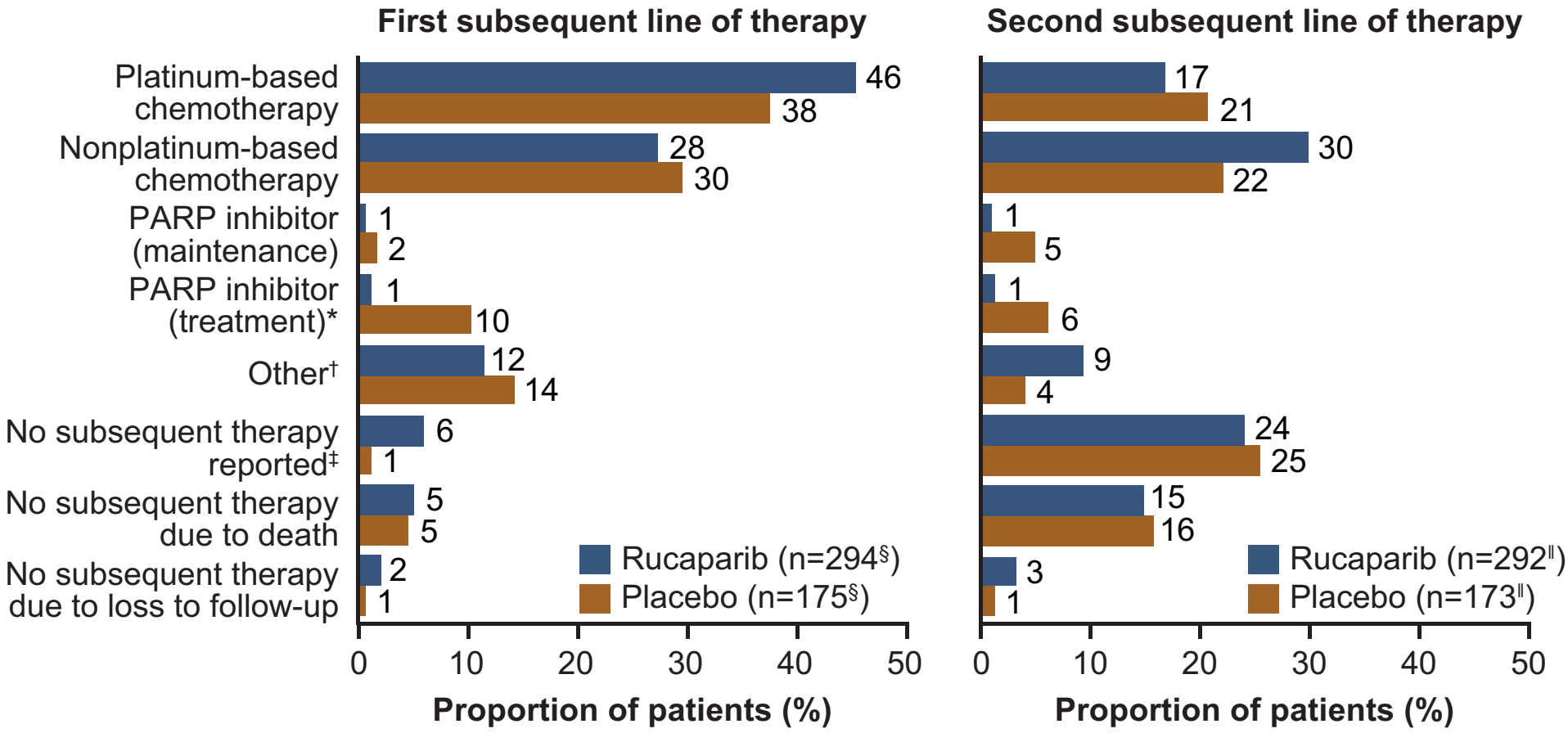

D
Not on second subsequent therapy (%)
Median, months
95% CI
Rucaparib (n=375) 22·4 19·1–24·5
Placebo (n=189) 17·3 14·9–19·4
HR 0·68;
95% CI 0·54–0·85;
p=0·0007
Months
Number at risk (censored)
Rucaparib 375 (0) 347 (16) 285 (22) 203 (31) 122 (70) 60 (109) 16 (143) 2 (156) 0 (158)
Placebo 189 (0) 174 (6) 129 (10) 79 (16) 39 (34) 17 (47) 5 (57) 2 (59) 0 (61)

Figure 3


First subsequent line of therapy
Second subsequent line of therapy
Platinum-based chemotherapy
Nonplatinum-based chemotherapy
PARP inhibitor (maintenance)
PARP inhibitor (treatment)*
Other†
No subsequent therapy reported‡
No subsequent therapy due to death
No subsequent therapy due to loss to follow-up
46
38
28
30
1
2
1
10
12
14
6
1
5
5
2
1
17
21
30
22
1
5
1
6
9
4
24
25
15
16
3
1
Rucaparib (n=294§)
Placebo (n=175§)
Rucaparib (n=292‖)
Placebo (n=173‖)
0
10
20
30
40
50
Proportion of patients (%)
Proportion of patients (%)

Suppl

Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): postprogression outcomes and updated safety from a randomised, placebo-controlled, phase 3 trial

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Abstract: 415

Manuscript body: 5434

Tables and figures: 5

References: 30

Key words: maintenance, ovarian cancer, PARP inhibitor, postprogression outcomes, rucaparib

ABSTRACT

Background In ARIEL3, rucaparib maintenance treatment significantly improved progression-free survival (PFS) versus placebo. Here we report prespecified, investigator-assessed, exploratory postprogression endpoints and updated safety data.

Methods In this ongoing (enrolment complete) phase 3, randomised, placebo-controlled trial (NCT01968213), patients with platinum-sensitive, recurrent ovarian carcinoma who had received at least two previous platinum-based chemotherapy regimens and

responded to their last platinum-based regimen were randomised 2:1 to oral rucaparib (600 mg twice daily) or placebo in 28-day cycles using a computer generated sequence (block size of six with stratification based on homologous recombination repair gene mutation status, progression-free interval following penultimate platinum-based regimen, and best response to most recent platinum-based regimen). Patients, investigators, site staff, assessors and the funder were masked to assignments. The primary endpoint of investigator-assessed progression-free survival has been previously reported. Prespecified, exploratory outcomes of chemotherapy-free interval (CFI), time to start of first subsequent therapy (TFST), time to disease progression on subsequent therapy or death (PFS2), and time to start of second subsequent therapy (TSST) and updated safety were analysed (31 Dec 2017 visit cutoff). Efficacy analyses were conducted in all patients randomised to three nested cohorts: patients with *BRCA* mutations, homologous recombination deficiencies, and the intention-to-treat population.

Findings Between 7 April 2014 and 19 July 2016, 564 patients were enrolled; median (interquartile range) follow-up was 28·1 (22·0–33·6) months. ~~Median (95% CI) TFST in the *BRCA*-mutant cohort (n=130 rucaparib *vs* n=66 placebo) was 18·9 (15·9–25·3) versus 7·2 (5·5–9·1) months (hazard ratio 0·28 [95% CI 0·20–0·41]; p<0·0001), in the homologous recombination-deficient cohort (236 *vs* 118) was 16·4 (12·5–17·9) versus 7·4 (6·5–9·1) months (0·39 [0·30–0·51]; p<0·0001), and in the~~ In the intention-to-treat population (n=375 rucaparib *vs* n=189~~)~~ placebo), median (95% CI) CFI was 14·3 (13·0–17·4) versus 8·8 (8·0–10·3) months (hazard ratio 0·43 [95% CI 0·35–0·53]; p<0·0001), median (95% CI) TFST was 12·4 (11·1–15·2) versus 7·2 (6·4–8·6) months (0·43 [0·35–0·52]; p<0·0001~~). Median~~), median (95% CI) PFS2 was ~~26·8 (23·4–41·4) versus 18·4 (15·7–23·6) months (0·56 [0·38–0·83]; p=0·0040), 25·3 (21·9–28·5) versus 18·4 (15·8–22·1) months (0·66 [0·49–0·87]; p=0·0042), and~~ 21·0 (18·9–23·6) versus 16·5 (15·2–18·4) months (0·66 [0·53–0·82]; p=0·0002), ~~respectively. CFI and~~ and median TSST was 22·4 (19·1–24·5) versus 17·3 (14·9–19·4) months (0·68 [0·54–0·85]; p=0·0007). CFI, TFST, PFS2, and TSST were also significantly longer with rucaparib than placebo ~~across~~ in the *BRCA*-mutant and homologous recombination-deficient cohorts. The most frequent treatment-emergent adverse events (TEAEs) of any grade

were nausea (76% *vs* 37%) and asthenia or fatigue (71% *vs* 44%). The most frequent grade 3 or greater ~~treatment-emergent adverse event~~TEAE was anaemia or decreased haemoglobin (~~21·5~~22% *vs* ~~0·5%).~~1%). Serious TEAEs were reported in 22% and 11% of patients in the rucaparib and placebo groups, respectively. TEAEs leading to death were reported in 2% and 1% of patients, respectively.

Interpretation In these exploratory analyses over a median follow-up duration of more than 2 years, rucaparib maintenance treatment led to a clinically meaningful delay in starting subsequent therapy and provided lasting clinical benefits versus placebo in all three analysis cohorts. Updated safety data were consistent with prior reports.

Funding Clovis Oncology.

RESEARCH IN CONTEXT

Evidence before this study

Data on postprogression outcomes for women with recurrent platinum-sensitive ovarian carcinoma who have received poly(ADP-ribose) polymerase (PARP) inhibitor maintenance treatment are limited. Postprogression outcomes can provide clinically meaningful information. Time to start of first subsequent therapy (TFST) can demonstrate a difference in the time before further therapy is started between patients who receive a PARP inhibitor and those who received placebo. Time to disease progression on the subsequent line of treatment or death (PFS2) can provide a “snapshot” of differences in postprogression outcomes to the time to second progression, which may be of particular use when overall survival data are unavailable due to trial immaturity or confounded by long postprogression survival and/or crossover to other treatments.

A search of all PubMed articles published up to 25 Sept 2019, using the search terms ("PARP inhibitor” OR “rucaparib” OR “olaparib” OR “niraparib” OR “veliparib” OR “talazoparib”) AND (“ovarian” AND [“cancer” OR “carcinoma”]) AND “maintenance” with no language restrictions, identified 13 peer-reviewed publications covering trials of PARP inhibitor monotherapy as second-line maintenance treatment, of which only three

provide postprogression outcomes data. Patients who received maintenance olaparib in Study 19 or SOLO2 (ie, those with a *BRCA1 or BRCA2* [*BRCA*] mutation) had significantly longer TFST, time to start of second subsequent therapy (TSST), and/or PFS2 than those in the placebo group. In NOVA, median chemotherapy-free interval (CFI) and TFST were significantly longer with maintenance niraparib than placebo in patients with a germline *BRCA* mutation and patients without a germline *BRCA* mutation (this subgroup included patients with a somatic *BRCA* mutation).

Added value of this study

Our analyses include a comprehensive assessment of CFI, TFST, PFS2, and TSST postprogression outcomes for patients from ARIEL3. To our knowledge, we provide the first report of mature PFS2 data in this setting in an all-comer (ie, intention to treat [ITT]) population that includes patients without a *BRCA* mutation. The significant improvements observed in these postprogression outcomes support the PFS benefit previously reported and the clinical benefit of rucaparib in the second-line maintenance setting.

Implications of all the available evidence

Evaluation of overall survival in clinical trials of ovarian cancer can be challenging given the long duration of postprogression survival, and can be confounded by highly effective subsequent treatments. Therefore, assessment of postprogression outcomes is important to demonstrate the clinical benefit of novel therapies, such as whether further anticancer therapies may be delayed and whether patients continue to derive benefit from subsequent therapies. Together, CFI, TFST, PFS2, and TSST provide a complementary and comprehensive assessment of the postprogression outcomes following rucaparib maintenance treatment. Our postprogression outcomes data are consistent with those from other studies, further demonstrating the clinical benefit of PARP inhibitors as second-line maintenance treatment for patients with ovarian cancer.

INTRODUCTION

Although most patients with advanced ovarian cancer respond to initial treatment, typically surgery followed by platinum- and/or taxane-based chemotherapy, the majority will experience disease recurrence and require subsequent therapies.[1] For patients with recurrent ovarian cancer who respond to second-line platinum-based chemotherapy, continuing therapy with bevacizumab as a maintenance therapy or introducing a targeted agent such as a poly(ADP-ribose) polymerase (PARP) inhibitor after chemotherapy has become a standard of care that should be offered to patients.[2-7] Maintenance therapy is intended to delay disease progression without negatively affecting patient quality of life.[8,9]

Rucaparib (formerly known as CO-338, AG-014447, and PF-01367338) is an oral, small molecule inhibitor of PARP1, 2, and 3.[10,11] In the phase 3 ARIEL3 study (CO-338-014; NCT01968213) in patients with advanced, recurrent ovarian cancer, rucaparib maintenance treatment significantly improved investigator-assessed progression-free survival (PFS) versus placebo in all of the study's three molecularly defined, nested cohorts: patients with a *BRCA1* or *BRCA2 (BRCA)*-mutated carcinoma (germline, somatic, or unknown origin); patients with a homologous recombination deficient (HRD) carcinoma (*BRCA* mutation + wild-type *BRCA* and high loss of heterozygosity [LOH]); and the intention-to-treat (ITT) population.[12] The median (95% CI) PFS in patients with a *BRCA*-mutant carcinoma was 16·6 (13·4–22·9) months in the rucaparib group versus 5·4 (3·4–6·7) months in the placebo group (hazard ratio [HR] 0·23 [95% CI 0·16–0·34]; p<0·0001). In patients with an HRD carcinoma, the median (95% CI) PFS was 13·6 (10·9–16·2) months versus 5·4 (5·1–5·6) months, respectively (HR 0·32 [95% CI 0·24–0·42]; p<0·0001). In the ITT population, the median (95% CI) PFS was 10·8 (8·3–11·4) months versus 5·4 (5·3–5·5) months, respectively (HR 0·36 [95% CI 0·30–0·45]; p<0·0001). Based on these results, rucaparib is approved in the United States and European Union as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.[13,14]

As new therapies become available and management of ovarian cancer evolves to incorporate strategies such as maintenance, it is important to understand how such treatments influence the postprogression survival of patients. Although overall survival remains the gold standard in oncology trials, including those for ovarian cancer, evaluation may be confounded by subsequent treatments, a long duration of postprogression survival, and crossover to the trial or similar drug.[15] This can be particularly problematic when numerous effective treatments are available. Thus, additional postprogression assessments are needed to help demonstrate the clinical benefit of an investigative therapy, and organisations such as the Gynecologic Cancer InterGroup (GCIG), Society of Gynecologic Oncology, European Society for Gynaecological Oncology, and European Society for Medical Oncology recommend their incorporation into clinical trials to support observed PFS benefits.[16-19]

Postprogression assessments include time to start of first subsequent therapy (TFST), time to disease progression on subsequent therapy or death (PFS2), and time to start of second subsequent therapy (TSST). Significant improvements in these endpoints demonstrate that clinically meaningful improvements in PFS observed during the study can be maintained beyond the first progression event, can delay the need for subsequent therapy, and can persist throughout the course of subsequent treatments.[15] Examination of PFS2 may also provide insight into the influence of an investigative therapy on the efficacy of subsequent therapies and serve as a surrogate for overall survival.[20] Additionally, trials of targeted therapy may assess the chemotherapy-free interval (CFI), defined as the time from the last dose of prior chemotherapy to initiation of subsequent chemotherapy, inclusive of the time on targeted therapy or placebo. This endpoint can help quantify the duration of time that patients avoid the need for chemotherapy, a treatment that may have a negative impact on patient quality of life; side effects associated with chemotherapy can be more frequent and/or severe than those associated with targeted therapies. Overall, these endpoints give complementary and comprehensive information on the postprogression benefits of an investigative therapy.

Here we present results from the analyses of CFI, TFST, PFS2, and TSST in ARIEL3 to investigate the durability of clinical benefit with rucaparib maintenance treatment following disease progression and the switch to a subsequent therapy. Additional safety data are also reported (31 Dec 2017 visit cutoff), which represents a more extensive analysis of safety with an additional 8 months of follow-up than reported previously (15 Apr 2017).[12]

METHODS

Study design and patients

Full details of this randomised, double-blind, multicentre, international, phase 3 trial have been published previously.[12] This trial was conducted at 87 hospitals and cancer centres in 11 countries. Patients were enrolled between 7 Apr 2014 and 19 July 2016. The redacted protocol for the ARIEL3 clinical study is available on ClinicalTrials.gov: https://clinicaltrials.gov/ProvidedDocs/13/NCT01968213/Prot_000.pdf.

Eligible patients were aged at least 18- years, had platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, had received at least two previous platinum-based chemotherapy regimens, had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and must have achieved either a complete response according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST), a partial response according to RECIST, or a serological response based on GCIG cancer antigen 125 (CA-125) response criteria to their last platinum-based regimen. Patients must have had documented radiological disease progression more than 6 months after the last dose of the penultimate platinum administered. For entry into the study, CA-125 had to be less than the upper limit of normal. Patients with symptomatic or untreated central nervous system metastases or who had received anticancer therapy 14 days or fewer before starting the study or previous treatment with a PARP inhibitor were excluded. Previous treatment with bevacizumab was permitted, with the exception of bevacizumab maintenance therapy after the most recent platinum-based regimen. On 4 Nov 2014,

after 91 patients had been randomised, we made an amendment to the protocol requiring that the most recent platinum-based regimen was to be administered as a chemotherapy doublet and for a minimum of four cycles. Full inclusion and exclusion criteria have been reported previously by Coleman et al (Supplemental Table S1 of that manuscript).[12]

The study was approved by national or local institutional review boards and was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. Patients provided written informed consent before participation.

Randomisation and masking

As reported previously,[12] randomisation was computer generated using a block size of six, with stratification factors that included homologous recombination repair gene mutation status (based on gene mutation only; mutation in *BRCA1* or *BRCA2*, mutation in a non-*BRCA* gene associated with homologous recombination, or no mutation in *BRCA* or a homologous recombination gene); progression-free interval following penultimate platinum-based regimen (6 to ≤12 months or >12 months); and best response to most recent platinum-based regimen (complete or partial response). Patients were assigned 2:1 to the rucaparib or placebo group in a masked manner via an interactive web and voice response system. Patients, investigators, site staff, assessors, and the funder were masked to assignments. To ensure masking was maintained, rucaparib and placebo tablets were manufactured to have identical appearances.

Procedures

In the screening phase prior to randomisation, patient medical history and archival tumour tissue were obtained. Central testing of DNA derived from patient archival tumour tissue samples was performed to detect mutations in homologous recombination pathway genes and assess genomic LOH. A cutoff of 16% or greater for ARIEL3 was prespecified as a discriminator for high genomic LOH.[12] Full details of the testing protocol have been reported previously.[12]

In ARIEL3, patients received oral rucaparib 600 mg twice daily or placebo in continuous 28-day cycles until disease progression (as assessed by RECIST), death, or other reason for discontinuation. Dose reductions (in 120 mg decrements to 240 mg twice daily) were permitted if a patient had a Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade 3 or greater or a persistent grade 2 adverse event (AE).

Treatment of study drug was to be withheld for any CTCAE grade 3 or 4 toxicities. At the discretion of the investigator, the dose of study drug may have been held and/or reduced for a CTCAE grade 2 toxicity not adequately controlled using concomitant medications and/or supportive care.

Treatment with study drug was to be held until the toxicity resolved to CTCAE grade 2 or less. Twice daily dosing could then be resumed at either the same dose or a lower dose at the discretion of the investigator. If treatment was resumed at the same dose, and the patient experienced the same toxicity, the dose was to be reduced following resolution of the event to CTCAE grade 2 or less. If the patient continued to experience toxicity, additional dose reduction steps were permitted; however, the investigator was expected to consult with the sponsor's medical monitor before reducing to 240 mg twice daily (BID). If a patient continued to experience toxicity despite two dose-reduction steps (ie, to a dose of 360 mg BID rucaparib or placebo), or if dosing with study drug was interrupted for more than 14 consecutive days due to toxicity, treatment was to be discontinued, unless otherwise agreed between the investigator and the sponsor.

We did disease assessments including computed tomography scans, and CA-125 measurements, at screening, every 12 weeks during treatment, following clinical symptoms, and at discontinuation of treatment. Samples were collected for central laboratory investigations of haematological and clinical chemistry parameters every 2 weeks for the first 2 cycles and then on day 1 of every subsequent cycle. Patients were monitored for adverse events during study participation, beginning after the first dose of study drug and until 28 days after the last dose of study drug. Following the 28-day window after treatment discontinuation, only serious adverse events assessed as related to study drug and all adverse events of special interest irrespective of causality,

were reported. After the initial treatment phase, long-term follow-up and overall survival data were collected for all patients. Subsequent treatments, secondary malignancy monitoring, and overall survival information will be collected for all patients every 12 weeks (±14 days) until death, loss to follow-up, withdrawal of consent from study, or closure of the study. For patients who discontinued due to disease progression, the schedule and type of subsequent disease assessments were not prespecified by the protocol and were left to the discretion of the investigator.

Outcomes

The primary efficacy endpoint (investigator-assessed PFS) and secondary endpoints (PFS according to blinded, independent, central radiology review, patient-reported outcomes, and safety) in ARIEL3 have been reported previously using the primary efficacy data after unblinding (15 Apr 2017 visit cutoff).[12] Data for the secondary endpoint of overall survival were not yet mature at the time of the present analyses, and the secondary endpoint of population pharmacokinetic modelling will be reported separately.

Here we report on the prespecified, investigator-assessed exploratory endpoints of CFI, TFST, PFS2, and TSST using a visit cutoff of 31 Dec 2017. CFI was defined as the time since the last dose of the most recent chemotherapy regimen to the date of the first dose of a subsequent anticancer therapy after study drug. TFST was defined as the time from randomisation to the date of the first dose of the first subsequent anticancer treatment regimen. PFS2 was defined as the time from randomisation to the second event of disease progression as assessed by the investigator or death due to any cause. This second progression event may have been a documented event as defined in the RECIST guidelines or an event of symptomatic or clinical or CA-125 progression. TSST was defined as the time from randomisation to the date of the first dose of the second subsequent anticancer treatment regimen.

Subsequent treatments are reported up to a visit cutoff date of 31 Dec 2017.

An updated analysis of safety using a visit cutoff date of 31 Dec 2017 is presented. Safety was assessed by monitoring AEs and vital signs, laboratory testing, and physical examination.

Statistical analysis

ARIEL3 was designed to enrol approximately 540 patients and include 180 to 200 patients with a *BRCA* mutation in their carcinoma (limited to 150 with a known deleterious germline *BRCA* mutation) and up to 360 patients without. Subgroup sizes were calculated to result in a 90% power to establish a significant difference between rucaparib and placebo at a one-sided α level of 0·025 given the following assumptions for investigator assessed median PFS for each analysis cohort: *BRCA* mutant (12·0 months in the rucaparib group *vs* 6·0 months in the placebo group; HR 0·5), HRD (10·0 months *vs* 6·0 months; HR 0·6), and the intention-to-treat population (8·5 months *vs* 6·0 months; HR 0·7).[12] Prespecified and post hoc exploratory analyses were performed for the three molecularly defined, nested cohorts: patients with a *BRCA*-mutated carcinoma, patients with an HRD carcinoma, and the ITT population. Post hoc exploratory analyses were performed for subgroups of patients with *BRCA* wild-type carcinomas based on LOH status (high, low, or indeterminate).

Time-to-event variables (CFI, TFST, PFS2, and TSST) were summarised using Kaplan-Meier methodology. A stratified log rank test that included the randomisation strata was used to compare treatments. Additionally, a stratified Cox proportional hazard model was used to calculate the HR between the treatment groups for each endpoint. Proportionality of hazards for the Cox proportional hazard assumption (ie, constant relative hazard) was verified graphically using log-log plots for PFS and PFS2 in the ITT population (appendix p ~~7~~8). As the assumption was met for these analyses (ie, the plot of the log of the cumulative hazard for the rucaparib and placebo groups resulted in parallel curves), the subgroup analyses were deemed appropriate. Per protocol, all endpoints were exploratory and tested at a one-sided 0·025 significance level, without any multiplicity adjustment.

For CFI, patients without a documented start of a subsequent anticancer therapy after study drug were censored on the date of their last available assessment. For TFST, patients without a documented start of a subsequent anticancer treatment after study drug were censored on the date of their last available assessment. For PFS2, patients without a documented second progression event were censored on the date of their last

available assessment. For TSST, patients without a documented start of a second subsequent anticancer treatment after study drug were censored on the date of their last available assessment.

We also report the post hoc, exploratory endpoint of PFS2–PFS1, defined as the time from investigator-assessed disease progression during ARIEL3 (PFS1) to the second event of investigator-assessed disease progression or death. For this endpoint, patients were censored if they did not experience a second event of progression or death at the last date known to be alive. Duration of PFS2–PFS1 was set to 1 day for patients who were censored for PFS1 and did not have any further follow-up information. The date of the second event of progression or censoring was used to calculate PFS2–PFS1 for patients who were censored for PFS1 but received subsequent anticancer treatment or had other follow-up data.

The safety population included all patients who received at least one dose of study treatment.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). This trial is registered with ClinicalTrials.gov, number NCT01968213.

Role of the funding source

ARIEL3 was designed by JAL, EMS, and RLC in collaboration with the funder. This article was written by the authors, with medical writing and copy editing support paid for by the funder. Data were collected by the investigators, analysed by the funder, and interpreted by all authors. All authors had full access to all trial data and had final responsibility for the decision to submit these data for publication.

RESULTS

Between 7 Apr 2014 and 19 July 2016, 564 patients were randomly allocated to the two groups: 375 (66~~-5~~%) to rucaparib and 189 (~~33-5~~34%) to placebo (ie, ITT population); the *BRCA* mutant cohort included 130 and 66 patients, respectively; and the HRD

cohort included 236 and 118 patients (figure 1). The majority of patients had an ECOG Performance Status of 0 (280 [74·775%] and 136 [72·0%], respectively) and a *BRCA* wild-type carcinoma (245 [65·3%] and 123 [65·1%]) (table 1). Most patients in ARIEL3 had received two previous platinum-based chemotherapy regimens (236 [62·963%] and 126 [66·767%]), with the remainder having received three (109 [29·1%] and 47 [24·925%]) or more than three (30 [8·0%] and 16 [8·5%]) previous platinum-based chemotherapy regimens. Protocol deviations have been reported in full by Coleman et al.[12] As of the 31 Dec 2017 visit cutoff (median [interquartile range] follow-up 28·1 months [22·0–33·6]), 60 (16·0%) patients in the rucaparib group and five (2·63%) in the placebo group had not yet progressed and were still receiving treatment.

The CFI was examined in all three nested cohorts. In the *BRCA*-mutant cohort, median (95% CI) CFI was significantly longer in the rucaparib group (20·8 [17·7–27·8] months) than placebo group (8·7 [7·2–10·9] months; HR 0·28 [95% CI 0·19–0·41]; p<0·0001; appendix p 8).75 [58%] events in the rucaparib group *vs* 56 [85%] events in the placebo group; appendix p 9). In the HRD cohort, median (95% CI) CFI was 18·0 (14·3–19·4) months in the rucaparib group, significantly longer than the 9·1 (8·0–10·8) months in the placebo group (HR 0·40 [95% CI 0·31–0·53]; p<0·0001; 152 [64%] *vs* 101 [86%] events; appendix p 1011). Median (95% CI) CFI in the ITT population was also significantly longer in the rucaparib group than placebo group (14·3 [13·0–17·4] months *vs* 8·8 [8·0–10·3] months; HR 0·43 [95% CI 0·35–0·53]; p<0·0001; 255 [68%] *vs* 164 [87%] events; figure 2A).

Among patients in the ITT population who discontinued and had not withdrawn consent for follow-up, 134 (45·646%) of 294 patients from the rucaparib group and 66 (37·738%) of 175 patients from the placebo group received platinum-based chemotherapy as their first subsequent therapy, with 81 (27·628%) and 52 (29·730%) patients receiving nonplatinum-based chemotherapy (figure 3). Four (1·4%) patients from the rucaparib group and 18 (10·3%) patients from the placebo group received PARP inhibitor treatment as their first subsequent therapy; two (0·71%) and three (1·72%), respectively, received PARP inhibitor maintenance as their first subsequent therapy (figure 3). Patients in the rucaparib group had a significantly longer TFST than patients

in the placebo group across all the cohorts, with a median (95% CI) TFST of 18·9 (15·9–25·3) versus 7·2 (5·5–9·1) months in the *BRCA*-mutant cohort (HR 0·28 [95% CI 0·20–0·41]; p<0·0001; 81 [62%] *vs* 58 [88%] events; appendix p ~~89~~), 16·4 (12·5–17·9) versus 7·4 (6·5–9·1) months in the HRD cohort (HR 0·39 [95% CI 0·30–0·51]; p<0·0001; 160 [68%] *vs* 106 [90%] events; appendix p ~~10~~11), and 12·4 (11·1–15·2) versus 7·2 (6·4–8·6) months in the ITT population (HR 0·43 [95% CI 0·35–0·52]; p<0·0001; 273 [73%] *vs* 172 [91%] events; figure 2B).

Median (95% CI) investigator-assessed PFS2 was significantly longer in the rucaparib group than placebo group in the *BRCA*-mutant cohort (26·8 [23·4–41·4] *vs* 18·4 [15·7–23·6] months; HR 0·56 [95% CI 0·38–0·83]; p=0·0040; 64 [49%] *vs* 42 [64%] events; appendix p ~~9~~10), the HRD cohort (25·3 [21·9–28·5] *vs* 18·4 [15·8–22·1] months; HR 0·66 [95% 0·49–0·87]; p=0·0042; 125 [53%] *vs* 78 [66%] events; appendix p ~~11~~12), and the ITT population (21·0 [18·9–23·6] *vs* 16·5 [15·2–18·4] months; HR 0·66 [95% CI 0·53–0·82]; p=0·0002; 223 [59%] *vs* 134 [71%] events; figure 2C). ~~Across~~In a post hoc analysis, across all three cohorts~~,~~ there was no significant difference in PFS2–PFS1 between the rucaparib and placebo groups (appendix p ~~12).~~13).

In the ITT population, among the 292 and 173 patients in the rucaparib and placebo groups who discontinued and had not withdrawn consent for follow-up, 170 (58~~·2~~%) and 100 (~~57·8~~58%), respectively, had received a second subsequent therapy as of the visit cutoff date. The most common second subsequent therapy was nonplatinum-based chemotherapy (87 [~~29·8~~30%] and 38 [22~~·0~~%] patients, respectively; figure 3). Of patients who received a second subsequent therapy, the proportion of those receiving a platinum-based chemotherapy (49 [~~16·8~~17%] and 36 [~~20·8~~21%] patients, respectively) was lower than the proportion of patients who received platinum-based chemotherapy as their first subsequent treatment (figure 3). Four (1~~·4~~%) patients from the rucaparib group and 11 (6~~·4~~%) patients from the placebo group received PARP inhibitor treatment as their second subsequent therapy; three (1~~·0~~%) and eight (~~4·6~~5%), respectively, received PARP inhibitor maintenance as their second subsequent therapy (figure 3).

For patients in the *BRCA*-mutant cohort, median (95% CI) TSST was 28·8 (24·4–34·2) months in the rucaparib group versus 17·7 (15·1–21·6) months in the placebo group

(HR 0·53 [95% CI 0·36–0·80]; p=0·0022; 65 [50%] *vs* 41 [62%] events; appendix p 910). In the HRD cohort, median (95% CI) TSST was significantly longer in the rucaparib group than the placebo group (26·2 [22·9–30·6] *vs* 19·0 [15·8–21·7] months; HR 0·67 [95% CI 0·50–0·91]; p=0·010; 123 [52%] *vs* 73 [62%] events; appendix p 1112). In the ITT population, there was also a significantly longer median TSST with rucaparib, with a median (95% CI) of 22·4 (19·1–24·5) months in the rucaparib group versus 17·3 (14·9–19·4) months in the placebo group (HR 0·68 [95% CI 0·54–0·85]; p=0·0007; 217 [58%] *vs* 128 [68%] events; figure 2D).

In post hoc analyses of subgroups of patients with *BRCA* wild-type carcinomas, median CFI, TFST, PFS2, and TSST were all longer with rucaparib than placebo regardless of LOH status (appendix p 1314), with median CFI and TFST being significantly longer in the rucaparib than placebo group.

The safety population included 372 (99-2%) patients who received rucaparib (three [0-8%]-1%] patients withdrew before receiving rucaparib), and 189 (100%) patients who received placebo. At the time of the extended visit cutoff date (31 Dec 2017), the median (interquartile range) treatment duration for patients in the safety population was 8·3 (3·4–18·1) months in the rucaparib group and 5·5 (2·8–8·3) months in the placebo group.

Overall, the updated safety profile was comparable to that reported by Coleman et al (2017), with only modest increases in incidences of treatment-emergent AEs (TEAEs) in the rucaparib and placebo groups (table 2; appendix p 4). In the updated safety analysis, a TEAE of any grade occurred in 372 (100%) of the patients in the rucaparib group, and 182 (96-3%) in the placebo group. The most common TEAEs of any grade (reported in at least 30% of patients in either group) were nausea, asthenia or fatigue, dysgeusia, anaemia or decreased haemoglobin, constipation, vomiting, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increased, diarrhoea, and abdominal pain (table 2). Grade 3 or higher TEAEs were reported in 222 (59-760%) of the patients in the rucaparib group and 30 (15-916%) in the placebo group (appendix pp 4-65-7), the most common of which were anaemia or decreased haemoglobin (80 [21-522%] patients *vs* 1 [0-51%] patient) and ALT or AST increased (38 [10-2%] *vs*

none). Serious TEAEs were reported in 83 (22-3%) of the patients in the rucaparib group and 20 (10-611%) in the placebo group, the most common of which werefrequently anaemia (16 [4-3%] in the rucaparib group *vs* 1 [0-51%] in the placebo group), vomiting (7 [1-92%] *vs* 2 [1-1%]), and pyrexia (6 [1-62%] *vs* 0none). Serious TEAEs were considered related to treatment by the investigator for 35 (9%) and 3 (2%) patients in the rucaparib and placebo groups, respectively, the most frequent of which was anaemia (16 [4%] *vs* 1 [1%]). Most TEAEs of anaemia or decreased haemoglobin were managed with dose reduction or treatment interruption and blood transfusions (for grade 2 or 3 events); less than 2% of patients received erythropoietin.

In this updated safety analysis, there were no new TEAEs of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) beyond those previously reported (three [0-81%] patients in the rucaparib group and none in the placebo group[12]).

Treatment interruption due to a TEAE occurred in 243 (65-3%) patients in the rucaparib group and 19 (10-1%) in the placebo group. The most common TEAEs leading to treatment interruption in the rucaparib group were thrombocytopenia or decreased platelets (64 [17-2%] patients), anaemia or decreased haemoglobin (56 [15-1%]), ALT or AST increased (38 [10-2%]), and nausea (38 [10-2%]), whereas the most common TEAE associated with treatment interruption in the placebo group was asthenia or fatigue (six [3-2%]).

Dose reduction due to a TEAE occurred in 206 (55-4%) patients in the rucaparib group and eight (4-2%) in the placebo group. The most common TEAEs leading to dose reduction in the rucaparib group were anaemia or decreased haemoglobin (47 [12-613%] patients), ALT or AST increased (41 [11-0%]), thrombocytopenia or decreased platelets (40 [10-811%]), and nausea (37 [9-910%]).

Fifty-seven (15-3%) patients in the rucaparib group and three (1-62%) in the placebo group discontinued because of a TEAE (excluding disease progression), of whom 49 (13-2%) and one (0-51%) discontinued because of a TEAE that was considered treatment related. The most common TEAEs leading to discontinuation in the rucaparib group were thrombocytopenia or decreased platelets (11 [3-0%] patients), anaemia or decreased haemoglobin (10 [2-73%]), and nausea (10 [2-73%]). These were also the

most common treatment-related TEAEs leading to discontinuation in the rucaparib group, with 10 (2·7 3%) patients discontinuing due to each TEAE.

In the previously published analysis (safety visit cutoff 15 Apr 2017), we reported 4 deaths in the rucaparib group considered unrelated to treatment by the investigator (2 [0·5 1%] due to progressive disease, 1 [0·3 [<1%] due to cardiac arrest, and 1 [0·3 [<1%] due to haematophagic histiocytosis) and 2 considered related to treatment (1 [0·3 [<1%] due to acute myeloid leukaemia and 1 [0·3 [<1%] due to myelodysplastic syndrome); 2 deaths occurred in the placebo group considered unrelated to treatment (1 [0·5 1%] due to disease progression and 1 [0·5 1%] due to pulmonary embolism).[12] At the time of the updated safety visit cutoff date (31 Dec 2017) there was one (0·3 (<1%) additional death due to a high-grade B-cell lymphoma in the rucaparib group, which was considered unrelated to rucaparib by the investigator, and none in the placebo group.

DISCUSSION

The prespecified, exploratory analyses reported here demonstrate the durable clinical benefit of rucaparib maintenance treatment in the postprogression period for patients with recurrent ovarian cancer. Median CFI, TFST, PFS2, and TSST were all significantly (1·3- to 2·6-times) longer for patients who received rucaparib maintenance treatment than those who received placebo, demonstrating a clinically meaningful improvement in these endpoints for all cohorts regardless of mutational status.

The extension of CFI indicated that patients receiving rucaparib were able to delay initiating additional anticancer therapy, potentially allowing them more time to recover from prior negative impacts of chemotherapy and postpone further side effects associated with anticancer therapy. In particular, the side effects associated with chemotherapy are of specific concern to patients with ovarian cancer.[21,22] The TFST findings were similarly clinically meaningful; in all cohorts, median TFST was approximately 2-times longer in the rucaparib group than the placebo group, and the significant differences in TFST demonstrated that patients who received rucaparib maintenance treatment were able to delay the start of further therapy for longer than patients receiving placebo. Among first subsequent therapies, the use of platinum-based chemotherapy was higher in the rucaparib group than placebo group, indicating

that rucaparib-treated patients had tumours that were still considered platinum-sensitive and that these patients remained fit enough to receive additional chemotherapy. Although a number of patients in the rucaparib group (six [2~~-0~~%]) of the ITT population did receive a different PARP inhibitor as their first subsequent treatment, the proportion of subsequent PARP inhibitor use was higher among patients in the placebo group (21 [12~~-0~~%]), which is consistent with the currently limited understanding regarding the efficacy of PARP inhibitors in patients who have received prior PARP inhibitor therapy. A greater number of patients received a PARP inhibitor as first subsequent therapy in the treatment setting than in the maintenance setting (22 [~~4-7~~5%] *vs* five [1~~-1~~%]).

The lasting benefit of rucaparib treatment was further supported by the PFS2 analyses; across cohorts, the median PFS2 was 1·5-times longer in the rucaparib group than the placebo group. The PFS2–PFS1 analyses suggest that rucaparib maintenance treatment did not adversely impact the possibility for patients to benefit from subsequent therapy. This is of particular importance as the duration of PFS following relapse has previously been shown to diminish with each line of chemotherapy in women with ovarian cancer.[23] Such reductions in PFS are likely related to the development of resistance through changes in the tumour, such as mutations or epigenetic modifications, which can accumulate and influence responsiveness to treatment.[24] It is possible that differences in the mechanism of action between rucaparib and other drug classes explain why rucaparib had no apparent impact on the efficacy of subsequent therapies. Furthermore, the benefit in PFS2 for patients who received rucaparib and the similarity in PFS2–PFS1 between rucaparib and placebo groups were seen even though 21 (12~~-0~~%) patients in the placebo group received a PARP inhibitor as the first subsequent therapy. Median TSST was also longer for patients who received rucaparib than those who received placebo across all cohorts, supporting the PFS2 analyses and the benefit of prior rucaparib maintenance treatment. As of the visit cutoff, most patients who had a second subsequent therapy received a nonplatinum-based chemotherapy, suggesting that fewer of these patients had tumours that were considered platinum-sensitive than those who received a first subsequent therapy. More patients received PARP inhibitor maintenance treatment as their second subsequent therapy (11 [2~~-4~~%]) than as a first subsequent therapy (five [1~~-1~~%]).

Rucaparib maintenance treatment provided durable clinical benefit for patients with recurrent, platinum-sensitive ovarian cancer, with 60 (16~~-0~~%) of 375 patients in the rucaparib group still participating in the study as of the 31 Dec 2017 visit cutoff date compared with five (~~2-6~~3%) of 189 patients in the placebo group. Our exploratory endpoint analyses suggest that rucaparib maintenance does not negatively affect the efficacy of subsequent treatments and further support the PFS benefit observed in patients receiving rucaparib during the study. For each postprogression endpoint, the difference between medians in the rucaparib and placebo groups were consistent with the difference in medians for PFS on study across all cohorts. Conversely, if rucaparib maintenance treatment had negatively affected postprogression outcomes, differences between the rucaparib and placebo groups would have been substantially shorter than the initial difference in median PFS.

Similar improvements in postprogression outcomes have been reported from clinical trials of other PARP inhibitors used as second-line maintenance treatment for ovarian cancer. In NOVA, maintenance niraparib significantly improved median CFI and median TFST versus placebo in patients with a germline *BRCA* mutation and patients without a germline *BRCA* mutation (this subgroup included patients with a somatic *BRCA* mutation).[4,25] In SOLO2, maintenance olaparib significantly improved median TFST, PFS2, and TSST versus placebo in patients with a *BRCA* mutation.[7] In Study 19, a phase 2 study of maintenance olaparib, median TFST and TSST were significantly longer with olaparib than placebo in patients with and those without a *BRCA* mutation.[26]

Safety results as of 31 Dec 2017 were comparable to those reported earlier by Coleman et al in terms of their incidence, severity, and nature.[12] The safety analysis included an additional 8 months of follow-up, and slight increases in the incidence of TEAEs were not unexpected considering the increased duration of treatment. There was no increase in the incidence of MDS or AML with the additional 8 months of follow-up; patients continue to be followed to monitor for these and other AEs that may develop over time. TEAEs such as gastrointestinal events, haematological toxicities, and fatigue are considered to be class effects, consistent with those of other PARP inhibitors.[3,7,12,27-30] TEAEs and laboratory abnormalities were managed with treatment interruption,

treatment modification, and/or supportive care, such as antiemetic medications for nausea or vomiting or red blood cell transfusions for anaemia. The low incidence of discontinuations due to AEs showed that management with supportive care and dose modifications was effective. The extended safety analysis demonstrated that rucaparib had a tolerable safety profile.

Limitations of the current analysis include the fact that the study is ongoing, and long-term follow-up data continue to be collected. Furthermore, overall survival data are not yet mature; these data will be reported when approximately 70% of the events have occurred. Although efforts were made to maintain treatment blinding for the overall survival analysis, treatment unblinding was permitted upon investigator request if a decision regarding subsequent treatment depended on whether or not a patient had received prior PARP inhibitor therapy (eg, prior PARP inhibitor use was an exclusion criterion for a subsequent study); therefore, the process of unblinding may have influenced the final selection of subsequent therapy.

The significant improvement in the clinically meaningful endpoints of CFI, TFST, PFS2, and TSST observed in patients who received rucaparib maintenance treatment compared with those who received placebo provides additional support to the significant improvement in PFS (the primary endpoint) observed with rucaparib versus placebo in ARIEL3. These significant improvements suggest that when compared with placebo, rucaparib maintenance treatment provided a meaningful delay in starting further therapy and did not impact the possibility of receiving benefit from subsequent therapies after first progression. As with the primary and key secondary efficacy endpoints, improvements in the postprogression endpoints were observed in the *BRCA*-mutant and HRD cohorts as well as in the ITT population. The updated rucaparib safety profile was consistent with prior reports, and no new safety signals were identified.

Contributors

JAL, EMS, and RLC designed the study in collaboration with the funder.

JAL, AMO, DL, CA, AO, AD, NC, JIW, ARC, GS, AL, RWH, MAG, PCF, JCG, DMO, DKA, SB, JG-D, EMS, and RLC treated patients.

JAL, AMO, DL, CA, AO, AD, NC, JIW, ARC, GS, AL, RWH, MAG, PCF, JCG, DMO, DKA, SB, JG-D, EMS, and RLC acquired the data.

All authors interpreted the data.

All authors contributed to the writing of the manuscript, reviewed and amended the drafts, and approved the final version for submission.

Declaration of interests

JAL has received lecture fees from Clovis Oncology, AstraZeneca, Merck/Merck Sharp & Dohme, Pfizer, and Tesaro; served on advisory boards for Clovis Oncology, Artios Pharma, AstraZeneca, Cristal Therapeutics, Merck/Merck Sharp & Dohme, Pfizer, Regeneron, Roche, Seattle Genetics, and Tesaro; and received research grants from AstraZeneca and Merck/Merck Sharp & Dohme.

AMO has served on advisory boards for Clovis Oncology, Amgen, Immunovaccine, and Verastem; received support for travel or accommodation from AstraZeneca; and received honoraria from WebRx.

DL has served in a consulting or advisory role for Clovis Oncology, AstraZeneca, ImmunoGen, Merck, PharmaMar, Roche, Takeda, and Tesaro and received support for travel or accommodation from PharmaMar and Roche.

CA has served on a steering committee for Clovis Oncology, AbbVie, Genentech, and Mateon Therapeutics; served on advisory boards for Clovis Oncology, Cerulean Pharma, Eisai/Merck, ImmunoGen, and Tesaro; received research grants from Clovis Oncology, AbbVie, AstraZeneca, and Genentech; and received honoraria from Clovis Oncology, Cerulean Pharma, Eisai/Merck, ImmunoGen, Mateon Therapeutics, and Tesaro.

AO has served on advisory boards for Clovis Oncology, AstraZeneca, ImmunoGen, Genmab/Seattle Genetics, PharmaMar, Roche, and Tesaro; received support for travel or accommodation from Clovis Oncology, AstraZeneca, PharmaMar, and Roche; and received research grants from Clovis Oncology, AbbVie Deutschland, Ability Pharmaceuticals, Advaxis, Aeterna Zentaris, Amgen SA, Aprea Therapeutics AB, Bristol-Meyers Squibb, Eisai, F. Hoffmann-La Roche, Regeneron Pharmaceuticals, ImmunoGen, Merck Sharp & Dohme de España SA, Millennium Pharmaceuticals, PharmaMar, and Tesaro.

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JIW has received research support from AbbVie and AstraZeneca and served on advisory boards for AstraZeneca.

ARC has served on advisory boards for AstraZeneca; received research funding from Clovis Oncology and AstraZeneca; and received support for travel and accommodation for congress attendance from Clovis Oncology, AstraZeneca, and Roche.

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RWH has served on speakers bureaus for Clovis Oncology, AstraZeneca, and Tesaro.

MAG has served on advisory boards for Clovis Oncology and on speakers bureaus for AstraZeneca, PharmaMar, and Roche.

PCF has served on advisory boards for Clovis Oncology and AstraZeneca and received honoraria from AstraZeneca.

JCG has served in a consulting or advisory role for AstraZeneca, Bristol-Meyers Squibb and Tesaro; served on speakers bureaus for Ipsen and Merck Sharp & Dohme; and received support for travel or accommodation from Astellas, AstraZeneca and Bristol-Myers Squibb.

DMO has served on advisory boards for Clovis Oncology, AbbVie, AstraZeneca, Eisai, Genentech/Roche, Genelux, Iovance Biotherapeutics, Janssen, Novocure, Regeneron, and Tesaro; has served on steering committees for Clovis Oncology, Agenus, Amgen, and Novocure; has served as a consultant for AbbVie, Ambry, AstraZeneca, Genentech/Roche, Gynecologic Oncology Group Foundation, and Tesaro; has given a presentation on ovarian cancer at the National Comprehensive Cancer Network; and his institution has received research support from Clovis Oncology, AbbVie, Agenus, Amgen, Ajinomoto, Array BioPharma, AstraZeneca, Bristol-Myers Squibb, Cerulean Pharma, Eisai, EMD Serono, ERGOMED Clinical Research, Genentech, Gynecologic Oncology Group, INC Research, inVentiv Health Clinical, Iovance Biotherapeutics, Janssen Research and Development, Ludwig Institute for Cancer Research, New Mexico Cancer Care Alliance, Novocure, PRA International, Regeneron Pharmaceuticals, Serono, Stemcentrx, Tesaro, TRACON Pharmaceuticals, VentiRx, Yale University.

DKA has served as a scientific advisor for Morphotek and received research funding from Clovis Oncology, Advaxis, AstraZeneca, Pfizer, Syndax, and Tesaro.

SB has served on advisory boards and received honoraria from Clovis Oncology, AstraZeneca, PharmaMar, Seattle Genetics, and Tesaro; received honoraria from Merck Serono and Roche; and received support for travel or accommodation from NuCana and Tesaro.

JG-D has received research funding from AstraZeneca, Pierre Fabre, and Pfizer; received personal fees from Clovis Oncology, Astellas, Pierre Fabre, and Pfizer; and received nonfinancial support from Astellas, Pierre Fabre, and Pfizer.

EMS has nothing to disclose.

TC, LM, and SG are employees of Clovis Oncology and may own stock or have stock options in that company.

RLC reports grants from Clovis Oncology, AstraZeneca, Gateway Foundation, Janssen, Judy Reis/Albert Pisani, MD, Ovarian Cancer Research Fund, Merck, National Institutes of Health, Roche/Genentech, and V-Foundation; has served as an advisor to Clovis Oncology, Agenus, AstraZeneca, GamaMabs, Genmab, Janssen, OncoQuest, Pfizer (Medivation), Regeneron, Roche/Genentech, and Tesaro; and has an endowment as the Ann Rife Cox Chair in Gynecology.

Data sharing

Requests for deidentified datasets 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 anonymisation. Data will be provided by Clovis Oncology. The redacted protocol for the ARIEL3 clinical study is available on ClinicalTrials.gov: https://clinicaltrials.gov/ProvidedDocs/13/NCT01968213/Prot_000.pdf. Clovis Oncology does not share identified participant data or a data dictionary.

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Table 1: **Patient demographics and baseline characteristics in intention-to-treat population**

	Rucaparib (n=375)	**Placebo (n=189)**
Age, years	61·0 (53·0–67·0)	62·0 (53·0–68·0)
ECOG Performance Status		
0	280 (74·7)75%)	136 (72·0)%)
1	95 (25·3)%)	53 (28·0)%)
Diagnosis		
Epithelial ovarian cancer	312 (83·2)%)	159 (84·1)%)
Fallopian tube cancer	32 (8·5)9%)	10 (5·3)%)
Primary peritoneal cancer	31 (8·3)%)	19 (10·1)%)
High-grade serous adenocarcinoma	0	1 (0·5)*1%)*
***BRCA* mutation in carcinoma**		
***BRCA* mutant**	130 (34·7)35%)	66 (34·9)35%)
BRCA1	80 (21·3)%)	37 (19·6)20%)
BRCA2	50 (13·3)%)	29 (15·3)%)
Germline	82 (21·9)22%)	48 (25·4)%)
Somatic	40 (10·7)11%)	16 (8·5)%)
Unknown†	8 (2·1)%)	2 (1·1)%)
***BRCA* wild type**	245 (65·3)%)	123 (65·1)%)
LOH high	106 (28·3)%)	52 (27·5)28%)
LOH low	107 (28·5)29%)	54 (28·6)29%)
LOH indeterminate‡	32 (8·5)9%)	17 (9·0)%)
Number of previous platinum-based regimens		
2	236 (62·9)63%)	126 (66·7)67%)
≥3	139 (37·1)%)	63 (33·3)%)
Time to progression with penultimate platinum-based regimen		
6 to ≤12 months	151 (40·3)%)	76 (40·2)%)
>12 months	224 (59·7)60%)	113 (59·8)60%)
Response to last platinum-based regimen		
CR according to RECIST	126 (33·6)34%)	64 (33·9)34%)
PR according to RECIST or serological response according to GCIG CA-125 criteria	249 (66·4)%)	125 (66·1)%)

Data are median (IQR) or n (%).
*According to the patient records, origin was fallopian tube or ovary.
†Tumour sample was *BRCA* mutant according to Foundation Medicine's T5 next-generation sequencing assay, but a blood sample was not available for central germline testing.
‡Tumour sample was not evaluable for percentage of genomic LOH because of low tumour content or aneuploidy.
CA-125=cancer antigen 125. CR=complete response. ECOG=Eastern Cooperative Oncology Group. GCIG=Gynecologic Cancer InterGroup. IQR=interquartile range. LOH=loss of heterozygosity. PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

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Table 2: **Treatment-emergent adverse events in the safety population: comparison of previously reported and updated data**

	Previous report: 15 Apr 2017 visit cutoff date[12]								Updated data:*: 31 Dec 2017 visit cutoff date							
	Rucaparib (n=372)				Placebo (n=189)				Rucaparib (n=372)				Placebo (n=189)			
Any grade TEAE	372 (100)				182 (96·3)				372 (100)				182 (96·3)			
Grade ≥3 TEAE	209 (56·2)				28 (14·8)				222 (59·7)				30 (15·9)			
Treatment interruption and/or dose reduction	263 (70·7)				20 (10·6)				267 (71·8)				20 (10·6)			
Treatment interruption due to a TEAE	237 (63·7)				19 (10·1)				243 (65·3)				19 (10·1)			
Dose reduction due to a TEAE	203 (54·6)				8 (4·2)				206 (55·4)				8 (4·2)			
Discontinuation due to a TEAE*	50 (13·4)				3 (1·6)				57 (15·3)				3 (1·6)			
Deaths relating to a TEAE	6 (1·6)				2 (1·1)				7 (1·9)				2 (1·1)			
Grade 1–2 TEAEs reported in ≥10% of patients and grade 3–4 TEAEs reported in ≥2% of patients†																
	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4
Nausea	280 (75·3%)	266 (71·5%)	14 (3·8%)	0	69 (36·5%)	68 (36·0%)	1 (0·5%)	0	282 (75·8%)	268 (72·0%)	14 (3·8%)	0	69 (36·5%)	68 (36·0%)	1 (0·5%)	0
Asthenia or fatigue	258 (69·4%)	233 (62·6%)	25 (6·7%)	0	83 (43·9%)	78 (41·3%)	5 (2·6%)	0	263 (70·7%)	237 (63·7%)	26 (7·0%)	0	84 (44·4%)	79 (41·8%)	5 (2·6%)	0
Dysgeusia	146 (39·2%)	146 (39·2%)	0	0	13 (6·9%)	13 (6·9%)	0	0	148 (39·8%)	148 (39·8%)	0	0	13 (6·9%)	13 (6·9%)	0	0
Anaemia or haemoglobin decreased	139 (37·4%)	69 (18·5%)	67 (18·0%)	3 (0·8%)	11 (5·8%)	10 (5·3%)	0	1 (0·5%)	145 (39·0%)	65 (17·5%)	77 (20·7%)	3 (0·8%)	10 (5·3%)	9 (4·8%)	0	1 (0·5%)
Constipation	136 (36·6%)	129 (34·7%)	7 (1·9%)	0	45 (23·8%)	43 (22·8%)	2 (1·1%)	0	141 (37·9%)	134 (36·0%)	7 (1·9%)	0	46 (24·3%)	44 (23·3%)	2 (1·1%)	0
Vomiting	136 (36·6%)	121 (32·5%)	15 (4·0%)	0	28 (14·8%)	26 (13·8%)	2 (1·1%)	0	138 (37·1%)	123 (33·1%)	15 (4·0%)	0	29 (15·3%)	27 (14·3%)	2 (1·1%)	0
ALT or AST increased	126 (33·9%)	87 (23·4%)	39 (10·5%)	0	7 (3·7%)	7 (3·7%)	0	0	129 (34·7%)	91 (24·5%)	38 (10·2%)	0	8 (4·2%)	8 (4·2%)	0	0

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Diarrhoea	118 (31.7 32%)	116 (31.2 %)	2 (0.5)1 %)	0	41 (21.7 22%)	39 (20.6 21%)	2 (1.1)%)	0	121 (32.5 33%)	119 (32.0 %)	2 (0.5) (1%)	0	41 (21.7 22%)	39 (20.6 21%)	2 (1.1)%)	0
Abdominal pain	111 (29.8 30%)	102 (27.4 %)	9 (2.4)%)	0	49 (25.9 26%)	48 (25.4 %)	1 (0.5)1 %)	0	112 (30.1 %)	101 (27.2 %)	11 (3.0)%)	0	49 (25.9 26%)	48 (25.4 %)	1 (0.5)1 %)	0
Thrombocytopenia or platelet count decreased	104 (28.0 %)	85 (22.8 23%)	13 (3.5)%)	6 (1.6)2 %)	5 (2.6)3 %)	5 (2.6)3 %)	0	0	109 (29.3 %)	89 (23.9 24%)	13 (3.5)%)	7 (1.9)2 %)	5 (2.6)3 %)	5 (2.6)3 %)	0	0
Decreased appetite	87 (23.4 %)	85 (22.8 23%)	2 (0.5)1 %)	0	26 (13.8 14%)	26 (13.8 14%)	0	0	88 (23.7 24%)	85 (22.8 23%)	3 (0.8)1 %)	0	26 (13.8 14%)	26 (13.8 14%)	0	0
Neutropenia or decreased neutrophil count	67 (18.0 %)	42 (11.3 %)	19 (5.1)%)	6 (1.6)2 %)	9 (4.8)5 %)	7 (3.7)4 %)	1 (0.5)1 %)	1 (0.5)1 %)	72 (19.4 %)	43 (11.6 12%)	22 (5.9)6 %)	7 (1.9)2 %)	9 (4.8)5 %)	7 (3.7)4 %)	1 (0.5) (1%)	1 (0.5)1 %)
Headache	67 (18.0 %)	66 (17.7 18%)	1 (0.3)(< 1%)	0	30 (15.9 16%)	29 (15.3 %)	1 (0.5)1 %)	0	71 (19.1 %)	70 (18.8 19%)	1 (0.3)(< 1%)	0	31 (16.4 %)	30 (15.9 16%)	1 (0.5)1 %)	0
Photosensitivity reaction	64 (17.2 %)	62 (16.7 17%)	2 (0.50) (1%)	0	1 (0.5)1 %)	1 (0.50) (1%)	0	0	68 (18.3 %)	66 (17.7 18%)	2 (0.5)1 %)	0	1 (0.5)1 %)	1 (0.5)1 %)	0	0
Blood creatinine increased	57 (15.3 %)	56 (15.1 %)	1 (0.3)(< 1%)	0	3 (1.6)2 %)	3 (1.6)2 %)	0	0	61 (16.4 %)	60 (16.1 %)	1 (0.3)(< 1%)	0	3 (1.6) (2%)	3 (1.6) (2%)	0	0
Arthralgia	57 (15.3 %)	55 (14.8 15%)	2 (0.5)1 %)	0	24 (12.7 13%)	24 (12.7 13%)	0	0	59 (15.9 16%)	57 (15.3 %)	2 (0.5)1 %)	0	24 (12.7 13%)	24 (12.7 13%)	0	0
Dizziness	54 (14.5 15%)	54 (14.5 15%)	0	0	15 (7.9)8 %)	14 (7.4)%)	1 (0.5)1 %)	0	57 (15.3 %)	57 (15.3 %)	0	0	15 (7.9)8 %)	14 (7.4)%)	1 (0.5)1 %)	0
Cough	54 (14.5 15%)	54 (14.5 15%)	0	0	25 (13.2 %)	25 (13.2 %)	0	0	55 (14.8 15%)	55 (14.8 15%)	0	0	25 (13.2 %)	25 (13.2 %)	0	0
Abdominal pain upper	52 (14.0 %)	50 (13.4 %)	2 (0.5)1 %)	0	10 (5.3)%)	10 (5.3)%)	0	0	54 (14.5 15%)	52 (14.0 %)	2 (0.5)1 %)	0	11 (5.8)6 %)	11 (5.8)6 %)	0	0
Dyspepsia	54 (14.5 15%)	53 (14.2 %)	1 (0.3)(< 1%)	0	9 (4.8)5 %)	9 (4.8)5 %)	0	0	54 (14.5 15%)	53 (14.2 %)	1 (0.3)(< 1%)	0	9 (4.8)5 %)	9 (4.8)5 %)	0	0
Insomnia	53 (14.2 %)	53 (14.2 %)	0	0	15 (7.9)8 %)	15 (7.9)8 %)	0	0	54 (14.5 15%)	54 (14.5 15%)	0	0	15 (7.9)8 %)	15 (7.9)8 %)	0	0
Dyspnoea	50 (13.4 %)	50 (13.4 %)	0	0	14 (7.4)%)	14 (7.4)%)	0	0	53 (14.2 %)	53 (14.2 %)	0	0	14 (7.4)%)	14 (7.4)%)	0	0

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Pruritus	47 (12·6) 13%)	47 (12·6) 13%)	0	0	19 (10·1) %)	19 (10·1) %)	0	0	51 (13·7) 14%)	51 (13·7) 14%)	0	0	20 (10·6) 11%)	20 (10·6) 11%)	0	0
Back pain	45 (12·1) %)	45 (12·1) %)	0	0	28 (14·8) 15%)	28 (14·8) 15%)	0	0	50 (13·4) %)	50 (13·4) %)	0	0	28 (14·8) 15%)	28 (14·8) 15%)	0	0
Rash	46 (12·4) %)	45 (12·1) %)	1 (0·3)(< 1%)	0	17 (9·0)%)	17 (9·0)%)	0	0	50 (13·4) %)	49 (13·2) %)	1 (0·3)(< 1%)	0	17 (9·0)%)	17 (9·0)%)	0	0
Pyrexia	44 (11·8) 12%)	44 (11·8) 12%)	0	0	8 (4·2)%)	8 (4·2)%)	0	0	45 (12·1) %)	45 (12·1) %)	0	0	9 (4·8)5 %)	9 (4·8)5 %)	0	0
Upper respiratory tract infection	41 (11·0) %)	41 (11·0) %)	0	0	6 (3·2)%)	4 (2·1)%)	2 (1·1)%)	0	44 (11·8) 12%)	44 (11·8) 12%)	0	0	6 (3·2)%)	4 (2·1)%)	2 (1·1)%)	0
Hypomagnesaemia	40 (10·8) 11%)	39 (10·5) %)	1 (0·3)(< 1%)	0	11 (5·8)6 %)	11 (5·8)6 %)	0	0	43 (11·6) 12%)	42 (11·3) %)	1 (0·3)(< 1%)	0	11 (5·8)6 %)	11 (5·8)6 %)	0	0
Abdominal distension	41 (11·0) %)	41 (11·0) %)	0	0	22 (11·6) 12%)	22 (11·6) 12%)	0	0	42 (11·3) %)	42 (11·3) %)	0	0	24 (12·7) 13%)	24 (12·7) 13%)	0	0
Oedema peripheral	39 (10·5) %)	38 (10·2) %)	1 (0·3)(< 1%)	0	14 (7·4)%)	14 (7·4)%)	0	0	41 (11·0) %)	40 (10·8) 11%)	1 (0·3)(< 1%)	0	14 (7·4)%)	14 (7·4)%)	0	0
Hypertension	34 (9·1)%)	26 (7·0)%)	8 (2·2)%)	0	16 (8·5)%)	12 (6·3)%)	4 (2·1)%)	0	36 (9·7)1 0%)	27 (7·3)%)	9 (2·4)%)	0	16 (8·5)%)	12 (6·3)%)	4 (2·1)%)	0

Data are n (%).

*~~Excluding disease progression.~~

‡~~Sorted~~Grade 1–2 TEAEs reported in ≥10% of patients and grade 3–4 TEAEs reported in ≥2% of patients in the updated safety analysis; sorted by decreasing incidence in the rucaparib arm ~~of the updated safety analysis~~.

ALT=alanine aminotransferase. AST=aspartate aminotransferase. TEAE=treatment-emergent adverse event.

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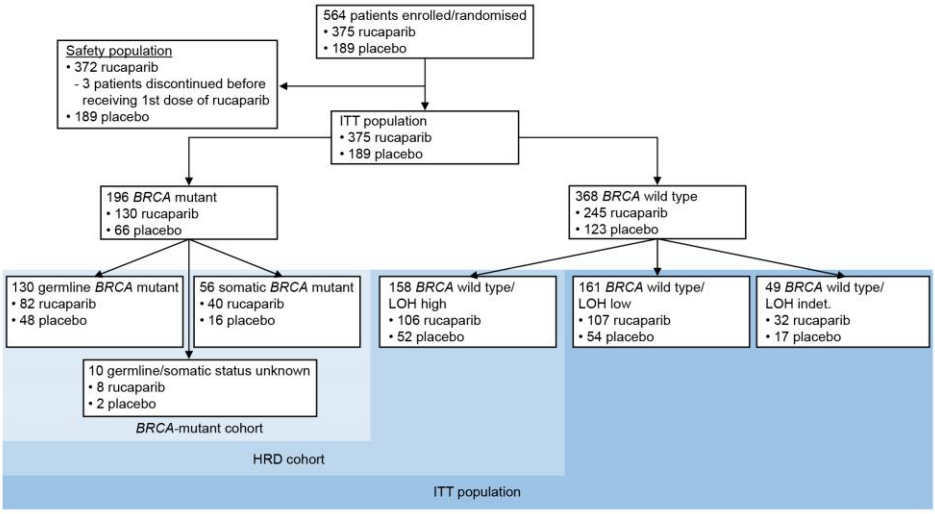
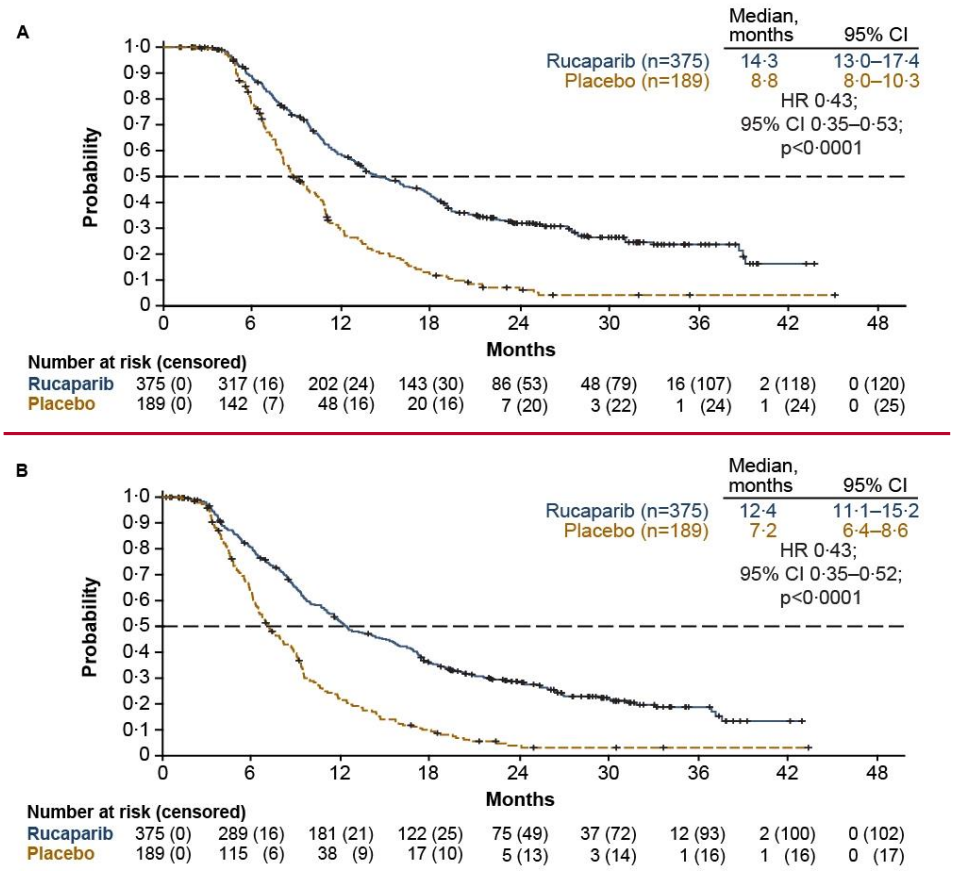
Figure 1: **Efficacy and safety populations**



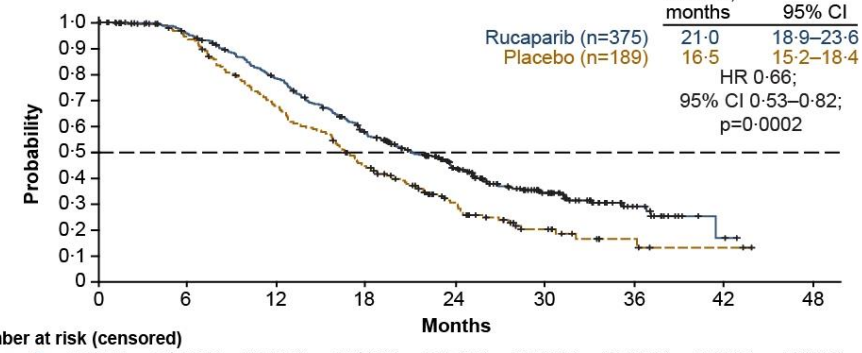
HRD=homologous recombination deficient. indet.=indeterminate. ITT=intention to treat. LOH=loss of heterozygosity.

Adapted by authors of the original material per the Author Rights section of the Elsevier Publishing Agreement, from: Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017; 390(10106): 1949-1961.

Figure 2: **Kaplan-Meier estimates of CFI (A), TFST (B), PFS2 (C), and TSST (D) in the ITT population**



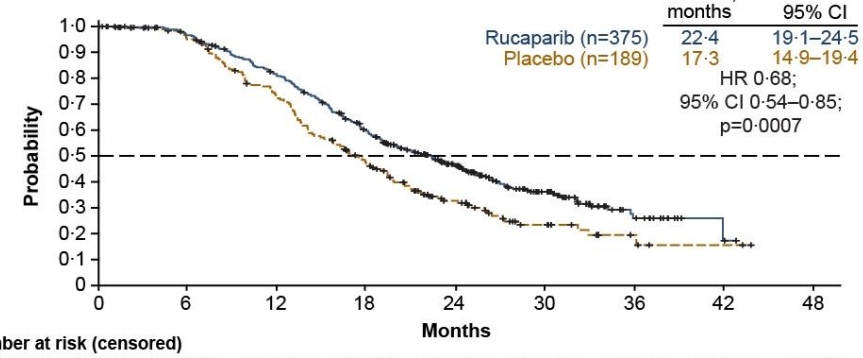
C



Number at risk (censored)

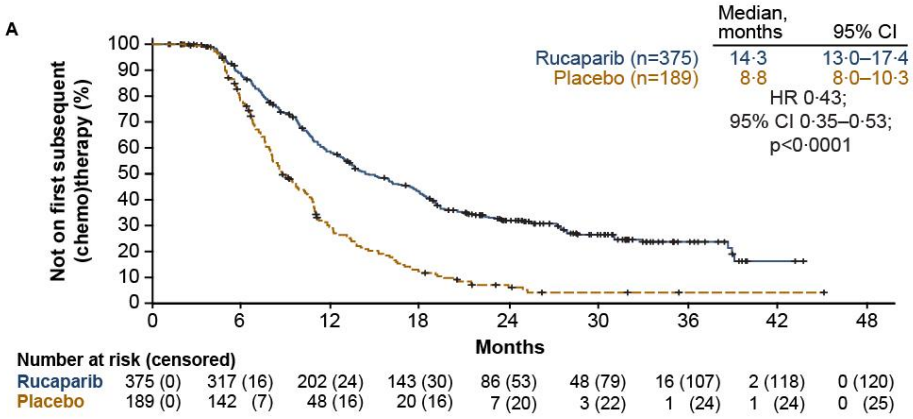
Rucaparib	375 (0)	344 (15)	276 (21)	194 (29)	116 (66)	59 (102)	18 (137)	2 (150)	0 (152)
Placebo	189 (0)	170 (7)	121 (10)	75 (14)	37 (31)	15 (43)	5 (51)	2 (53)	0 (55)

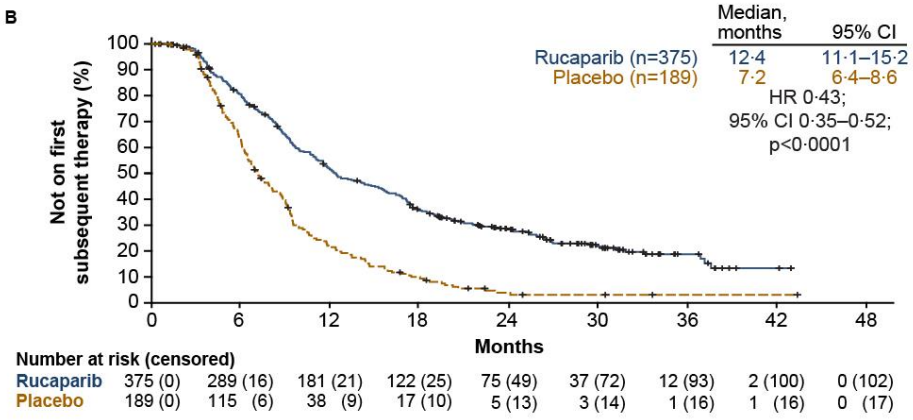
D

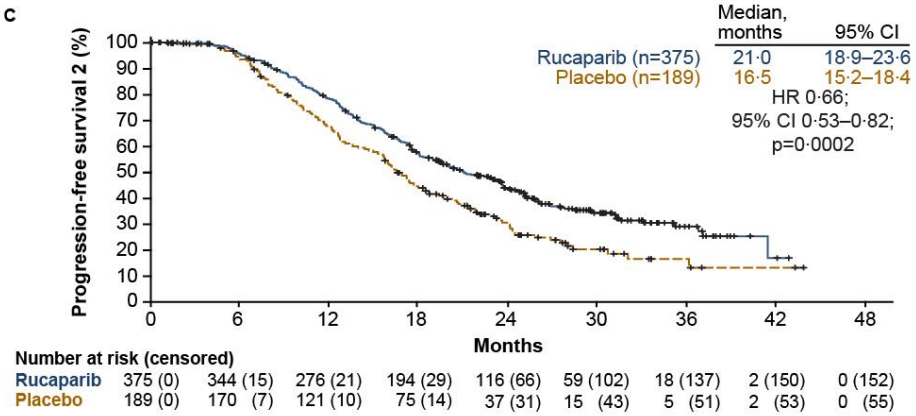


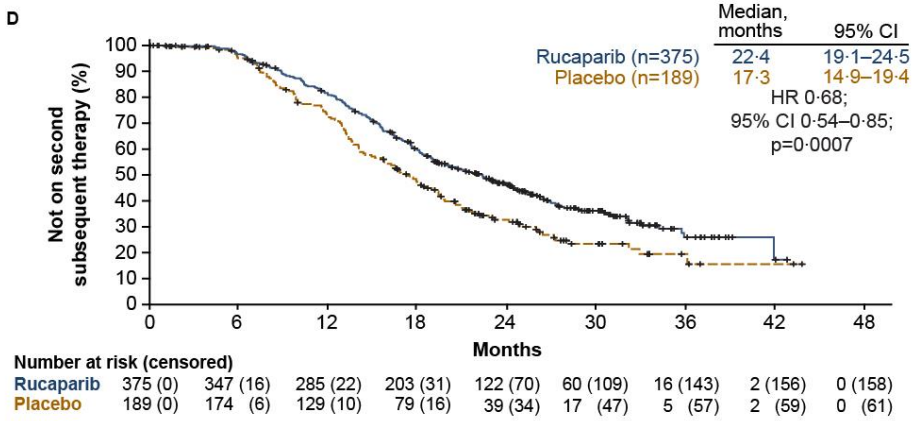
Number at risk (censored)

Rucaparib	375 (0)	347 (16)	285 (22)	203 (31)	122 (70)	60 (109)	16 (143)	2 (156)	0 (158)
Placebo	189 (0)	174 (6)	129 (10)	79 (16)	39 (34)	17 (47)	5 (57)	2 (59)	0 (61)


A
Median, months
95% CI
Rucaparib (n=375) 14·3 13·0–17·4
Placebo (n=189) 8·8 8·0–10·3
HR 0·43;
95% CI 0·35–0·53;
p<0·0001
Not on first subsequent (chemo)therapy (%)
100
90
80
70
60
50
40
30
20
10
0
0 6 12 18 24 30 36 42 48
Months
Number at risk (censored)
Rucaparib 375 (0) 317 (16) 202 (24) 143 (30) 86 (53) 48 (79) 16 (107) 2 (118) 0 (120)
Placebo 189 (0) 142 (7) 48 (16) 20 (16) 7 (20) 3 (22) 1 (24) 1 (24) 0 (25)

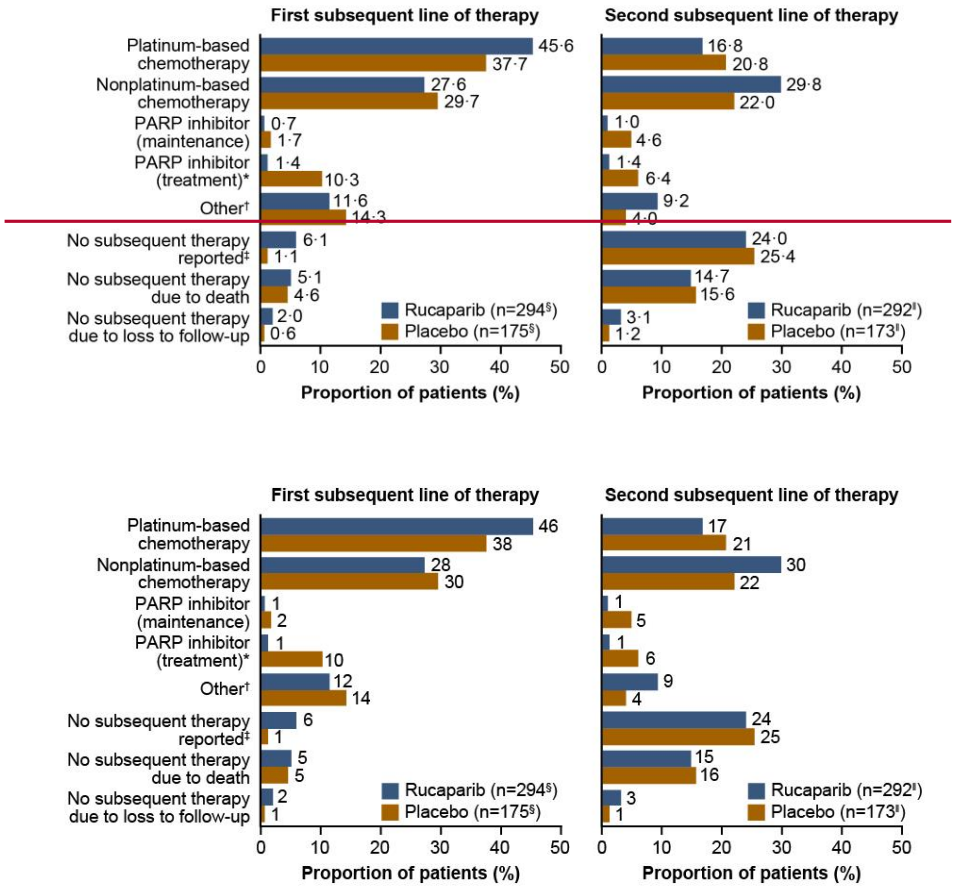

B
Median, months
95% CI
Rucaparib (n=375) 12·4 11·1–15·2
Placebo (n=189) 7·2 6·4–8·6
HR 0·43;
95% CI 0·35–0·52;
p<0·0001
Not on first subsequent therapy (%)
100
90
80
70
60
50
40
30
20
10
0
0 6 12 18 24 30 36 42 48
Months
Number at risk (censored)
Rucaparib 375 (0) 289 (16) 181 (21) 122 (25) 75 (49) 37 (72) 12 (93) 2 (100) 0 (102)
Placebo 189 (0) 115 (6) 38 (9) 17 (10) 5 (13) 3 (14) 1 (16) 1 (16) 0 (17)





CFI=chemotherapy-free interval. HR=hazard ratio. ITT=intention to treat. PFS2=time to disease progression on subsequent therapy or death. TFST=time to start of first subsequent therapy. TSST=time to start of second subsequent therapy.

Figure 3: **First and second subsequent lines of therapy for the ITT population**



Visit cutoff 31 December 2017.

Values in graph are shown as % rounded to nearest whole number.

*As first subsequent therapy, three patients received olaparib plus cediranib (rucaparib, n=1; placebo, n=2), two received olaparib plus durvalumab (placebo, n=2), and one received olaparib plus radiotherapy (rucaparib, n=1); as second subsequent therapy, one patient received olaparib plus cediranib (rucaparib, n=1) and one received olaparib plus vistusertib (placebo, n=1).

†Other includes: VEGF inhibitor; hormonal therapy; immunotherapy; investigational treatment (unspecified); radiation; and hyperthermic intraperitoneal chemotherapy.

‡Patient may not have started any subsequent treatment as of the visit cutoff or was transferred to palliative care.

§Eligible patients who discontinued from ARIEL3, excludes 21 patients from the rucaparib group and 9 patients from the placebo group who withdrew consent during treatment or follow-up.

‖Eligible patients who discontinued from ARIEL3, excludes 23 patients from the rucaparib group and 11 patients from the placebo group who withdrew consent during treatment or follow-up.

ITT=intention to treat. PARP=poly(ADP-ribose) polymerase. VEGF=vascular endothelial growth factor.

Online Supplementary Appendix

Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): postprogression outcomes and updated safety from a randomised, placebo-controlled, phase 3 trial

Jonathan A Ledermann, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew R Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Susana Banerjee, Jesus García-Donas, Elizabeth M Swisher, Terri Cameron, Lara Maloney, Sandra Goble, Robert L Coleman

Table of Contents

ARIEL3 CENTRES

Principal Investigator	Site	Patients enrolled
Oza, Amit	Princess Margaret Cancer Centre, University Health Network, Toronto, Canada	28
Lorusso, Domenica	Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy	25
Aghajanian, Carol	Memorial Sloan Kettering Cancer Center, New York, USA	13
	Memorial Sloan Kettering Cancer Center, Rockville Centre, USA	3
	Memorial Sloan Kettering at Phelps Memorial Hospital Center, Sleepy Hollow, USA	3
	Memorial Sloan Kettering Cancer Center, Basking Ridge, USA	2
Coleman, Robert	The University of Texas MD Anderson Cancer Center, Houston, USA	20
Oaknin, Ana	Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain	19
Ledermann, Jonathan	UCL Cancer Institute, University College London and UCL Hospitals, London, UK	18
Colombo, Nicoletta	University of Milan-Bicocca and European Institute of Oncology (IEO), Milan, Italy	16
Weberpals, Johanne	Ottawa Hospital Research Institute, Ottawa, Canada	16
Dean, Andrew	Saint John of God Subiaco Hospital, Subiaco, Australia	16

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Principal Investigator	Site	Patients enrolled
Clamp, Andrew	The Christie NHS Foundation Trust and University of Manchester, Manchester, UK	15
Scambia, Giovanni	Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy	14
Leary, Alexandra	Gustave Roussy Cancer Center, INSERM U981, and Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), Villejuif, France	13
Holloway, Robert	Florida Hospital Cancer Care, Orlando, USA	12
Fong, Peter	Auckland City Hospital, Auckland, New Zealand	11
Goh, Jeffrey	Royal Brisbane and Women's Hospital, Herston, Australia	11
Amenedo Gancedo, Margarita	Oncology Center of Galicia, La Coruña, Spain	11
O'Malley, David	The Ohio State University, James Cancer Center, Columbus, USA	11
Armstrong, Deborah	Johns Hopkins University School of Medicine, Baltimore, USA	10
Swisher, Elizabeth	University of Washington, Seattle, USA	10
García-Donas, Jesus	HM Hospitales—Centro Integral Oncológico Hospital de Madrid Clara Campal, Madrid, Spain	10
Banerjee, Susana	Royal Marsden Hospital, Sutton, UK	5
	The Royal Marsden NHS Foundation Trust, London, UK	5
Floquet, Anne	Institut Bergonié, Bordeaux, France	9
Scott, Clare	Peter MacCallum Cancer Centre, Melbourne, Australia	9
McNeish, Iain	Beatson West of Scotland Cancer Centre, Glasgow, UK	9
Lortholary, Alain	Centre Catherine de Sienne, Nantes, France	8
Chen, Lee-may	University of California San Francisco, San Francisco, USA	8
Tredan, Olivier	Centre Léon Bérard, Lyon, France	8
You, Benoit	Centre Hospitalier Lyon Sud, Pierre-Benite, France	8
Morris, Robert	Karmanos Cancer Institute, Detroit, USA	8
Provencher, Diane	Centre Hospitalier de L'Université de Montréal, Montréal, Canada	7
Harnett, Paul	Westmead Hospital, Westmead, Australia	7
Medioni, Jacques	Hôpital Européen Georges Pompidou, Paris, France	7
Parkinson, Christine	Addenbrooke's Hospital, Cambridge, UK	7
Pignata, Sandro	Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy	6
Welch, Stephen	London Regional Cancer Centre, London, Canada	6
Vergote, Ignace	Universitair Ziekenhuis Leuven, Leuven, Belgium	6
Konecny, Gottfried	University of California Los Angeles, Los Angeles, USA	6
Ghatage, Prafull	Tom Baker Cancer Center, Calgary, Canada	6
Elit, Laurie	Juravinski Cancer Centre, Hamilton, Canada	6
Denys, Hannelore	Universitair Ziekenhuis Gent, Gent, Belgium	5
Plante, Marie	Centre Hospitalier Universitaire de Quebec, Quebec, Canada	5
Leviov, Michelle	The Lady Davis Carmel Medical Center, Haifa, Israel	5
Shapira-Frommer, Ronnie	Chaim Sheba Medical Center, Tel HaShomer, Israel	4
Birrer, Michael	Massachusetts General Hospital, Boston, USA	4
Chambers, Setsuko	University of Arizona Cancer Center, Tucson, USA	4
Friedlander, Michael	Prince of Wales Hospital, Randwick, Australia	4
Sabbatini, Roberto	Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy	4
Morgan, Mark	University of Pennsylvania, Philadelphia, USA	4
Tamberi, Stefano	Ospedale Civile degli Infermi, Faenza, Italy	4
Guerra, Eva María	Hospital Ramón y Cajal, Madrid, Spain	4
Wimberger, Pauline	Technische Universität Dresden, Dresden, Germany	4
Amit, Amnon	Rambam Medical Center, Haifa, Israel	4

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Principal Investigator	Site	Patients enrolled
Casado Herraez, Antonio	Hospital San Carlos Madrid, Madrid, Spain	4
Gladieff, Laurence	Institut Claudius Régaud, Toulouse, France	3
Kichenadasse, Ganessan	Flinders Medical Centre, Bedford Park, Australia	3
Ma, Ling	Rocky Mountain Cancer Centers, Lakewood, USA	3
Buck, Martin	Sir Charles Gairdner Hospital, Nedlands, USA	3
Zamagni, Claudio	Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy	3
Dirix, Luc	AZ Sint Augustinus, Antwerp, Belgium	3
Jackson, David	Saint James's University Hospital, Leeds, UK	3
Buss, Mary	Beth Israel Deaconess Medical Center, Boston, USA	2
Krabisch, Petra	Klinikum Chemnitz gGmbH, Chemnitz, Germany	2
Kovel, Svetlana	Assaf Harofeh Medical Center, Zerifin, Israel	2
Powell, Melanie	Saint Bartholomew's Hospital, London, UK	2
O'Donnell, Anne	Wellington Regional Hospital, Wellington, New Zealand	2
Neunhöffer, Tanja	HELIOS Dr. Horst Schmidt Kliniken Wiesbaden, Klinik für Gynäkologie und Gyn. Onkologie, Wiesbaden, Germany	2
Lotz, Jean-Pierre	Hôpital Tenon, Paris, France	2
Romero, Ignacio	Instituto Valenciano de Oncología, Valencia, Spain	2
Vanderkwaak, Timothy	Hope Women's Cancer Centers, Asheville, USA	2
Safra, Tamar	Tel Aviv Sourasky Medical Center, Tel Aviv, Israel	2
Gabra, Hani	Imperial College Healthcare NHS Trust	2
Sánchez, Alfonso	Hospital Regional Universitario Carlos Haya de Málaga, Málaga, Spain	2
Stemmer, Salomon	Rabin Medical Center, Petah Tikva, Israel	2
Hänle, Claudia	Klinikum Ludwigsburg-Bietigheim gGmbH, Ludwigsburg, Germany	1
Bologna, Alessandra	Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy	1
Mutch, David	Washington University School of Medicine, Saint Louis, USA	1
Joly, Florence	Cancer François Baclesse, Caen, France	1
Palacio, Isabel	Hospital Universitario Central de Asturias, Asturias, Spain	1
Slomovitz, Brian	Sylvester Comprehensive Cancer Center, Miami, USA	1
Drew, Yvette	Freeman Hospital - Northern Centre for Cancer Care, Newcastle upon Tyne, UK	1
Pölcher, Martin	Rotkreuzklinikum München gGmbH, Munich, Germany	1
Vulfovich, Michel	Memorial Healthcare System, Hollywood, USA	1
El-Balat, Ahmed	Universitätsklinikum Frankfurt, Frankfurt, Germany	1
Total		**564**

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SUPPLEMENTAL RESULTS

***~~Table S1~~Table S1:* Summary of TEAEs in the safety population: comparison of previously reported and updated data**

	Previous report*: 15 Apr 2017 visit cutoff date		Updated data: 31 Dec 2017 visit cutoff date	
	Rucaparib (n=372)	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**
Any grade TEAE	372 (100%)	182 (96%)	372 (100%)	182 (96%)
Grade ≥3 TEAE	209 (56%)	28 (15%)	222 (60%)	30 (16%)
Treatment interruption and/or dose reduction	263 (71%)	20 (11%)	267 (72%)	20 (11%)
Treatment interruption due to a TEAE	237 (64%)	19 (10%)	243 (65%)	19 (10%)
Dose reduction due to a TEAE	203 (55%)	8 (4%)	206 (55%)	8 (4%)
Discontinuation due to a TEAE†	50 (13%)	3 (2%)	57 (15%)	3 (2%)
Deaths relating to a TEAE	6 (2%)	2 (1%)	7 (2%)	2 (1%)

Data are n (%).
*Coleman RL et al. *Lancet*. 2017; 390(10106): 1949-1961.
†Excluding disease progression.
TEAE=treatment-emergent adverse event.

***Table S2*: Grade 3 or higher TEAEs occurring in at least one patient in the safety population (31 Dec 2017 visit cutoff date)**

	Rucaparib (n=372)			Placebo (n=189)		
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
TEAE						
Anaemia or haemoglobin decreased	77 (20·7)21 %)	3 (0·8)1%)	0	0	1 (0·5)1%)	0
ALT or AST increased	38 (10·2)%)	0	0	0	0	0
Neutropenia or neutrophil count decreased	22 (5·9)6%)	7 (1·9)2%)	0	1 (0·5)1%)	1 (0·5)1%)	0
Asthenia or fatigue	26 (7·0)%)	0	0	5 (2·6)3%)	0	0
Thrombocytopenia or platelet count decreased	13 (3·5)%)	7 (1·9)2%)	0	0	0	0
Vomiting	15 (4·0)%)	0	0	2 (1·1)%)	0	0
Nausea	14 (3·8)4%)	0	0	1 (0·5)1%)	0	0
Abdominal pain	11 (3·0)%)	0	0	1 (0·5)1%)	0	0
Hypertension	9 (2·4)%)	0	0	4 (2·1)%)	0	0
Constipation	7 (1·9)2%)	0	0	2 (1·1)%)	0	0
Febrile neutropenia	0	5 (1·3)%)	0	0	0	0
Malignant neoplasm progression	3 (0·8)1%)	0	2 (0·5)1%)	2 (1·1)%)	0	0
Transaminases increased	5 (1·3)%)	0	0	0	0	0
White blood cell count decreased	4 (1·1)%)	1 (0·3)(<1 %)	0	0	0	0
Dehydration	4 (1·1)%)	0	0	0	0	0
Intestinal obstruction	4 (1·1)%)	0	0	1 (0·5)1%)	1 (0·5)1%)	0
Small intestinal obstruction	3 (0·8)1%)	1 (0·3)(<1 %)	0	4 (2·1)%)	0	0
Weight decreased	4 (1·1)%)	0	0	0	0	0
Decreased appetite	3 (0·8)1%)	0	0	0	0	0
Gamma-glutamyltransferase increased	3 (0·8)1%)	0	0	0	0	0
Pancytopenia	2 (0·5)1%)	1 (0·3)(<1 %)	0	0	0	0
Pulmonary embolism	2 (0·5)1%)	1 (0·3)(<1 %)	0	0	0	1 (0·5)1%)
Urinary tract obstruction	3 (0·8)1%)	0	0	0	0	0
Abdominal pain upper	2 (0·5)1%)	0	0	0	0	0
Acute kidney injury	1 (0·3)(<1 %)	1 (0·3)(<1 %)	0	0	0	0
Arthralgia	2 (0·5)1%)	0	0	0	0	0
Ascites	2 (0·5)1%)	0	0	1 (0·5)1%)	0	0

	Rucaparib (n=372)			Placebo (n=189)		
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
Cell death	2 (~~0·5~~1%)	0	0	0	0	0
Diarrhoea	2 (~~0·5~~1%)	0	0	2 (1~~·1~~%)	0	0
Gastroenteritis	2 (~~0·5~~1%)	0	0	0	0	0
Hepatic enzyme increased	2 (~~0·5~~1%)	0	0	0	0	0
Incarcerated hernia	1 (~~0·3~~)(<1 %)	1 (~~0·3~~)(<1 %)	0	0	0	0
Lethargy	2 (~~0·5~~1%)	0	0	0	0	0
Leukopenia	2 (~~0·5~~1%)	0	0	0	0	0
Lymphocyte count decreased	2 (~~0·5~~1%)	0	0	0	0	0
Lymphoedema	2 (~~0·5~~1%)	0	0	0	0	0
Mucosal inflammation	2 (~~0·5~~1%)	0	0	1 (~~0·5~~1%)	0	0
Myelodysplastic syndrome	0	1 (~~0·3~~)(<1 %)	1 (~~0·3~~)(<1 %)	0	0	0
Photosensitivity reaction	2 (~~0·5~~1%)	0	0	0	0	0
Sepsis	0	2 (~~0·5~~1%)	0	0	0	0
Syncope	2 (~~0·5~~1%)	0	0	0	0	0
Urinary tract infection	2 (~~0·5~~1%)	0	0	1 (~~0·5~~1%)	0	0
Abdominal hernia	1 (~~0·3~~)(<1 %)	0	0	0	0	0
Acute myeloid leukaemia	0	0	1 (~~0·3~~)(<1 %)	0	0	0
Acute pulmonary oedema	1 (~~0·3~~)(<1 %)	0	0	0	0	0
Acute respiratory distress syndrome	0	1 (~~0·3~~)(<1 %)	0	0	0	0
Anxiety	1 (~~0·3~~)(<1 %)	0	0	0	0	0
Arthritis infective	1 (~~0·3~~)(<1 %)	0	0	0	0	0
Atrial fibrillation	1 (~~0·3~~)(<1 %)	0	0	0	0	0
Atypical pneumonia	1 (~~0·3~~)(<1 %)	0	0	0	0	0
B-cell unclassifiable lymphoma high grade	0	0	1 (~~0·3~~)(<1 %)	0	0	0
Bile duct obstruction	1 (~~0·3~~)(<1 %)	0	0	0	0	0

	Rucaparib (n=372)			Placebo (n=189)		
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
Blood cholesterol increased	1 (0·3)(<1 %)	0	0	0	0	0
Blood creatinine increased	1 (0·3)(<1 %)	0	0	0	0	0
Bowen's disease	1 (0·3)(<1 %)	0	0	0	0	0
Cardiac arrest	0	0	1 (0·3)(<1 %)	0	0	0
Cellulitis	1 (0·3)(<1 %)	0	0	0	0	0
Cholecystisis	1 (0·3)(<1 %)	0	0	0	0	0
Cholelithiasis	1 (0·3)(<1 %)	0	0	0	0	0
Cholestasis	0	1 (0·3)(<1 %)	0	0	0	0
Cognitive disorder	1 (0·3)(<1 %)	0	0	0	0	0
Colonic pseudo-obstruction	1 (0·3)(<1 %)	0	0	0	0	0
Creatinine renal clearance increased	1 (0·3)(<1 %)	0	0	0	0	0
Device related infection	1 (0·3)(<1 %)	0	0	0	0	0
Drug-induced liver injury	0	1 (0·3)(<1 %)	0	0	0	0
Duodenal obstruction	1 (0·3)(<1 %)	0	0	0	0	0
Dyslipidaemia	1 (0·3)(<1 %)	0	0	0	0	0
Dyspepsia	1 (0·3)(<1 %)	0	0	0	0	0
Exostosis	1 (0·3)(<1 %)	0	0	0	0	0
Faecaloma	1 (0·3)(<1 %)	0	0	0	0	0
Female genital tract fistula	0	1 (0·3)(<1 %)	0	0	0	0
Femoral neck fracture	1 (0·3)(<1 %)	0	0	1 (0·5)1%)	0	0
Femur fracture	1 (0·3)(<1 %)	0	0	0	0	0

	Rucaparib (n=372)			Placebo (n=189)		
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
Fibula fracture	1 (0·3)(<1 %)	0	0	0	0	0
Gastrointestinal pain	1 (0·3)(<1 %)	0	0	0	0	0
Gastrointestinal stoma output increased	1 (0·3)(<1 %)	0	0	0	0	0
General physical health deterioration	1 (0·3)(<1 %)	0	0	0	0	0
Glomerular filtration rate decreased	1 (0·3)(<1 %)	0	0	0	0	0
Haematocrit decreased	1 (0·3)(<1 %)	0	0	0	0	0
Headache	1 (0·3)(<1 %)	0	0	1 (0·5)1%)	0	0
Hepatic failure	1 (0·3)(<1 %)	0	0	0	0	0
Histiocytosis haematophagic	0	0	1 (0·3)(<1 %)	0	0	0
Hypercholesterolaemia	0	1 (0·3)(<1 %)	0	0	0	0
Hypernatraemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypertransaminasaemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypertriglyceridaemia	1 (0·3)(<1 %)	0	0	0	0	0
Hyperuricaemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypoacusis	1 (0·3)(<1 %)	0	0	0	0	0
Hypoalbuminaemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypocalcaemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypokalaemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypomagnesaemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypophosphataemia	1 (0·3)(<1 %)	0	0	0	0	0
Hypotension	1 (0·3)(<1 %)	0	0	0	0	0

	Rucaparib (n=372)			Placebo (n=189)		
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion related reaction	1 (0·3)(<1 %)	0	0	0	0	0
Jaundice	1 (0·3)(<1 %)	0	0	0	0	0
Leukocytosis	1 (0·3)(<1 %)	0	0	1 (0·5)1%)	0	0
Lower respiratory tract infection	1 (0·3)(<1 %)	0	0	0	0	0
Malignant bowel obstruction	1 (0·3)(<1 %)	0	0	0	0	0
Muscular weakness	1 (0·3)(<1 %)	0	0	0	0	0
Neutropenic colitis	1 (0·3)(<1 %)	0	0	0	0	0
Oedema peripheral	1 (0·3)(<1 %)	0	0	0	0	0
Oral herpes	1 (0·3)(<1 %)	0	0	0	0	0
Osteoarthritis	1 (0·3)(<1 %)	0	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	1 (0·3)(<1 %)	0	0	0	0	0
Pelvic pain	1 (0·3)(<1 %)	0	0	0	0	0
Pericardial effusion	0	1 (0·3)(<1 %)	0	0	0	0
Pleural effusion	1 (0·3)(<1 %)	0	0	0	0	0
Pyelonephritis	0	1 (0·3)(<1 %)	0	0	0	0
Rash	1 (0·3)(<1 %)	0	0	0	0	0
Renal failure	1 (0·3)(<1 %)	0	0	0	0	0
Renal impairment	1 (0·3)(<1 %)	0	0	0	0	0
Sciatica	1 (0·3)(<1 %)	0	0	0	0	0
Seizure	1 (0·3)(<1 %)	0	0	0	0	0
Squamous cell carcinoma of lung	1 (0·3)(<1 %)	0	0	0	0	0

	Rucaparib (n=372)			Placebo (n=189)		
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
Tibia fracture	1 (0·3)(<1 %)	0	0	0	0	0
Tonsilitis	1 (0·3)(<1 %)	0	0	0	0	0
Tooth abscess	1 (0·3)(<1 %)	0	0	0	0	0
Toothache	1 (0·3)(<1 %)	0	0	0	0	0
Traumatic fracture	1 (0·3)(<1 %)	0	0	0	0	0
Type 2 diabetes mellitus	1 (0·3)(<1 %)	0	0	0	0	0
Viral infection	1 (0·3)(<1 %)	0	0	0	0	0
Viral upper respiratory tract infection	1 (0·3)(<1 %)	0	0	0	0	0
Wound complication	1 (0·3)(<1 %)	0	0	0	0	0
Upper respiratory tract infection	0	0	0	2 (1·1%)	0	0
Abnormal behaviour	0	0	0	1 (0·5)1%)	0	0
Blepharitis	0	0	0	1 (0·5)1%)	0	0
Bone pain	0	0	0	1 (0·5)1%)	0	0
Cataract	0	0	0	1 (0·5)1%)	0	0
Dizziness	0	0	0	1 (0·5)1%)	0	0
Forearm fracture	0	0	0	1 (0·5)1%)	0	0
Hyponatraemia	0	0	0	1 (0·5)1%)	0	0
Incisional hernia	0	0	0	1 (0·5)1%)	0	0
Lung infection	0	0	0	1 (0·5)(1%)	0	0
Metastases to meninges	0	0	0	0	0	1 (0·5)1%)
Sinus bradycardia	0	0	0	1 (0·5)1%)	0	0
Stoma site infection	0	0	0	1 (0·5)1%)	0	0

Data are n (%).
*Sorted by decreasing incidence of grade ≥3 TEAEs in the rucaparib arm of the updated safety analysis.
ALT=alanine aminotransferase. AST=aspartate aminotransferase. TEAE=treatment-emergent adverse event.

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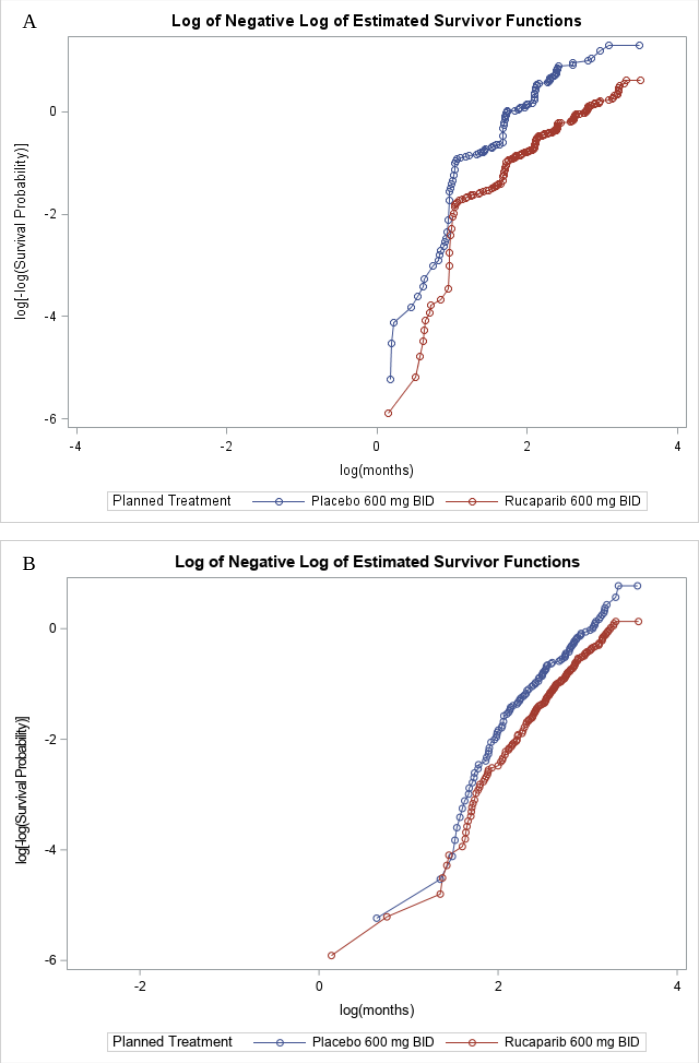
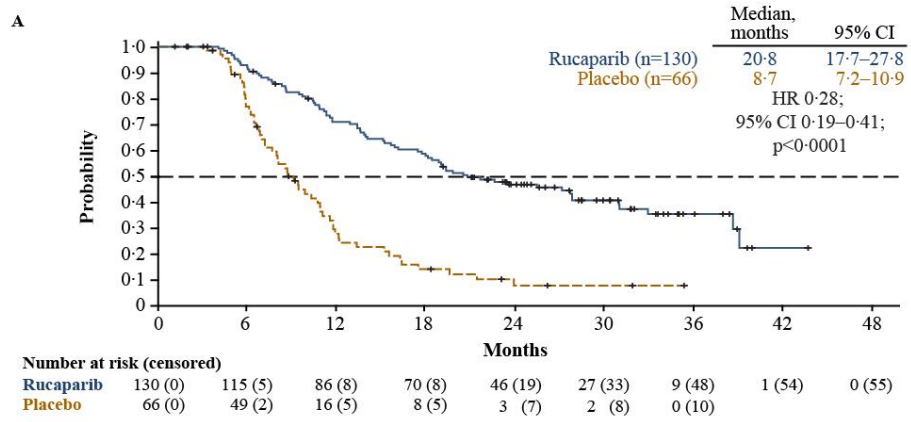
Figure S1: **Plots of the log of the cumulative hazard**

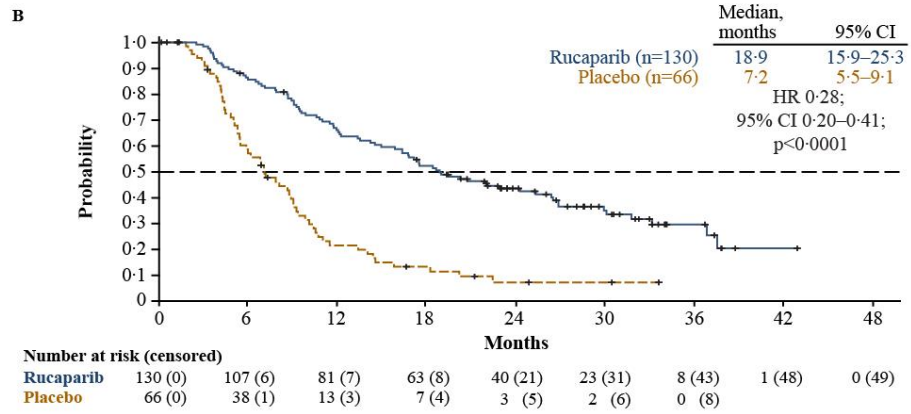
Log-log plots of the time to investigator-assessed disease progression or death during ARIEL3 (PFS1; A) and the time to investigator-assessed disease progression on subsequent therapy or death (PFS2; B) in the rucaparib (red) and placebo (blue) groups for patients in the intention-to-treat population.



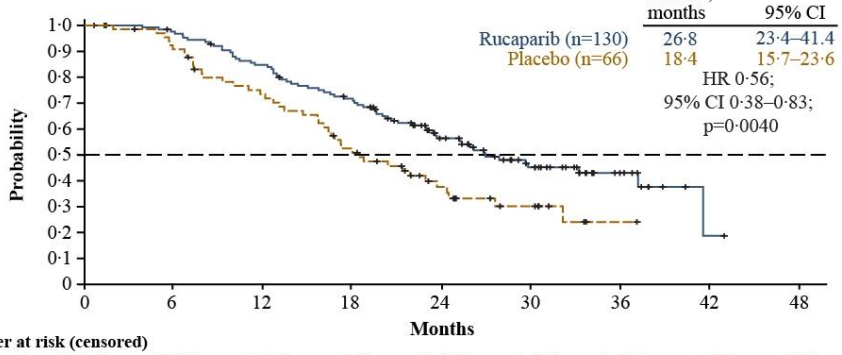
BID=twice daily.

Figure S2: **Kaplan-Meier estimates of CFI (A), TFST (B), PFS2 (C), and TSST (D) in the *BRCA*-mutant cohort**



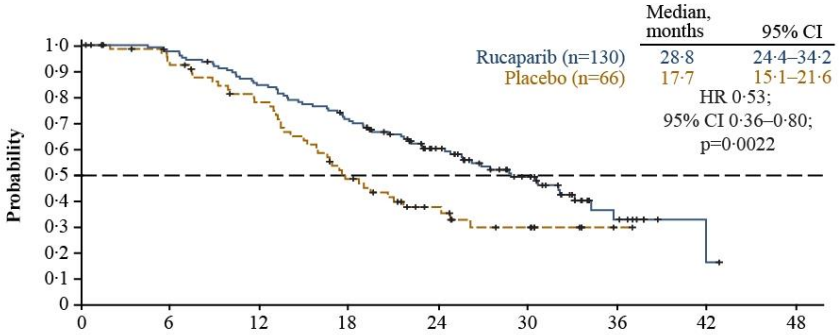


C

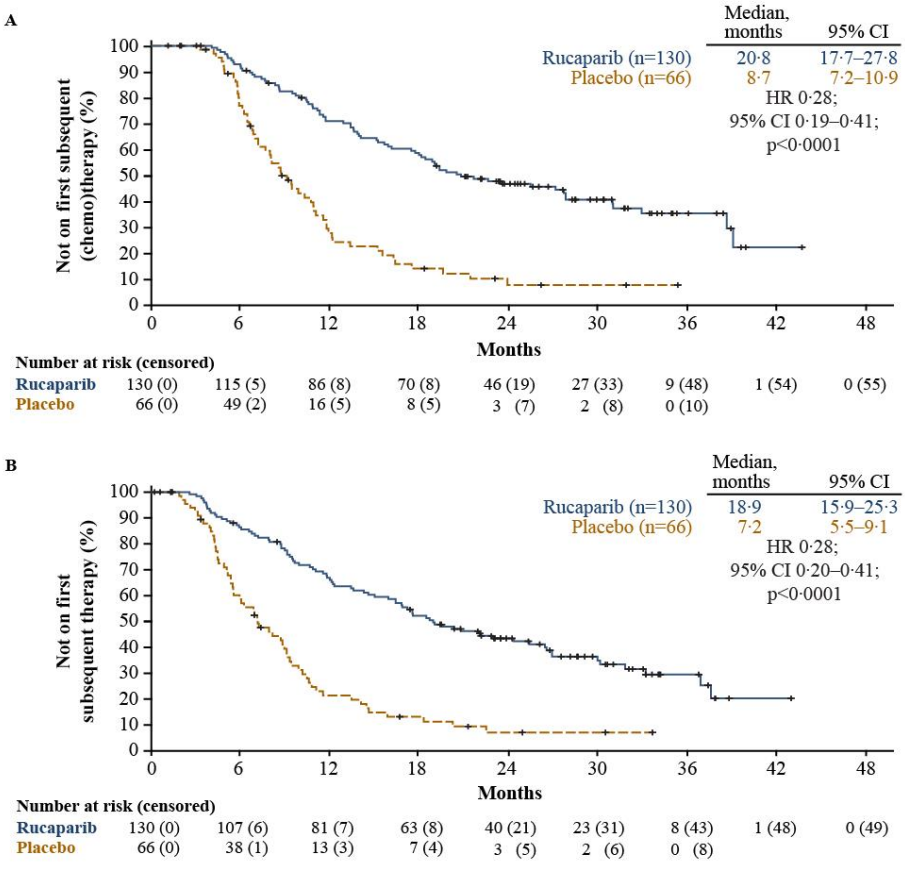


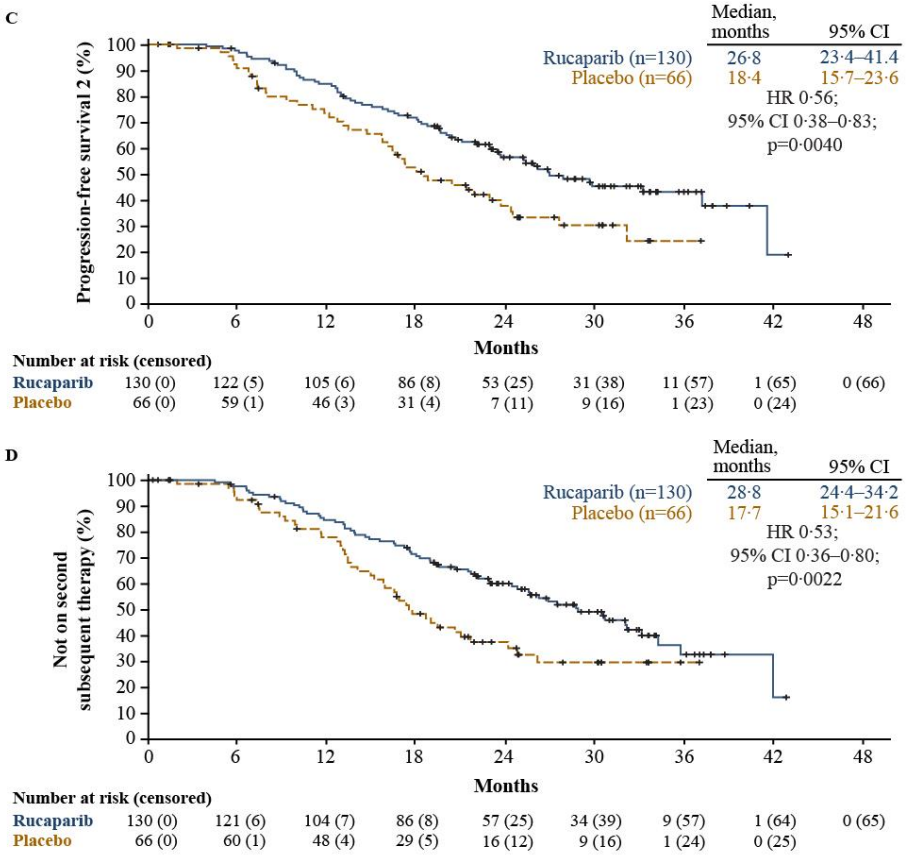
Number at risk (censored)									
Rucaparib	130 (0)	122 (5)	105 (6)	86 (8)	53 (25)	31 (38)	11 (57)	1 (65)	0 (66)
Placebo	66 (0)	59 (1)	46 (3)	31 (4)	7 (11)	9 (16)	1 (23)	0 (24)	

D



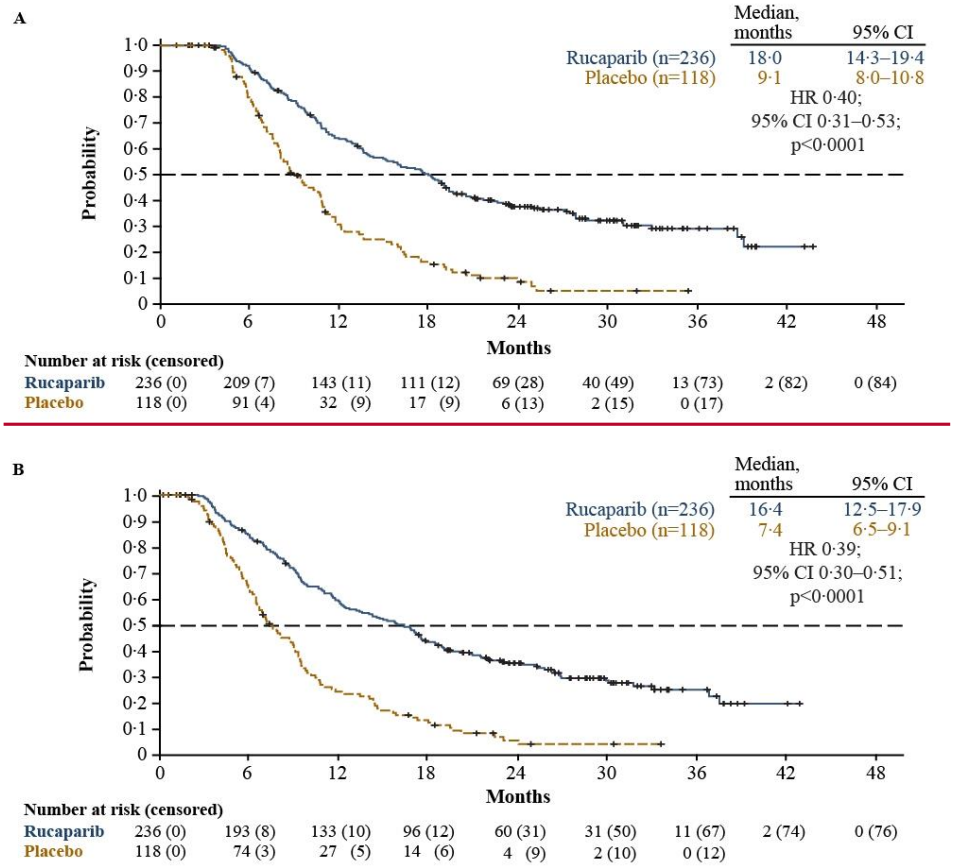
Number at risk (censored)									
Rucaparib	130 (0)	121 (6)	104 (7)	86 (8)	57 (25)	34 (39)	9 (57)	1 (64)	0 (65)
Placebo	66 (0)	60 (1)	48 (4)	29 (5)	16 (12)	9 (16)	1 (24)	0 (25)	


A
Median, months
95% CI
Rucaparib (n=130) 20·8 17·7–27·8
Placebo (n=66) 8·7 7·2–10·9
HR 0·28;
95% CI 0·19–0·41;
p<0·0001
Not on first subsequent (chemo)therapy (%)
Months
Number at risk (censored)
Rucaparib 130 (0) 115 (5) 86 (8) 70 (8) 46 (19) 27 (33) 9 (48) 1 (54) 0 (55)
Placebo 66 (0) 49 (2) 16 (5) 8 (5) 3 (7) 2 (8) 0 (10)
B
Median, months
95% CI
Rucaparib (n=130) 18·9 15·9–25·3
Placebo (n=66) 7·2 5·5–9·1
HR 0·28;
95% CI 0·20–0·41;
p<0·0001
Not on first subsequent therapy (%)
Months
Number at risk (censored)
Rucaparib 130 (0) 107 (6) 81 (7) 63 (8) 40 (21) 23 (31) 8 (43) 1 (48) 0 (49)
Placebo 66 (0) 38 (1) 13 (3) 7 (4) 3 (5) 2 (6) 0 (8)

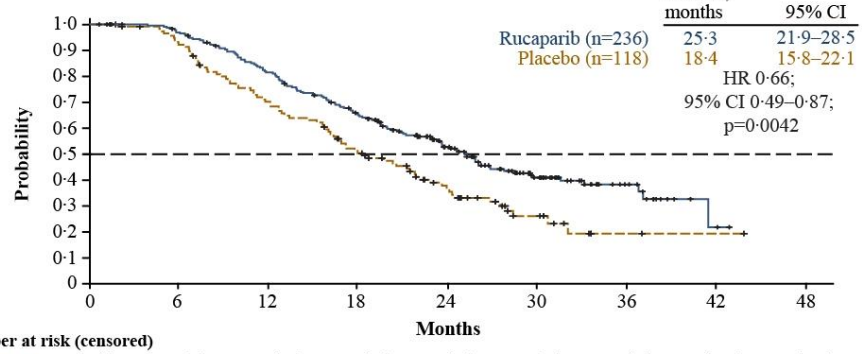


CFI=chemotherapy-free interval. HR=hazard ratio. PFS2=time to disease progression on subsequent therapy or death. TFST=time to start of first subsequent therapy. TSST=time to start of second subsequent therapy.

Figure S3: **Kaplan-Meier estimates of CFI (A), TFST (B), PFS2 (C), and TSST (D) in the HRD cohort**

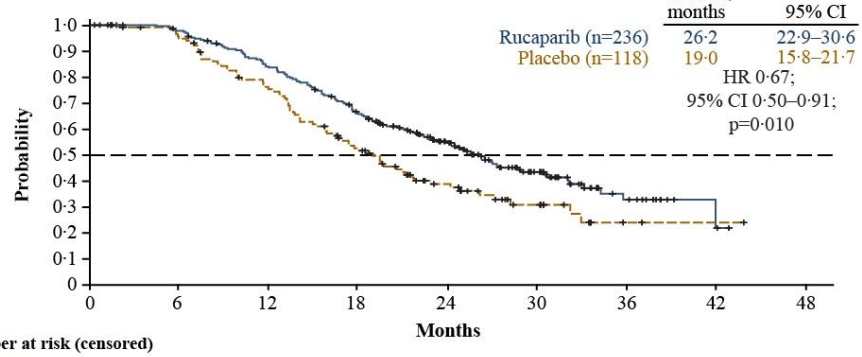


C

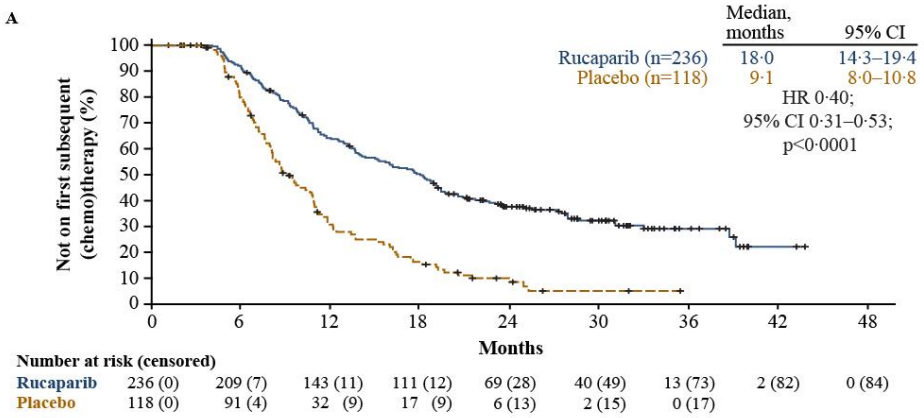


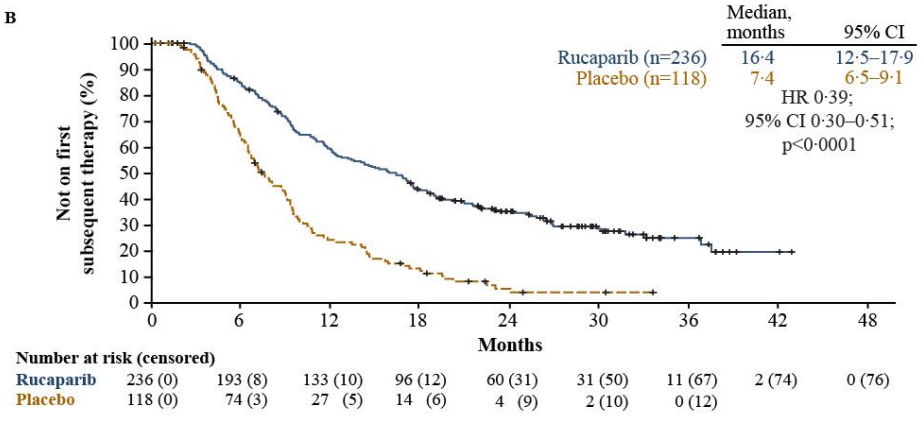
Number at risk (censored)									
Rucaparib	236 (0)	222 (7)	184 (10)	142 (15)	88 (45)	45 (71)	16 (98)	2 (109)	0 (111)
Placebo	118 (0)	106 (3)	79 (5)	54 (8)	31 (18)	12 (30)	2 (38)	1 (39)	0 (40)

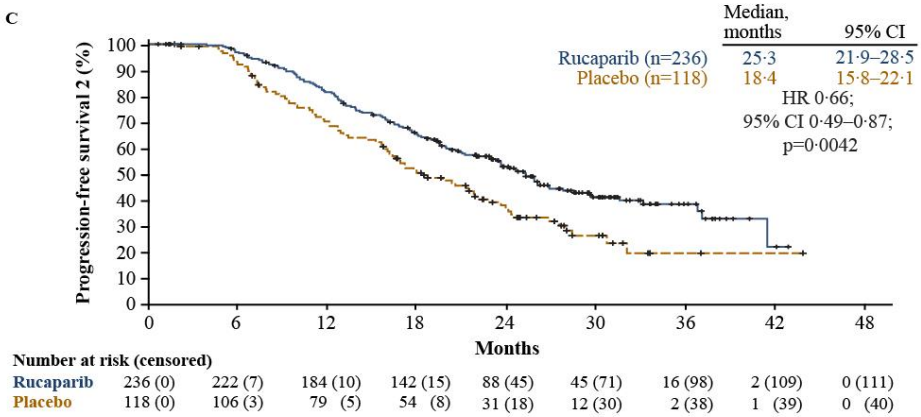
D

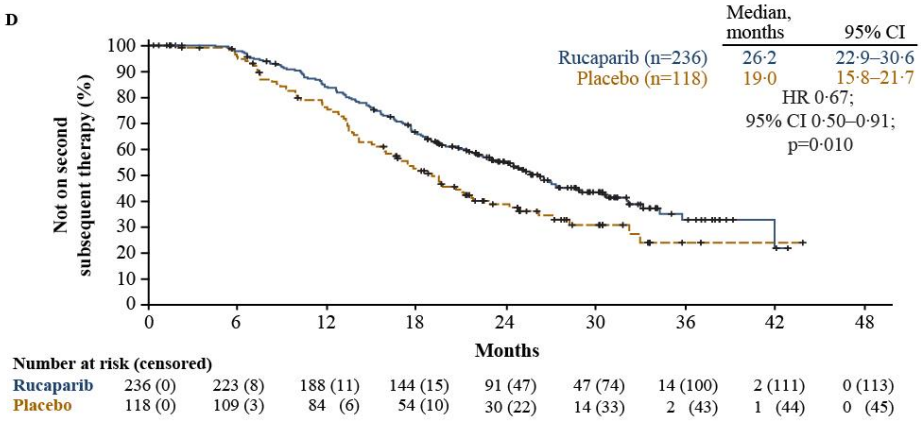


Number at risk (censored)									
Rucaparib	236 (0)	223 (8)	188 (11)	144 (15)	91 (47)	47 (74)	14 (100)	2 (111)	0 (113)
Placebo	118 (0)	109 (3)	84 (6)	54 (10)	30 (22)	14 (33)	2 (43)	1 (44)	0 (45)


A
Median, months
95% CI
Rucaparib (n=236) 18·0 14·3–19·4
Placebo (n=118) 9·1 8·0–10·8
HR 0·40;
95% CI 0·31–0·53;
p<0·0001
Not on first subsequent (chemo)therapy (%)
Months
Number at risk (censored)
Rucaparib 236 (0) 209 (7) 143 (11) 111 (12) 69 (28) 40 (49) 13 (73) 2 (82) 0 (84)
Placebo 118 (0) 91 (4) 32 (9) 17 (9) 6 (13) 2 (15) 0 (17)

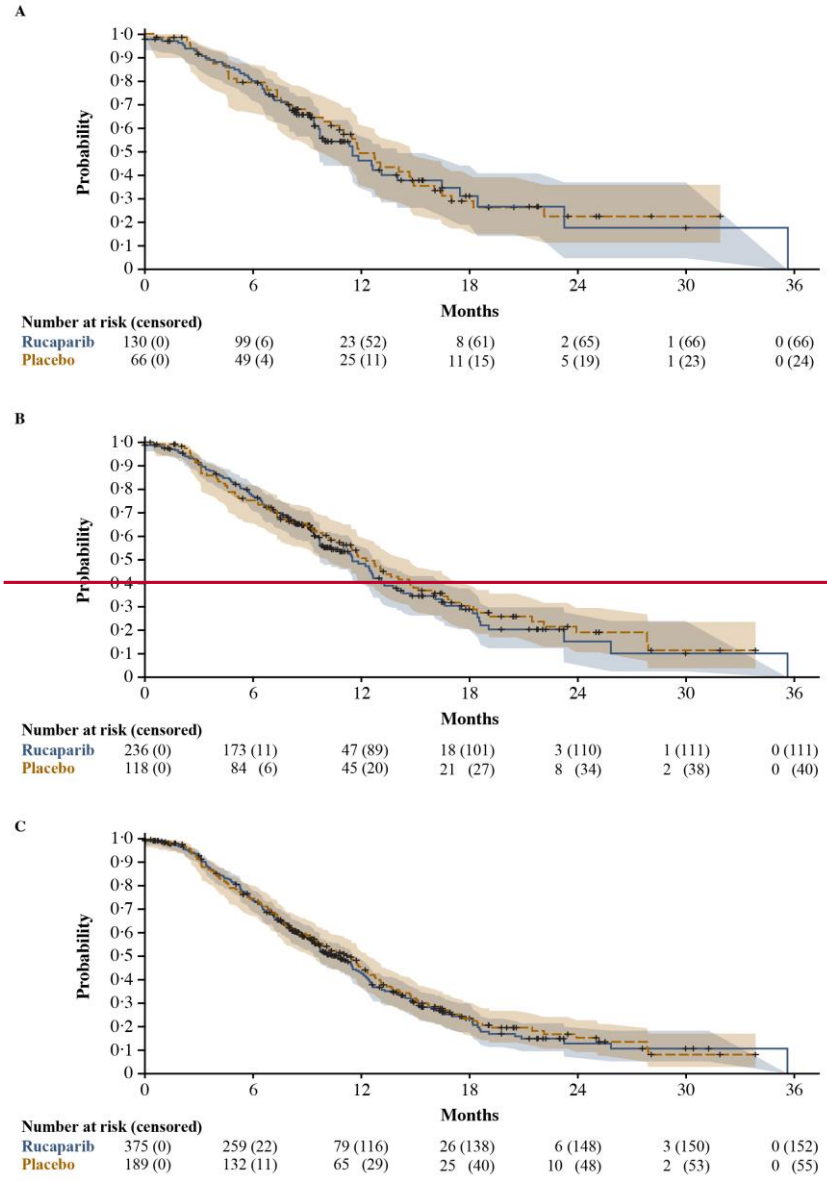

B
Median, months
95% CI
Rucaparib (n=236) 16·4 12·5–17·9
Placebo (n=118) 7·4 6·5–9·1
HR 0·39;
95% CI 0·30–0·51;
p<0·0001
Not on first subsequent therapy (%)
Months
Number at risk (censored)
Rucaparib 236 (0) 193 (8) 133 (10) 96 (12) 60 (31) 31 (50) 11 (67) 2 (74) 0 (76)
Placebo 118 (0) 74 (3) 27 (5) 14 (6) 4 (9) 2 (10) 0 (12)

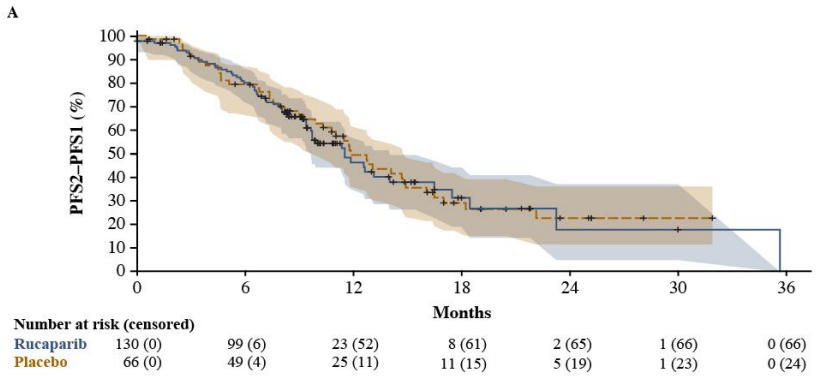


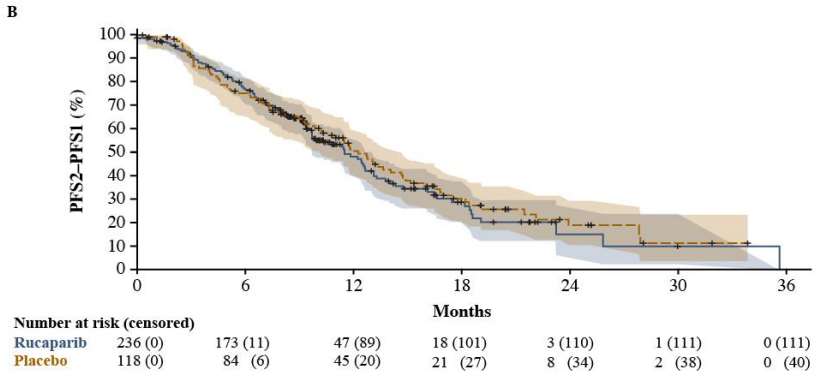


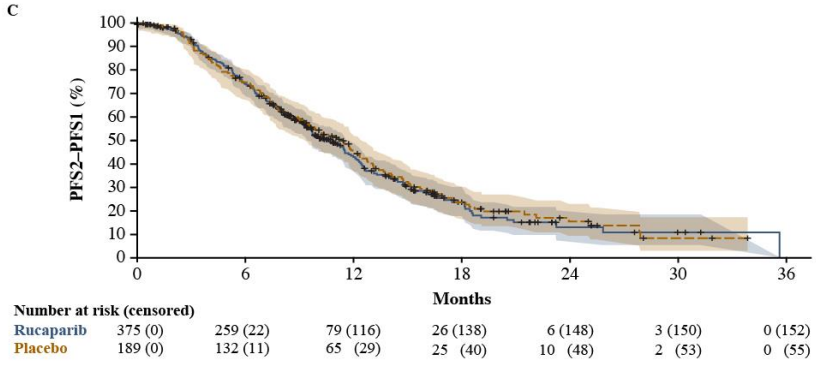
CFI=chemotherapy-free interval. HR=hazard ratio. HRD=homologous recombination deficient. PFS2=time to disease progression on subsequent therapy or death. TFST=time to start of first subsequent therapy. TSST=time to start of second subsequent therapy.

Figure S4. **Kaplan-Meier estimates of PFS2–PFS1 in the *BRCA*-mutant cohort (A), HRD cohort (B), and ITT population (C)**





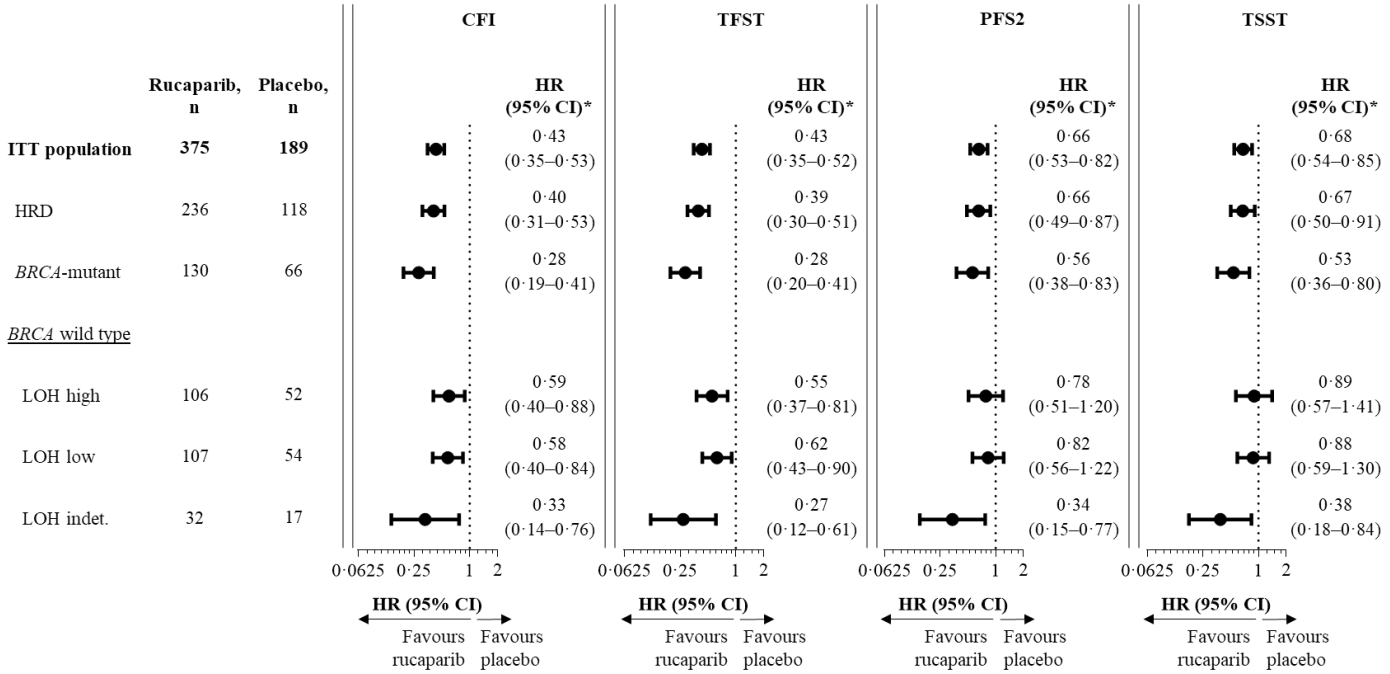




Shaded areas indicate 95% confidence intervals.

HRD=homologous recombination deficient. ITT=intention to treat. PFS1=time to first disease progression event or death. PFS2=time to disease progression on subsequent therapy or death.

Figure S5: **Postprogression outcomes in predefined cohorts and subgroups of patients with *BRCA* wild-type carcinomas based on LOH status**



*Cox proportional hazard model.
CFI=chemotherapy-free interval. HR=hazard ratio. HRD=homologous recombination deficient. indet.=indeterminate. ITT=intention to treat. LOH=loss of heterozygosity. PFS2=time to disease progression on subsequent therapy or death. TFST=time to start of first subsequent therapy. TSST=time to start of second subsequent therapy.

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CONSORT Checklist

CONFIDENTIAL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer

Protocol Number:	CO-338-014
Investigational Product:	Oral rucaparib (CO-338)
Eudra CT Number:	2013-000518-39
IND Number:	106,289
Development Phase:	Phase 3
Indications Studied:	Platinum-sensitive, high-grade serous and endometrioid epithelial ovarian, primary peritoneal, and fallopian tube cancer
Sponsor Name and Address:	Clovis Oncology, Inc. 2525 28th Street Boulder, CO 80301 USA Phone Number: 303-625-5000 Facsimile Number: 303-245-0360
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and ICH GCP Guidelines. Essential study documents will be archived in accordance with applicable regulations.
Protocol Date:	September 9, 2013

CONFIDENTIALITY STATEMENT

The information in this document contains commercial information and trade secrets that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

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Protocol Approval Signature Page

Protocol: CO-338-014

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Date: September 9, 2013

Reviewed and Approved by:

[redacted]

Date

[redacted]

Date

[redacted]

Date

[redacted]

Date

Protocol Acceptance Form

Protocol: CO-338-014

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer

Date: September 9, 2013

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature _____ Date _____

Name (printed) _____

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1 SYNOPSIS

Protocol Number	CO-338-014
Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Study Phase	Phase 3
Introduction	Rucaparib is an orally available, small molecule inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) being developed for treatment of ovarian cancer associated with homologous recombination deoxyribonucleic acid (DNA) repair deficiency. The safety and efficacy of rucaparib has been evaluated in several Phase 1 and Phase 2 studies. Normal cells repair single-strand breaks (SSBs) in DNA primarily through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP-1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by homologous recombination DNA repair, a complex process involving multiple proteins, including those encoded by breast cancer susceptibility gene 1 and 2 (*BRCA1* and *BRCA2*), as well as many others. Homologous recombination pathway defects, either as an initiating event or late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. An analysis of the Cancer Genome Atlas (TCGA), which examined molecular changes in high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patients with HGSOC have homologous recombination deficiency (HRD).[1] Drivers of HRD include: 1. Germline mutations in the *BRCA1* and *BRCA2* genes (*gBRCA*). These are the strongest known hereditary factors for epithelial ovarian cancer (EOC), accounting for up to 15% of all EOC.[2, 3] These patients carry heterozygous deleterious mutations in their germline DNA and develop tumors when the remaining wild-type functional allele is inactivated (i.e., "second hit"). 2. Somatic *BRCA1/2* mutations (*sBRCA*) (approximately 6 – 8% of HGSOC patients)[1, 4] 3. Mutation in a homologous recombination gene other than *BRCA1/2* (approximately 16% of HGSOC patients).[1] Nonclinical studies by several groups have identified RAD proteins (e.g. RAD51, RAD51C, RAD52, RAD54L),[5, 6, 7, 8] Fanconi Anemia proteins (e.g. FANCA, FANCC, FANCD2),[9, 10, 11] and many others (e.g. ATM, ATR, CHEK1, CHEK2)[12, 13, 14, 15] as being involved in homologous recombination. 4. Functional silencing of homologous recombination genes, such as through *BRCA* promoter methylation (approximately 10% of HGSOC patients)[1] or other mechanisms Inhibition of DNA damage repair in cancer cells, which are intrinsically genetically unstable, represents an attractive opportunity for the development of new therapies. Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect, whereas inhibition of multiple DNA repair pathways may lead to cell death, a concept known as synthetic lethality. Normal

Introduction (cont)	cells, with only one DNA repair pathway affected by inhibition of PARP, still have an intact DNA repair pathway that can compensate, whereas cancer cells with pre-existing HRD that are treated with a PARP inhibitor develop critically DNA repair deficiency and enter apoptosis. This concept of synthetic lethality has been demonstrated in landmark *in vitro* and *in vivo* studies[16, 17]as well as in several clinical trials that evaluated a single agent PARP inhibitor for the treatment of relapsed ovarian cancer and metastatic breast cancer with or without an associated germline *BRCA* mutation.[18, 19, 20, 21, 22, 23, 24] In vitro studies have also shown that cells deficient in or depleted of homologous recombination proteins other than BRCA1/2 have been associated with PARP inhibitor sensitivity.[25, 26, 27, 28] It is possible that the 24% ORR observed in ovarian cancer patients without evidence of a *gBRCA1/2* mutation and treated with olaparib[21] was due to HRD driven by a *sBRCA1/2* mutation or by an alteration in another key homologous recombination gene. Clinical activity in HGSOC has also been observed with switch maintenance PARP inhibitor therapy following response to platinum-based chemotherapy. Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median PFS (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio (HR) of 0.35 (95% CI, 0.25 – 0.49).[29] Patients with a *BRCA* mutation derived the most benefit (median PFS 11.2 vs 4.3 months; HR=0.18; 95% CI 0.11-0.31; $P<0.00001$).[30] It should be noted that the outcomes of *sBRCA* + *gBRCA* mutant patients were the same as *gBRCA* mutant patients alone, suggesting that, for stratification and analysis purposes in the present study, it is appropriate to not differentiate between germline and somatic mutations. Patients without a *BRCA* mutation also experienced significant benefit from treatment with olaparib (HR=0.53; 95% CI 0.33-0.84; $P=0.007$), suggesting that patients with DNA repair defects in genes other than *BRCA* are likely contributing to the overall PFS result.[30] The purpose of this study is to evaluate progression-free survival (PFS) of patients with platinum-sensitive, relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy. Prior to final analysis, patients will be placed into molecularly defined subgroups of HRD based on the Final Clinical Trial Assay (FCTA). It is anticipated that rucaparib will provide therapeutic benefit and increase PFS in patients with HRD.
Study Overview	This is a randomized, international, double-blind, placebo-controlled Phase 3 study evaluating rucaparib maintenance therapy in advanced ovarian cancer. The primary endpoint is PFS by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[31] as assessed by the investigator. Risk/benefit will be assessed regularly by an Independent Data Monitoring Committee that will have access to unblinded datasets. This study will enroll patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved either a complete response (CR) by RECIST v1.1 or a partial response (PR), defined as either a RECIST v1.1 PR or a cancer antigen 125 (CA-125) response by Gynecologic Cancer Intergroup (GCIG) criteria,[32] to their last platinum-based regimen. All responses will require CA-125 that is within the upper limit of normal (ULN).

Study Overview (cont'd)	During the screening phase, each patient will have archival tumor tissue analyzed for mutations in homologous recombination pathway genes. Genes of interest will be sequenced using Foundation Medicine's next generation sequencing (NGS) test, which examines a panel of cancer-related genes, including *BRCA1/2* and other homologous recombination pathway genes. Patients will be stratified into one of three HRD subgroups (*BRCA1/2* mutation in tumor tissue [tBRCA], HRD due to mutation in a homologous recombination gene other than *BRCA1/2* [nonBRCA HRD (nbHRD)], or biomarker negative) for randomization based on the results obtained with Foundation Medicine's Initial Clinical Trial Assay (ICTA) (Appendix A). Enrollment of patients known *a priori* to harbor a *gBRCA* mutation classified as deleterious (pathogenic), suspected deleterious, or equivalent, on the most recent assessment, will be limited to 150. Enrollment of patients with a *BRCA* gene mutation detected in tumor tissue (tBRCA), including those known to harbor a *gBRCA* mutation, will be limited to 200. Once this cap is reached, newly screened patients identified as having a *BRCA* mutation in tumor tissue will be offered treatment in another study. The complete results of the Foundation Medicine NGS test, which examines exons of 287 genes as well as introns of 19 genes, will be provided to all patients who opt to receive this information and provide appropriate consent. Tumor tissue results for the *BRCA* genes will be provided to patients upon availability. Results for the remainder of the gene panel will be provided to patients upon study treatment discontinuation. In the event a mutation associated with hereditary cancer or other syndrome is detected in tumor tissue, the patient will be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline *BRCA* testing, this result will be entered into the clinical trial database. Mutations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether any mutation identified is of germline or somatic origin. Tumor DNA will also be assessed by the NGS test to detect the presence of genomic scars.[33, 34, 35, 36] Analysis of specific genomic scarring patterns may identify tumors with HRD regardless of the underlying mechanism(s). The extent of genomic scarring and its utility in predicting clinical outcome with rucaparib will be assessed in a Phase 2 study (CO-338-017) that will be initiated in parallel with this Phase 3 study, but will be completed earlier. The insights from study CO-338-017 will be applied prospectively to the analysis of this Phase 3 study. The FCTA analysis plan (gene mutation and/or genomic scarring) and classification of HRD subgroups will be finalized and locked down prior to the completion of the Phase 3 study and applied prospectively to the primary efficacy analysis. The Sponsor will remain blinded to all tumor tissue and germline test results until the primary efficacy analysis is conducted.
Number of Patients	Approximately 540 patients will be enrolled. A minimum of 180 and a maximum of 200 patients with a deleterious *tBRCA* mutation will be enrolled. Enrollment of patients with a known deleterious *gBRCA* mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined.

Number of Sites	This is a multicenter, multinational study. Patients will be enrolled from approximately 90 – 100 study sites.
Study Duration	Q4 2013 – Q4 2016
Study Objectives	The primary objective of this study is: • To evaluate PFS by RECIST, as assessed by the investigator, in molecularly-defined HRD subgroups The secondary objectives of this study are: • To evaluate PFS by RECIST, as assessed by independent radiology review (IRR), in molecularly-defined HRD subgroups • To evaluate patient-reported outcome (PRO) of disease-related symptoms utilizing the disease-related symptoms – physical (DRS–P) subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Ovarian Symptom Index 18 (FOSI-18) • To evaluate PRO utilizing the complete FOSI-18 • To evaluate survival benefit • To evaluate safety • To determine the population pharmacokinetics (PK) of rucaparib The exploratory objectives of this study are: • To evaluate the relationship between cancer antigen 125 (CA-125) levels and invPFS • To evaluate PFS2 (PFS on the subsequent line of treatment) • To evaluate overall response rate (ORR) • To evaluate duration of response (DOR) • To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D) • To explore the relationship between rucaparib exposure, efficacy, and safety
Study Population	**Inclusion Criteria** All patients enrolling into the study must meet all of the following inclusion criteria: 1. Have signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation 2. Be ≥18 years of age at the time the informed consent form is signed 3. Have a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer – For mixed histology, >50% of the primary tumor must be confirmed to be high-grade serous or endometrioid 4. Received prior platinum-based therapy and have platinum-sensitive disease (i.e. documented radiologic disease progression >6 months following the last dose of the penultimate platinum administered) – Received ≥2 prior platinum-based treatment regimens, including platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to 1 non-platinum is permitted. – There is no upper limit on the number of prior platinum-based regimens that may have been received, but the patient must have been sensitive to the penultimate platinum-based regimen administered.

Study Population (cont'd)	– If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this will be considered 1 treatment regimen – Prior continuous (e.g. bevacizumab) or switch maintenance therapy following any prior treatment regimen is permitted 5. Achieved best response of either CR (defined as complete radiologic response by RECIST) or PR (defined as partial response by RECIST and/or a GCIG CA-125 response) to the most recent platinum-based regimen administered (4 cycles minimum) and maintained response through completion of chemotherapy – All responses require that CA-125 be <ULN. Response must have been maintained to permit entry into the study. – All disease assessments performed prior to and during this chemotherapy regimen must be adequately documented in the patient's medical record 6. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 x 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 to 12 x 10 µm sections, or equivalent) available for planned analyses. – The most recently collected tumor tissue should be provided, if available – Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample. – Sample must be received at the central laboratory at least 3 weeks prior to planned start of treatment in order to enable stratification for randomization 7. Have CA-125 measurement <ULN 8. Have ECOG performance status of 0 to 1 9. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug: a. Bone Marrow Function – Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L – Platelets $>100 \times 10^9$/L – Hemoglobin ≥9 g/dL b. Hepatic Function – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN; if liver metastases, then ≤5 × ULN – Bilirubin ≤1.5 × ULN c. Renal Function – Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate (GFR) ≥45 mL/min using the Cockcroft Gault formula **Exclusion Criteria** Patients will be excluded from participation if any of the following criteria apply: 1. History of a prior malignancy except: a. Curatively treated non-melanoma skin cancer b. Breast cancer treated curatively >3 years ago, or other solid tumor treated curatively >5 years ago, without evidence of recurrence c. Synchronous endometrioid endometrial cancer (Stage 1A G1/G2)

Study Population (cont'd)	2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible. 3. Required drainage of ascites during the final 2 cycles of the last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomization to maintenance treatment in this study 4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks. 5. Prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with absorption of study drug 6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C. 7. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test <3 days prior to first dose of study drug 8. Received treatment with chemotherapy, radiation, hormones, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > NCI CTCAE Grade 1 9. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of study drug or have on-going requirements for these medications (Appendix F) 10. Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration 11. Presence of any other condition that may increase the risk associated with study participation or interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for the study Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Patients of reproductive potential must practice an effective method of contraception during treatment and for 6 months following the last study drug dose. No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolled into the study.
Study Treatment	Eligible patients will be randomized 2:1 to receive rucaparib (600 mg bid) or placebo. Randomization will occur by a central randomization procedure using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced: • HRD classification (tBRCA, nbHRD, or biomarker negative) by the ICTA (Appendix A). • Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 or >12 months) by radiologic assessment • Best response to the most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST or PR [defined as partial response by RECIST and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN.

Study Treatment (cont'd)	Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy. Study drug will be taken orally twice daily (12 hours apart) with at least 8 oz (240 mL) of water. Study drug may be taken with an empty stomach or with food. Patients will take study drug twice daily for continuous 28-day cycles until disease progression by RECIST as assessed by the investigator, or other reason for discontinuation. Treatment interruptions and/or dose reductions are permitted in the event of unacceptable toxicity.
Withdrawal Criteria	A patient must be discontinued from treatment with study drug if any of the following apply: • Consent withdrawal at the patient's own request or at the request of their legally authorized representative • Progression of patient's underlying disease by RECIST as assessed by the investigator • Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient • An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy
Disease Assessments for Efficacy	Efficacy measures will include clinical examination, CA-125 measurement, and appropriate imaging (CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. Disease assessment will be performed at screening, at the end of every 12 weeks of treatment, at discontinuation of treatment, and as clinically indicated. Disease progression will be determined by RECIST (Appendix B). Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria (Appendix C) for disease progression should have a radiologic assessment by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST per the protocol schedule. Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans and CA-125 measurement performed at 12 (± 2) week intervals until disease progression, as assessed by the investigator.
Safety Assessments	Safety assessments will include adverse events (AEs), hematology, serum chemistry, vital signs, body weight, concomitant medications/procedures, ECOG performance status (Appendix D), and study drug modifications.
Statistical Procedures	**Sample Size Justification** The total enrollment planned is 540 patients. A minimum of 180 and a maximum of 200 patients with a deleterious *tBRCA* mutation will be enrolled. Enrollment of patients with a known deleterious *gBRCA* mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined. Prior to final efficacy analysis, HRD classification will be determined by the FCTA that will evaluate homologous recombination gene mutations and/or extent of

Statistical Procedures (cont'd)

genomic scarring in tumor tissue.

The table below provides estimated sample sizes and power calculations.

Group	Hazard Ratio	Cumulative N	Minimum Number of Events (70%)	Median PFS Placebo vs Rucaparib (months)	Power	One-sided Alpha
tBRCA	0.50	180	126	6 vs 12	90%	0.025
All HRD (tBRCA + nbHRD)	0.60	300	210	6 vs 10	90%	0.025
ITT Population (tBRCA + nbHRD + Biomarker Negative)	0.70	540	378	6 vs 8.5	90%	0.025

Analysis Populations

Safety: The safety population will consist of all patients who received at least one dose of protocol-specified treatment.

Intent-to-treat (ITT): The ITT population will consist of all randomized patients.

Response evaluable: The response evaluable population will consist of all patients who have measurable or evaluable disease at study entry, received at least one dose of study drug, and who had at least one post-baseline disease assessment.

General Statistical Considerations

Quantitative variables will be summarized using descriptive statistics. For variables registered on a continuous scale, the following will be presented: N, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The primary and key secondary endpoints will be tested among the tBRCA subgroup, all HRD subgroup, and all randomized patients, using an ordered step-down multiple comparisons procedure. Investigator determined PFS (invPFS) in the tBRCA subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the tBRCA subgroup is statistically significant, then irrPFS in the tBRCA subgroup will be tested at a one-sided 0.025 significance level and if significant, invPFS and irrPFS will be tested in the all HRD subgroup followed by invPFS and irrPFS in all randomized patients. Continuing in an ordered step-down manner, the PRO of disease symptoms utilizing the DRS-P subscale of the FOSI-18 will be tested at the one-sided 0.025 significance level in the tBRCA, all HRD, and all randomized patients subgroups and then for the remaining key secondary endpoints of PRO utilizing the FOSI-18 total score and OS. Once statistical significance is not achieved for one test the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure.

<u>Primary Efficacy Analysis</u>

The primary efficacy analysis for the study is investigator-determined PFS (invPFS) by RECIST. Investigator-determined PFS is defined as the time from

Statistical Procedures (cont'd)	randomization to disease progression, according to RECIST v1.1 criteria as assessed by the investigator, or death due to any cause, whichever occurs first. The stratification factors included in the primary analysis of invPFS will be HRD classification (tBRCA, nbHRD or biomarker negative), interval between completion of penultimate platinum regimen and disease progression (6 to 12 months or >12 months) by radiologic assessment, and best response to the most recent platinum-based regimen (either CR [defined as complete radiologic response by RECIST] or PR [defined as partial response by RECIST and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN. Tumor HRD status by the FCTA will be determined after randomization, but before the final efficacy analysis, so that the primary endpoint (PFS in molecularly defined subgroups) can be assessed prospectively. Secondary Efficacy Analyses Secondary efficacy endpoints include: • PFS by RECIST v1.1 as assessed by IRR • PRO of disease-related symptoms as measured by the DRS-P subscale score of the FOSI-18 • PRO as measured by the total score of the FOSI-18 • OS PFS for secondary efficacy analysis is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by IRR, or death due to any cause, whichever occurs first. The time to an event in PRO of worsening of disease symptoms will be defined as the time from randomization to a 4-point reduction in the FOSI-18 DRS–P subscale score. Similarly, an event in worsening of PRO utilizing the FOSI-18 total score will be defined as the time from randomization to an 8-point reduction in the total score. OS, time to death from any cause, is defined as the number of days from the date of randomization to the date of death (due to any cause). Patients without a known date of death will be censored on the date the patient was last known to be alive. Safety Analysis Data from all patients who receive at least one dose of study drug will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, and concomitant medications / procedures will be tabulated and summarized. AEs will be summarized overall, with separate summaries for serious AEs, AEs leading to treatment discontinuation or death, and CTCAE Grade 3 or higher AEs. **Independent Data Monitoring Committee (IDMC)** No formal efficacy interim analyses for early stopping are planned. An IDMC will meet to review the efficacy and safety data from this study. The IDMC will: • Review efficacy and safety of rucaparib compared to placebo to ensure the study is beneficial to patients; • Ensure the study is conducted in a high quality manner; and • Monitor the size of the tBRCA subgroup and known gBRCA subgroup

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha-1 acid glycoprotein
ADP	adenosine diphosphate
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BER	base excision repair
BID	twice a day
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BUN	blood urea nitrogen
CA-125	cancer antigen 125
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 4.0)
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-strand break
DRS−P	disease-related symptoms−physical
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOC	epithelial ovarian cancer
EQ-5D	Euro-Quality of Life 5D
EQ-VAS	Euro-Quality Visual Analogue Scale
FCTA	Final Clinical Trial Assay
FDA	Food and Drug Administration

FFPE	formalin-fixed paraffin-embedded
FOSI-18	FACT-Ovarian Symptom Index 18
GALT	gut-associated lymphoid tissue
gBRCA	germline *BRCA*
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
h	hour
hERG	human ether-a-go-go-related gene
HGSOC	high grade serous ovarian cancer
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
ICH	International Conference on Harmonization
ICTA	Initial Clinical Trial Assay
IC_{xx}	concentration where maximum response is inhibited by XX%
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
invPFS	disease progression according to RECIST v1.1 as assessed by the investigator, or death from any cause
IRB	Institutional Review Board
IRR	independent radiology review
ITT	Intent-to-treat
irrPFS	disease progression according to RECIST v1.1, as assessed by IRR, or death from any cause
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LOH	loss of heterozygosity
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	minute
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mut	mutant
nbHRD	non-BRCA homologous recombination deficiency
NCCN-FACT	National Comprehensive Cancer Network-Functional Assessment of Cancer
NCI	National Cancer Institute
NGS	next generation sequencing
NOAEL	no-observed-adverse-effect level
ORR	overall response rate

OS	overall survival
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PLD	PEGylated liposomal doxorubicin
PFS	progression-free survival
PFS2	second event of progression-free survival
P-gp	P-glycoprotein
PID	poly (adenosine diphosphate [ADP]-ribose) polymerase inhibiting dose
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PS	performance status
QD	once a day
RECIST	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	serious adverse event
SAS	statistical analysis software
SD	stable disease
SNP	single-nucleotide polymorphism
SOC	system organ class
SOP	Standard operating procedure
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse events
T_{max}	time to maximum concentration
TMZ	temozolomide
unk	unknown
UV	ultraviolet
WBC	white blood cell
WT	wild type

3 INTRODUCTION

3.1 Ovarian Cancer

3.1.1 General Overview

Ovarian cancer is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer.[37, 38] After initial therapy, most women will have a progression-free interval of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy.[39] Relapse still occurs, however, in the majority of cases, and only 10–30% of women experience long-term survival.[39] Advanced stage disease is associated with a 5-year survival rate of only 30–40%.[37]

Approximately 90% of ovarian tumors are surface epithelial in origin, and the papillary serous histology subtype accounts for approximately 75%, of which the large majority (70%) is high-grade.[39] The site of origin of epithelial ovarian cancer (EOC) remains unclear. Some studies suggest that serous EOC and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium[40, 41]; however, other studies suggest an origin within stem cells of the ovarian surface epithelium.[39, 42] EOC, PPC and fallopian tube cancer behave very similarly, and are therefore treated in the same way.

The median age at presentation of EOC is 60 years. Many women present with advanced disease and therefore have a poor prognosis.

3.1.2 Treatment of Ovarian Cancer

The standard approach to treatment of advanced ovarian cancer is cytoreductive surgery (either at time of diagnosis or interval debulking following 2 – 3 cycles of neoadjuvant chemotherapy), with the goal of minimizing residual tumor to no visible residual disease, a major prognostic indicator for improved survival. Six to eight cycles of platinum- and taxane-based chemotherapy is the global standard of care. If initial cytoreduction is not performed, interval debulking surgery is considered. This surgery may be carried out after three or four cycles of primary chemotherapy, followed by three further cycles of chemotherapy. Platinum analogues, such as carboplatin and cisplatin, are the most active agents, mediating their effects through the formation of inter- and intra-strand cross-links with deoxyribonucleic acid (DNA).[43, 44]

The choice of treatment for relapsed disease is based on the treatment-free interval relative to last therapy administered and chemotherapy agents used. As many patients experience multiple relapses, prognosis and response to therapy decreases as the interval between last chemotherapy exposure and disease relapse shortens. The treatment-free, or specifically the platinum-free interval, provides further prognostic information for patients, as therapeutic options lessen and survival shortens as a patient's tumor becomes less responsive to platinum-based therapy.

Platinum-based regimens dominate ovarian cancer therapy and define treatment groups.[44] In general, patients whose disease progresses during treatment with a platinum-based regimen are considered to have platinum-refractory disease; patients whose disease relapses within 6 months after the last platinum agent was administered are considered to have platinum-resistant disease;

and patients whose disease relapses more than 6 months after the last platinum-based therapy was administered are considered to have platinum-sensitive disease. These classifications are clinical, and not based on a mechanistic definition of platinum sensitivity or resistance.

PARP inhibitor monotherapy has elicited objective responses in patients with platinum-sensitive disease as well as in patients with platinum-resistant disease, although response rates are higher in the former population.[21, 22, 23] This indicates that using platinum-sensitivity alone as a selection marker for PARP inhibitor therapy is not a very effective tool, although it is a reasonable place to begin predictive biomarker development.

Maintenance therapy following a response to standard treatment provides an opportunity to extend the disease-free period. Maintenance strategies evaluated to date for ovarian cancer have focused on the prolonged use of single-agent chemotherapy, antiangiogenesis agents, hormonal therapy, vaccines, and intraperitoneal chemotherapy. The OCEANS study evaluated carboplatin and gemcitabine with or without bevacizumab as part of the initial treatment and then as maintenance in women with platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer who were in their first relapse following primary chemotherapy. The addition of bevacizumab resulted in a statistically significant improvement in PFS (median 12.4 vs 8.4 months; HR=0.484 [95% CI, 0.388 to 0.605; log-rank P<0.00001]).[45] The PFS benefit of bevacizumab administered together with chemotherapy followed by single agent bevacizumab maintenance treatment compared to chemotherapy alone and placebo maintenance was further established in two front-line Phase 3 studies, GOG-218 (HR=0.717 [95% CI, 0.625 to 0.824; log-rank P<0.001])[46] and ICON-7 (HR=0.81 [95% CI, 0.70 to 0.94; log-rank P<0.04]).[47] Based on these trials, the European Medicines Agency approved bevacizumab, in combination with carboplatin and paclitaxel, for front-line treatment of advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian-tube, or primary peritoneal cancer, and, in combination with carboplatin and gemcitabine, for treatment of first recurrence of platinum-sensitive epithelial ovarian, fallopian-tube or primary peritoneal cancer in women who have not received prior therapy with bevacizumab or other vascular-endothelial-growth-factor (VEGF) inhibitors or VEGF-receptor-targeted agents.

3.1.3 Homologous Recombination Deficiency

DNA is constantly damaged by both endogenous and exogenous (environmental) assaults. A common type of DNA damage is the formation of DNA single-strand breaks (SSBs). During normal cell cycling, DNA is replicated and replication forks are eventually stalled by persistent SSBs. If stalled replication forks are not rapidly repaired, they can often degenerate and form DNA double-strand breaks (DSBs), which are highly likely to be lethal to the cell.

Normal cells repair single-strand breaks (SSBs) in DNA primarily through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by homologous recombination DNA repair, a complex process involving multiple proteins, including those encoded by breast cancer susceptibility gene 1 and 2 (*BRCA1* and *BRCA2*), among others.

If either the BER or homologous recombination pathway is rendered non-functional, the remaining functional pathway can compensate to ensure ongoing DNA repair and cell cycling. For example, when the BRCA-associated homologous recombination pathway is lost or dysfunctional, repair shifts towards the BER repair pathway that is dependent on PARP enzymes. In contrast, in the setting in which both repair pathways (BER and homologous recombination) are rendered non-functional, the cell dies. This concept, where a defect in either of two pathways can be withstood by a cell, but defects in both are lethal, is referred to as synthetic lethality. This type of lethality can arise from a variety of different interactions. In the case of DNA damage repair, dual non-functionality can be achieved by enzymatic inhibition of PARP in the context of a genetic mutation in the *BRCA1* or *BRCA2* genes.

Synthetic lethality has been demonstrated in landmark *in vitro* and *in vivo* studies as well as in several clinical trials that evaluated a single agent PARP inhibitor for the treatment of relapsed ovarian cancer and metastatic breast cancer. Bryant and colleagues showed that cell lines and a tumor xenograft deficient in homologous recombination (via a defect in a *BRCA* or other homologous recombination gene) were highly sensitive to PARP inhibition.[16] This study also showed that synthetic lethality could be achieved regardless of whether the mutation was in *BRCA1* or *BRCA2*. In a parallel set of experiments, Farmer and colleagues illustrated that chemical inhibition of PARP1 was more potent in homozygous *BRCA*-deficient cell lines than in heterozygous mutant or wild-type cell lines.[17] These findings were also supported by a *BRCA2*-deficient murine model. Taken together, these studies provided support for the treatment of patients with a *BRCA*-deficient tumor with a PARP inhibitor.

3.1.4 Role of HRD in Ovarian Cancer

Homologous recombination pathway defects, either as an initiating event or late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. An analysis of the Cancer Genome Atlas (TCGA), which examined molecular changes associated with high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patient with HGSOC have homologous recombination deficiency (HRD).[1] Drivers of HRD in ovarian cancer include:

1. Germline mutations in the *BRCA1* and *BRCA2* genes (*gBRCA*). These are the strongest known hereditary factors for epithelial ovarian cancer (EOC), accounting for up to 15% of all EOC.[2, 3] These patients carry heterozygous deleterious mutations in their germline DNA and develop tumors when the remaining wild-type functional allele is inactivated (i.e., “second hit”).

2. Somatic *BRCA1/2* mutations (*sBRCA*) (approximately 6 – 8% of HGSOC patients)[1, 4]

3. Mutation in a homologous recombination gene other than *BRCA1/2* (approximately 16% of HGSOC patients).[1] Nonclinical studies by several groups have identified RAD proteins (e.g. RAD51, RAD51C, RAD52, RAD54L),[5, 6, 7, 8] Fanconi Anemia proteins (e.g. FANCA, FANCC, FANCD2),[9, 10, 11] and many others (e.g. ATM, ATR, CHEK1, CHEK2)[12, 13, 14, 15] as being involved in homologous recombination.

4. Functional silencing of homologous recombination genes, such as through *BRCA* promoter methylation (approximately 10% of HGSOC patients)[1] or other mechanisms

All patients in the TCGA HGSOC study received platinum-based therapy. In general, patients identified as having defects in homologous recombination pathway genes were more sensitive to platinum-based treatment. This differential survival effect is hypothesized to be related to improved response to platinum-based therapies in patients whose tumors have evidence of HRD, since attenuation of platinum's pharmacodynamic effect (DNA cross-linking) is also mediated by DNA repair.

3.2 PARP Inhibitors

PARP inhibitors have been evaluated in the clinic for the past decade. Olaparib (AZD-2281), the most advanced investigational PARP inhibitor, has demonstrated compelling Phase 2 clinical activity, both in treatment and maintenance settings, in relapsed, HGSOC patients (both germline *BRCA* mutant and wild-type) and in metastatic breast cancer patients with a *gBRCA* mutation. The concept of synthetic lethality was exploited in two proof-of-concept clinical studies with olaparib in patients with *BRCA*-associated tumor types. These studies evaluated the efficacy and safety of continuous oral dosing with olaparib in women with either relapsed ovarian cancer or advanced breast cancer and a *gBRCA* mutation.[19, 20] In these patients, who had received a median of three prior chemotherapy regimens, encouraging overall response rates of 33% and 41%, were observed, in *gBRCA* ovarian and *gBRCA* breast cancer, respectively. In a third study, olaparib treatment was associated with a greater overall response rate (ORR) in patients with *gBRCA*-associated ovarian cancer compared with the patients in the non-*gBRCA* associated cohort (41% vs 24%, respectively).[21] In a fourth study that evaluated olaparib versus PEGylated liposomal doxorubicin (PLD) in patients with a *gBRCA* mutation and relapsed ovarian cancer, the efficacy of olaparib was consistent with that observed in previous studies.[22]

Activity in HGSOC has also been observed with PARP inhibitor switch maintenance therapy following response to platinum-based chemotherapy.[29, 30] Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median PFS (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio of 0.35 (95% CI, 0.25 – 0.49).[29] Patients with a *BRCA* mutation derived the most benefit (median PFS 11.2 vs 4.3 months; HR=0.18; 95% CI 0.11-0.31; $P<0.00001$).[30] It should be noted that the outcomes of *sBRCA* + *gBRCA* mutant patients were the same as *gBRCA* mutant patients alone, suggesting that, for stratification and analysis purposes in the present study, it is appropriate to not differentiate between germline and somatic mutations. Patients without a *BRCA* mutation also experienced significant benefit from treatment with olaparib (HR=0.53; 95% CI 0.33-0.84; $P=0.007$).[30]

Niraparib (MK-4827) has exhibited clinical activity in a Phase 1 study in both *BRCA*-mutated ovarian cancer (8 RECIST PRs) and sporadic ovarian cancer (5 RECIST PRs and/or GCIG CA-125 responses).[23] In a Phase 1 evaluation of BMN 673, 11 of 17 *BRCA*-mutated ovarian cancer patients treated at doses ≥100 μg/day exhibited a RECIST and/or CA-125 response.[24]

Taken together, these data support the potential role for the PARP inhibitor rucaparib in the treatment of patients with *BRCA*-associated ovarian cancer. Furthermore, the 24% ORR and HR

of 0.53 in the non-*BRCA* cohorts described above[21,30] suggests that the clinical utility of PARP inhibitors can be extended to a larger patient group. Patients with HRD due to defects in homologous recombination genes other than *BRCA*, i.e., nbHRD, may be part of this larger group.

3.3 Rucaparib

Rucaparib (formerly known as AG-014447 and PF-01367338) refers to the free base. The camphorsulfonic acid salt form (also referred to as camsylate salt) CO-338 (formerly known as PF-01367338-BW) will be used in this clinical trial.

Rucaparib is a small molecule inhibitor of PARP1 and PARP2. Nonclinical evaluation has demonstrated exquisite sensitivity of *BRCA1* and *BRCA2* homozygous mutant cell lines to rucaparib and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary deficiencies of *BRCA1* and/or *BRCA2*. Rucaparib has also shown antitumor activity as a single agent in the MDA-MB-436 (*BRCA1* mutant) xenograft mouse model. The activity of rucaparib in these nonclinical experiments was similar to that of olaparib.

The details of these and other nonclinical experiments are provided in the Investigator's Brochure.

3.3.1 Nonclinical Experience

3.3.1.1 Rucaparib Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetics (PK) and toxicokinetics of rucaparib (as camsylate salt) following oral administration, the intended route of administration in humans, was evaluated in the mouse, rat, and dog. The time at which the peak plasma concentrations were observed (T_{max}) occurred at 1–3 hours post dose in the mouse and dog, with the rat generally exhibiting a later T_{max} (4–8 hours). The oral bioavailability was 17%, 36%, and 62%, respectively, in the mouse (50 mg/kg), rat (100 mg/kg), and dog (20 mg/kg). In the rat and dog, there were no marked gender-related differences and no accumulation after repeat oral administration. A less than dose-proportional increase in exposure was observed in the rat and dog when rucaparib was administered as a suspension in 0.5% methylcellulose; however, a greater than dose-proportional increase in exposure was observed in the 1-month dog toxicity study when rucaparib was administered in capsules.

In vitro plasma protein binding studies in mouse, rat, and dog plasma showed moderate binding and ranged from 49.5% to 73%. Plasma protein binding in humans ranged from 55% to 75%.

Recombinant cytochrome P450 (CYP) studies indicated that CYP2D6, CYP1A2, and to a lesser extent, CYP3A4, have the ability to metabolize rucaparib. Rucaparib moderately inhibited CYP1A2, CYP2C19, and CYP2C8. In addition, rucaparib showed mixed inhibition of CYP2C9. Based on bi-directional experiments of digoxin transport carried out using Caco-2 cells, it was determined that rucaparib is a moderate P-glycoprotein (P-gp) inhibitor. Patients taking dixogin should have their dixogin levels monitored regularly according to standard institutional practices.

Quantitative whole body autoradiography studies in Long Evans rats showed [^{14}C] rucaparib radioequivalents were rapidly and widely distributed to tissues following IV administration, consistent with a large volume of distribution. At 2 minutes after dosing, highest concentrations were found in kidney, lung, thyroid gland, heart, stomach mucosa, liver adrenal glands, spleen, and blood. Little radioactivity was present in brain; levels were undetectable at 15 minutes after dosing. Activity was undetectable in most tissues by 96 hours after dosing, however levels in the choroid/retina declined more slowly, and persistent radioactivity was also found in hair follicles through 192 hours, indicating that drug equivalents have high affinity and long half-life in pigmented tissues. High levels of radioactivity were observed in ureters, bladder, and bile ducts, indicating both renal and biliary routes eliminated drug equivalents.

3.3.1.2 Multiple-Dose Toxicity Studies

Rucaparib was evaluated in both rat and dog in oral and IV infusion toxicity studies. Only the multiple-dose toxicity studies utilizing the oral formulation are summarized below. Details of all other toxicity studies are provided in the Investigator's Brochure.

Target organs identified in studies where rucaparib was administered orally include the hematopoietic system and gastrointestinal tract. No cardiovascular findings were noted in any of the oral toxicity studies.

Multiple-Dose Oral Toxicity in Rats

Administration of rucaparib camsylate salt via oral gavage was generally well-tolerated in the rat up to 1000 mg/kg/day for 7 days and up to 150 mg/kg/day for 28 days. Decreases in body weight gain and food consumption were noted in both studies. In the 7-day study, target organs identified microscopically were bone marrow, spleen, and thymus. Minimal to mild bone marrow hypocellularity was noted in all dose groups. The no-observed-adverse-effect-level (NOAEL) was established at 500 mg/kg/day.

In the 28-day study, there were 3 rucaparib-related deaths at 500 mg/kg/day immediately after blood collection on Day 28 (n=1) or Day 29 (first day of recovery phase (n=2). These deaths likely resulted from the marked anemia identified hematologically. Other rucaparib-related clinical signs at 500 mg/kg/day included thinning haircoat and pale eyes. Identified target organs included bone marrow, spleen, lymphoid tissue (thymus, gut-associated-lymphoid tissue [GALT], and lymph nodes), and cecum (at 500 mg/kg/day only). Following cessation of rucaparib dosing, most findings reversed. In this study, the severe toxic dose in 10% of the animals (STD10) was 500 mg/kg/day and the NOAEL was 50 mg/kg/day.

Multiple-Dose Oral Toxicity in Dogs

Oral gavage administration of the camsylate salt form of rucaparib to dogs for 7 days resulted in gastrointestinal clinical signs at the 80 mg/kg/day high-dose group. Hematopoietic effects of decreased reticulocytes were noted in mid- to high-dose groups and leukopenia was exhibited in all treatment groups. Lymphoid atrophy occurred in both sexes and in all treatment groups. Decreased bone marrow cellularity was seen in both sexes (males at all doses; females at 80 mg/kg/day). A 7-day repeat-dose toxicity study using oral capsules in dogs was repeated in order to characterize the toxicity of a new lot of rucaparib camsylate. Similar to the results of the

prior 7-day study in dog, gastrointestinal clinical findings were noted at 80 mg/kg/day. Vomiting was observed throughout the dosing phase for males as well as liquid and/or mucoid feces in both genders. Decreased food consumption was observed at 80 mg/kg/day that correlated with the body weight loss that was considered adverse. Decreases in erythroid, platelet, and leukocyte parameters were observed primarily at 80 mg/kg/day and occasionally at 20 or 5 mg/kg/day. These data indicated that the drug targeted multiple bone marrow lineages in a dose-related pattern.

Rucaparib camsylate salt in capsules was administered orally to dogs for 30 consecutive days with a 29-day recovery. Gastrointestinal clinical signs were noted at ≥ 5 mg/kg/day, with decrease in food consumption at 75 mg/kg/day. Adverse hematological changes (decrease in erythroid, myeloid, and megokaryocytic lineages) occurred at ≥ 20 mg/kg/day. Effects were fully reversible. The NOAEL in this study was 5 mg/kg/day.

Rucaparib camsylate in capsules was also given orally to dogs at doses of 3, 15/10, 40/30/20 mg/kg/day for 91 consecutive days with a 29-day recovery period. Body weight losses and inappetance observed at the high dose in both sexes during the first quarter of the dosing phase were considered adverse and resulted in dose reductions (40 to 30 to 20 mg/kg/day for toxicity and 15 to 10 mg/kg day in order to maintain multiples of exposures for optimal testing of dose response) for the remainder of the study. Clinical pathology findings were indicative of bone marrow toxicity; these changes were non-progressive over time suggesting potential adaptation to these initial effects. Hematological findings at 40/30/20 mg/kg/day correlated with erythroid atrophy of the bone marrow detected microscopically. By Day 29 of recovery, most effects reversed. The highest non-severely toxic dose (HNSTD) for this study was 20 mg/kg/day for male dogs. No HNSTD was established for female dogs. The NOAEL was 10 and 20 mg/kg/day for male and female dogs, respectively.

3.3.1.3 Additional Observations

In vitro genetic toxicology assays demonstrated oral rucaparib to be clastogenic. Bacterial mutagenicity data for rucaparib were clearly negative in four microbial tester strains, both with and without metabolic activation, and equivocal in a fifth tester strain.

In an in vitro assay for human ether-a-go-go-related gene (hERG) activity, the IC_{50} and IC_{20} for the inhibitory effects of rucaparib (50% inhibitory concentration and 20% inhibitory concentration) on hERG potassium currents were 24 µM (7761 ng/mL) and 7 µM (2264 ng/mL), respectively. These values are 9-fold and 2.6-fold higher, respectively, than the mean unbound steady state plasma concentration (858 ng/mL) observed to date in humans at a dose of 600 mg BID rucaparib administered orally.

Effects on appearance and behavior, motor activity, body temperature, and a number of neurofunctional tests and reflexes were evaluated in rats. A dose of 50 mg/kg of rucaparib administered via IV infusion (mean C_{max}=13629 ng/mL) resulted in a significant reduction in motor activity compared with vehicle-treated animals; however, there were no effects on neurofunctional or reflex testing at this dose. The plasma concentration measured at this dose is 4.7-fold above the mean steady state plasma concentration (2880 ng/mL) observed to date in humans at a dose of 600 mg BID rucaparib administered orally.

Administration of rucaparib to Long-Evans rats orally at doses up to 750 mg/kg/dose, followed by a single exposure to solar-simulated ultraviolet radiation approximately 4 hours after the final dose elicited no skin or ocular reactions indicative of phototoxicity. The no-observed-effect-level (NOEL) for phototoxicity was >750 mg/kg/day.

3.3.2 Clinical Experience

The early clinical program assessed safety and efficacy of rucaparib in patients with malignancies commonly treated with chemotherapeutic agents. Initially, the IV formulation of rucaparib was administered in combination with a variety of chemotherapies; later, the oral formulation of rucaparib was administered in combination with chemotherapy and as a monotherapy. The oral formulation as monotherapy is the focus of current development efforts.

3.3.2.1 Rucaparib Monotherapy

Clovis-sponsored study CO-338-010 is a 2-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered daily for continuous 21-day cycles. Part 1 is a Phase 1 portion in patients with any solid tumor, including lymphoma, who have progressed on standard treatment. The primary objective of Part 1 is to determine the optimal monotherapy dose for orally administered rucaparib. Part 2 is a Phase 2 portion in patients with platinum-sensitive relapsed ovarian cancer with evidence of a *gBRCA* mutation who have received at least 2, but no more than 4, prior regimens. The primary objective of Part 2 is to assess the overall objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST).

Study CO-338-010 was initiated in Q4 2011. As of 9 September 2013, 52 patients (median age 51 yrs [range 21–71]; 47 female; 26 breast cancer, 18 ovarian/peritoneal cancer, 8 other tumor) have been treated at dose levels of 40, 80, 160, 300, and 500 mg once daily (QD), and 240, 360, 480, 600, and 840 mg twice daily (BID) rucaparib administered continuously. One of 6 patients treated with 360 mg BID rucaparib experienced a dose-limiting toxicity (DLT) of Common Toxicity Criteria for Adverse Events (CTCAE) Grade 3 nausea despite maximal intervention in Cycle 1 of treatment. No DLTs were observed during Cycle 1 in the 480 (n=9), 600 (n=5), and 840 mg BID (n=3) cohorts; however, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1. The dose of 600 mg BID rucaparib was selected as the recommended dose for Phase 2 and Phase 3 studies based on the overall safety & tolerability, PK, and clinical activity profile.

Twenty-one patients are ongoing and 31 patients have discontinued. Reasons for discontinuation include disease progression (n=27), adverse event unrelated to study treatment (n=2), withdrawal of consent (n=1), eligibility criteria violation (n=1). No patient discontinued rucaparib due to a treatment-related adverse event.

The median number of cycles administered is 3 (range 1–21+). Twenty-four patients have received ≥4 cycles of treatment. Nine patients have had their dose of rucaparib escalated. Six patients had their dose of rucaparib reduced due to a treatment-related AE. Events leading to dose reduction included: Grade 3 thrombocytopenia (n=1, rucaparib reduced from 480 to 360 mg BID), Grade 3 anemia (n=1, rucaparib reduced from 600 to 480 mg BID), Grade 3 nausea (n=1, rucaparib reduced from 360 to 240 mg BID), Grade 2 neutropenia (n=2 total, rucaparib reduced

from 600 to 480 mg BID [n=1] and from 500 to 300 mg QD [n=1]), and a constellation of Grade 1-2 gastrointestinal toxicities and inability to ingest 14 x 60 mg tablets (n=1; rucaparib reduced from 840 to 480 mg BID). Four patients experienced a retreatment delay between cycles. One patient was delayed due Grade 3 thrombocytopenia. One patient was delayed due to Grade 3 thrombocytopenia and Grade 3 anemia. Two patients were delayed due to Grade 2 neutropenia.

As of 9 September 2013, safety data are available for 52 treated patients. Treatment-related adverse events (AEs) (all grades) reported in ≥5 patients include nausea (n=13, 26%), fatigue (n=10, 20%), vomiting (n=9, 18%), decreased appetite (n=6, 12%), and diarrhea (n=6, 12%). Mild to moderate (Grade 1 – 2) elevations of ALT and/or AST have been reported in patients treated at higher doses, primarily 480, 600, and 840 mg BID. These elevations were not accompanied by any changes in bilirubin levels and were either transient, and resolved to within normal ranges, or stabilized. Patients were asymptomatic and no dosing modifications were required. Grade 1 – 2 photosensitivity of skin has also been reported.

Overall, treatment-related Grade 3 events have been minimal and no Grade 4 events have been reported. Grade 3 related events include anemia (n=2, 4%), thrombocytopenia (n=2, 4%), neutropenia (n=1, 2%), fatigue (n=1, 2%), and nausea (n=1, 2%). As has been observed with rucaparib and other PARP inhibitors, myelosuppression may be delayed and observed after a period of continuous dosing. Three patients died within 30 days of last dose of study drug; all deaths were assessed as due to disease progression and not related to rucaparib.

To date, one patient (breast cancer, *gBRCA* mutation) has achieved a RECIST CR and 6 patients (2 ovarian cancer, 3 breast cancer, 1 pancreatic cancer; all with *gBRCA* mutation) have achieved a RECIST PR during the dose escalation phase (n=2 at 300 mg QD; n=1 at 360 mg BID; n=2 at 480 mg BID; and n=1 at 600 mg BID). The duration of the PR for one of the breast cancer patient was 5.1 months; all other patients with a CR or PR are still ongoing. An additional 12 patients (7 ovarian cancer, 4 breast cancer, 1 colorectal; 9 with *gBRCA* mutation 2 with unknown *gBRCA* status, 1 *gBRCA* wild-type) achieved a best response of stable disease (SD) >12 wks. Three patients with ovarian cancer and a *gBRCA* mutation have achieved prolonged stable disease and are ongoing at 62, 32, and 30 weeks. An additional 6 ovarian cancer patients are ongoing at less than 12 weeks of treatment. The overall disease control rates (CR or PR or SD>12 weeks and CR or PR or SD>24 weeks) to date in all evaluable ovarian cancer patients across all dose levels are 91% (10/11) and 50% (5/10), respectively (*Table 1*).

Table 1. Disease Control of Ovarian Cancer Patients Treated with Rucaparib in Study CO-338-010

***BRCA* Status**	**Disease Control Rate (%) (CR, PR, or SD>12 weeks)**	**Disease Control Rate (%) (CR, PR, or SD>24 weeks)**
gBRCA mutation	100 (9/9)	63 (5/8)
gBRCA unknown	100 (1/1)	0 (0/1)
gBRCA wild-type	0 (0/1)	0 (0/1)
Overall	91 (10/11)	50 (5/10)

After once daily oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. T_{max} and $t_{1/2}$ were independent of dose. Steady state exposure increased by an average of 89%, consistent with accumulation expected for a compound exhibiting a $t_{1/2}$ of approximately 17 hours administered once daily. Following BID oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. Moreover, BID dosing delivered a lower C_{max} with a low peak to trough plasma concentration variation. The target trough level of 2 μM was achieved in 100% of patients (n=14) at ≥240 mg BID with low inter-patient variability (<4-fold) within each dose group. Steady state trough levels also exhibited low intra-patient variability (24% CV). No sporadically high exposures were observed. The effect of food on rucaparib PK was evaluated at 40 mg (n=3) and 300 mg (n=6) doses administered once daily. There was no food effect; patients may take rucaparib on an empty stomach or with food.

Study A4991014

Clovis-sponsored study A4991014 is an ongoing Phase 1, open-label, multicenter, dose escalation study. The primary objectives are to determine the safety and PK of rucaparib when administered in combination with different chemotherapeutic regimens in adult patients with advanced solid tumors. The study was initially designed to explore escalating doses of IV rucaparib (as phosphate salt) in combination with different chemotherapeutic regimens, but was subsequently amended to evaluate the oral formulation of rucaparib in combination with carboplatin; all other treatment arms were discontinued.

As of 28 August 2013, a total of 84 patients (median age=54.5 [range 20-76]; 54 female; 36 ECOG PS=0) have been treated in this study. Of these, 52 patients were treated with IV and/or oral rucaparib on Days 1–3 in combination with various chemotherapeutic regimens. Thirty-two patients have been treated with escalating doses of oral rucaparib (Days 1 – 14) in combination with carboplatin.

Oral rucaparib doses of 80, 120, 180, 240, and 360 mg were administered with AUC3 carboplatin, followed by 360 mg rucaparib with AUC4, and subsequently AUC5, carboplatin. Two of 5 patients treated with AUC5 carboplatin and 360 mg rucaparib experienced a dose-limiting toxicity (Grade 4 thrombocytopenia and Grade 3 neutropenia in 1 patient; Grade 4 thrombocytopenia and Grade 4 neutropenia in 1 patient) in Cycle 1 of treatment. Evaluation of 240 mg rucaparib in combination with AUC5 carboplatin is nearly complete. To date, 1 of 5 patients treated with that dose combination has experienced DLT of Grade 4 thrombocytopenia. The 6th patient in the cohort is currently completing Cycle 1 of treatment.

As of 28 August 2013, safety data is available for 32 patients treated with oral rucaparib (14 days) and carboplatin. Adverse events (all grades) occurring in ≥25% of patients include nausea (n=21, 66%), fatigue (n=17, 53%), anemia (n=15, 47%), vomiting (n=15, 47%), constipation (n=14, 44%), thrombocytopenia (n=13, 41%), abdominal pain (n=11, 34%), decreased appetite (n=10, 31%), neutropenia (n=9, 28%), and diarrhea (n=9, 28%), Two patients treated with oral rucaparib and carboplatin died within 30 days of last dose of study drug; both deaths were assessed as due to disease progression and not related to study drugs.

To date, 3 patients have achieved a RECIST PR. One patient (ovarian cancer, *gBRCA*^{wt}, AUC3 carboplatin and 180 mg rucaparib) had a PR of 5.1 months duration. One patient (breast cancer, *gBRCA2*^{mut}, AUC5 carboplatin and 360 mg rucaparib) had a PR of 3 months duration. One patient (ovarian cancer, *gBRCA1*^{mut}, AUC5 carboplatin and 240 mg rucaparib) achieved a PR at the end of Cycle 2 and is currently ongoing in Cycle 3. Two ovarian cancer patients (1 *gBRCA*^{unk}, 1 *gBRCA*^{wt}) discontinued carboplatin (after 4 and 8 cycles, respectively) and continued on rucaparib (additional 4 and 25+ cycles, respectively). Overall disease control rate (CR, PR, or SD>12 weeks) in ovarian cancer patients across all dose levels was 60% (6/10).

After a single oral administration, rucaparib was rapidly absorbed with C_{max} achieved within 4 hours. C_{max} and $AUC_{0-\infty}$ increased in an approximately dose-proportional manner. Apparent terminal half-life ($t_{1/2}$) ranged from 13 to 21 hours. The absolute bioavailability of the rucaparib immediate-release tablet was dose-independent and was estimated to be 36%. Rucaparib exposure was not meaningfully changed by carboplatin co-administration.

Study A4991002 and A4991005

Further details of these studies are provided in the Investigator's Brochure.

3.4 Rationale for Study

In vitro studies have shown that cells deficient in BRCA1/2 as well as cells deficient in or depleted of homologous recombination proteins other than BRCA1/2 have been associated with PARP inhibitor sensitivity in vitro.[16, 17, 25, 26, 27, 28] Clinical data have shown that ovarian cancer patients with and without evidence of a *gBRCA* mutation benefit from treatment with a PARP inhibitor[18, 19, 20, 21, 22] and that maintenance treatment with a PARP inhibitor following a response to platinum-based treatment increases PFS in patients with ovarian cancer.[29, 30] While patients with a *BRCA* mutation derived the most benefit, patients without evidence of a BRCA mutation also derived significant benefit.[21, 30] The purpose of this study is to evaluate PFS of patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy in order to identify the patients most likely to benefit from treatment with rucaparib. It is anticipated that rucaparib will provide therapeutic benefit and increase PFS in patients with HRD associated with a *BRCA* gene mutation or other HR gene alteration.

Patients will be stratified into one of 3 HRD subgroups (tBRCA, nbHRD, and biomarker negative) (Appendix A) by Foundation Medicine's ICTA, which will determine HRD status through analysis of homologous recombination gene mutations in tumor tissue. Tumor DNA will also be assessed to detect the presence of genomic scars.[33, 34, 35, 36] Analysis of specific genomic scarring patterns may identify tumors with HRD regardless of the underlying mechanism(s). Homologous recombination gene mutation analysis and genomic scarring will also be assessed in a Phase 2 study (CO-338-017) that will be initiated in parallel with this Phase 3 study. The insights from study CO-338-017 will be applied prospectively to the analysis of this Phase 3 trial. The FCTA analysis plan (gene mutation and/or genomic scarring) and classification of HRD subgroups will be finalized and locked down prior to the completion of the Phase 3 study and applied prospectively to the analysis of this Phase 3 study.

4 STUDY OBJECTIVES

4.1 Objectives and Endpoints

This is a double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, relapsed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy.

Primary, secondary, and exploratory objectives and endpoints are shown in Table 2.

Table 2. Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
1. To evaluate PFS by RECIST, as assessed by the investigator, in molecularly-defined HRD subgroups	1. Disease progression according to RECIST Version 1.1 (v1.1), as assessed by the investigator, or death from any cause (invPFS), in molecularly defined subgroups
Secondary Objectives	**Secondary Endpoints**
1. To evaluate PFS by RECIST, as assessed by independent radiology review (IRR), in molecularly-defined HRD subgroups	1. Disease progression according to RECIST v1.1, as assessed by IRR, or death from any cause (irrPFS), in molecularly defined subgroups
2. To evaluate patient-reported outcome (PRO) of disease related symptoms utilizing the disease-related symptoms – physical (DRS–P) subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Ovarian Symptom Index 18 (FOSI-18)	2. Time to a 4-point decrease in the DSR–P subscale of the FOSI-18
3. To evaluate PRO utilizing the complete FOSI-18	3. Time to an 8-point decrease in the total score of the FOSI-18
4. To evaluate survival benefit	4. OS
5. To evaluate safety	5. Incidence of AEs, clinical laboratory abnormalities, and dose modifications
6. To determine the population PK of rucaparib	6. Individual model parameter estimates of rucaparib and covariates identification
Exploratory Objectives	**Exploratory Endpoints**
1. To evaluate the relationship between cancer antigen 125 (CA-125) levels and invPFS	1. Association between the change from baseline in CA-125 measurements and invPFS
2. To evaluate PFS2 (PFS on the subsequent line of treatment)	2. Time to the next event of disease progression or death, as assessed by the investigator
3. To evaluate ORR	3. ORR per RECIST v1.1, as assessed by both investigator and IRR, in patients with measureable disease at study entry
4. To evaluate duration of response (DOR)	4. DOR per RECIST Version 1.1, as assessed by both investigator and IRR
5. To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D)	5. PRO as measured by the total score on the EQ-5D
6. To explore the relationship between rucaparib exposure, efficacy, and safety	6. Rucaparib PK, invPFS, irrPFS, CA-125, AEs, clinical laboratory abnormalities, and dose modifications

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy.

5.1.1 Screening Phase

All patients will undergo screening assessments within 90 days prior to randomization.

The study will enroll patients with platinum-sensitive (defined as disease with confirmed radiologic relapse >6 months after the last dose of the penultimate platinum regimen received), high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved a response to platinum-based chemotherapy administered for relapsed disease. Patients must have received ≥2 prior platinum-based treatment regimens, inclusive of the regimen that must have been administered immediately prior to maintenance therapy in this trial. There is no limit on the number of prior platinum-regimens that may have been received, but the patient must have been sensitive to the penultimate platinum regimen received. In addition, up to 1 prior non-platinum regimen is permitted. Prior continuous or switch maintenance therapy may have been administered with any prior treatment. For the last chemotherapy course prior to study entry, patients must have received a platinum-based regimen (minimum 4 cycles) and have achieved a CR (defined as complete radiologic response by RECIST [Appendix A] or PR (defined as partial response by RECIST [Appendix A] and/or a GCIG CA-125 response [Appendix C]. All responses require that CA-125 be <ULN. The response must be maintained to permit entry into the study.

Screening assessments will include demographics and medical history, prior treatments for serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (and other malignancies, if applicable), prior and current medications and procedures, 12 lead electrocardiogram (ECG), ECOG performance status, central laboratory hematology, serum chemistry, and CA-125 measurement, serum pregnancy (for women of childbearing potential only), urinalysis, physical examination, height, weight, and vital signs measurements, adverse events, and radiologic assessment by CT or MRI. PRO will be collected using the FOSI-18 and EQ-5D instruments.

Germline *BRCA* mutation results should be obtained for all patients who are known to have been tested prior to enrollment in order to determine whether any mutation was reported and if so, whether the mutation was classified as deleterious / pathogenic or other. Enrollment of patients with a *gBRCA* mutation classified as deleterious (i.e., pathogenic), suspected deleterious, or the equivalent, on the most recent assessment by a testing laboratory will be limited to 150. Patients with a *BRCA* mutation detected in tumor tissue (tBRCA) will be limited to 200. Once this cap is reached, newly screened patients identified as having a *BRCA* mutation in tumor tissue will be offered treatment in another study.

The complete results of the Foundation Medicine NGS test, which examines exons of 287 genes as well as introns of 19 genes, will be provided to all patients who opt to receive this information and provide appropriate consent. Results for the *BRCA* genes will be provided to patients upon availability. Results for the remainder of the gene panel will be provided to patients upon treatment discontinuation. In the event a mutation associated with hereditary cancer or other syndrome is detected in tumor tissue, the patient will be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline *BRCA* testing, this result will be entered into the clinical trial database. The Sponsor will remain blinded to all NGS test results, including all *tBRCA* results, until the primary efficacy analysis is conducted.

Mutations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether any mutation identified is of germline or somatic origin. This data will be generated in a research setting and will not be provided to the investigator or patient.

Enrollment will require Clovis (or designee) review of eligibility, including, but not limited to:

- a list of all prior cancer therapies and dates administered;
- documentation supporting platinum sensitivity;
- documentation supporting a RECIST or GCIG CA-125 response to most recent platinum-based treatment;
- local *gBRCA* test result if patient has previously been tested; and
- confirmation that sufficient tumor tissue was submitted for HRD stratification for randomization and storage for potential bridging to a validated companion diagnostic test.

5.1.2 Randomization

Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy, and is described in more detail in Section 7.2. Study treatment must be initiated within 3 days of randomization.

5.1.3 Double-Blind Treatment Phase

During the double-blind treatment phase (continuous 28-day treatment cycles), patients will be monitored for safety and efficacy. Assessments will include AEs, physical examination, vital signs and weight measurement, central laboratory hematology, serum chemistry, including alpha-1 acid glycoprotein (AAG) analysis on days where a blood sample is taken for PK, and CA-125 measurement, serum or urine pregnancy for women of childbearing potential, concomitant medications, therapies and procedures, disease status assessment, study drug

administration and accountability, and PRO. ECGs and urinalysis will be performed as clinically indicated. Blood samples will also be collected for population PK.

Patients will be assessed for disease status per RECIST v1.1 at the end of every 3 cycles (12 weeks) of treatment. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from treatment and enter follow-up. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST v1.1 per the protocol schedule of assessments.

All CT scans (and other imaging, as appropriate) performed during the treatment period and at treatment discontinuation will be collected for IRR.

Patients will be continuously monitored for safety. An Independent Data Monitoring Committee (IDMC) with multidisciplinary representation will evaluate safety in compliance with a prospective charter.

5.1.4 Treatment Discontinuation

Upon treatment discontinuation, regardless of reason, patients will have a Treatment Discontinuation visit. Assessments will include AEs, physical examination, vital signs and weight measurements, central laboratory hematology, serum chemistry, and CA-125 measurement, serum pregnancy (for women of childbearing potential only), concomitant medications, therapies and procedures, disease status assessment, study drug accountability, and PRO. Additionally, all patients discontinued from treatment will be followed for 28 days following the last dose of study drug for the collection of AEs and PRO. An optional tumor biopsy will be collected from patients who experience disease progression and provide appropriate consent.

5.1.5 Follow-Up Phase

After the Treatment Discontinuation visit, all patients will be followed for AEs up to 28-days after last dose of study drug. Patients will also be followed for survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks until death, loss to follow-up, withdrawal of consent, or study closure.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans and CA-125 measurement performed at 12 (± 2) week intervals until disease progression by RECIST v1.1, as assessed by the investigator.

5.2 Study Schema

An overview of the study design is provided in Figure 1.

5.3 End of Study

The trial will close when the required number of PFS events has been observed. Upon formal closure of the study, individual patients who are continuing to benefit from treatment with rucaparib at the time of study closure, and who do not meet any of the criteria for withdrawal, will have the option of entering an extension protocol in which they can continue to receive rucaparib.

5.4 Discussion of Study Design

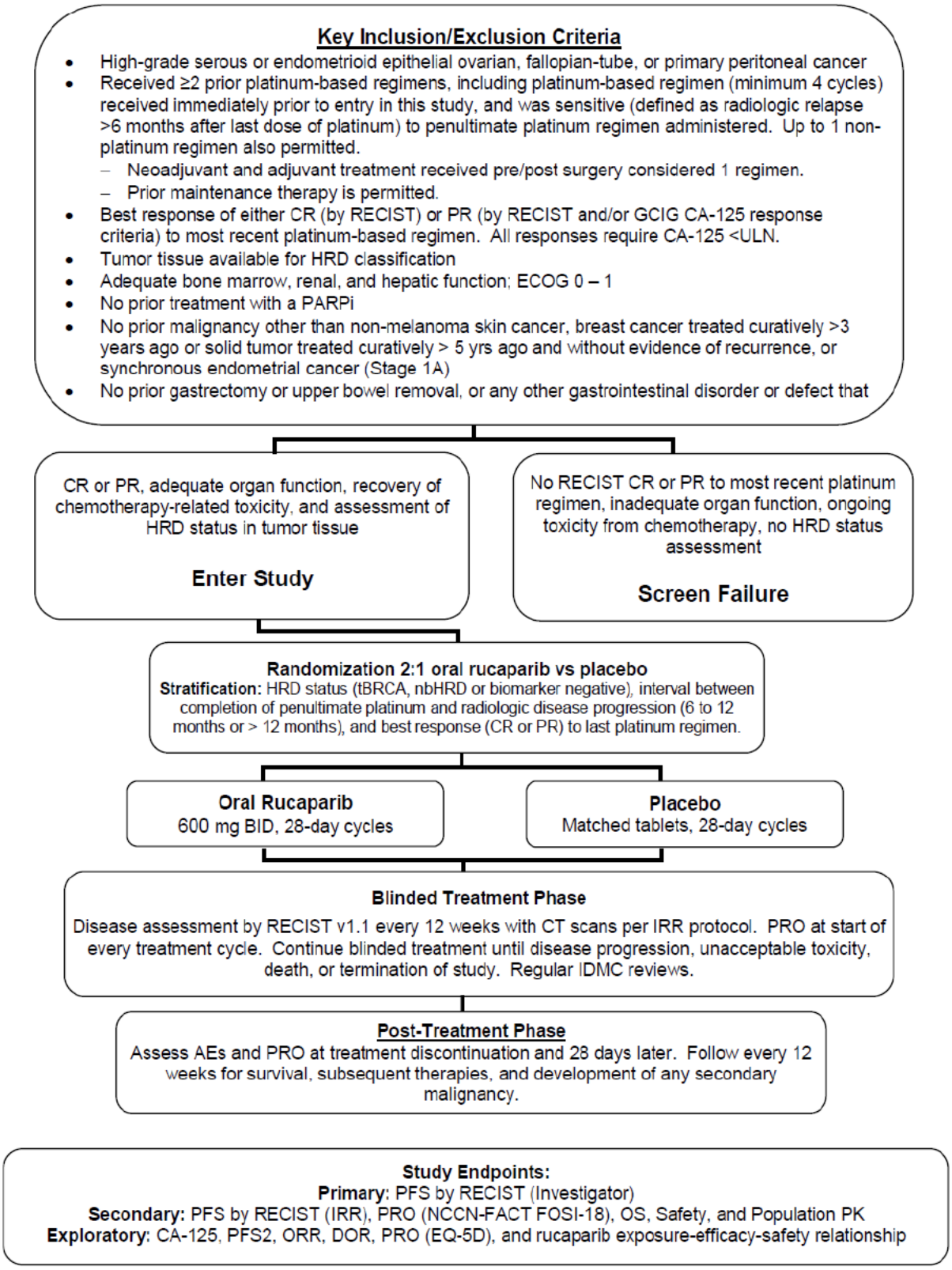
This is a multicenter, randomized, double-blind, placebo-controlled study.

Sponsor personnel (with the exception of individuals responsible for clinical supply chain), investigator and clinical site staff, and patient will all be blinded to study treatment to avoid bias in the interpretation of the efficacy and safety results. To avoid bias between treatment groups, patients will be randomized to treatment with active drug or placebo with stratification according to HRD classification, interval between completion of penultimate platinum-based regimen and disease progression by radiologic assessment, and best response to platinum regimen received immediately before initiation of maintenance therapy.

PFS by RECIST will be assessed by the investigator for the primary endpoint (invPFS) and by a blinded independent radiologist for the secondary endpoint (irrPFS).

Risk/benefit will be assessed regularly by an IDMC that will have access to unblinded datasets.

Figure 1 Study Schema



6 STUDY POPULATION

6.1 Number of Patients and Sites

Approximately 540 patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer will be enrolled at approximately 90 – 100 study sites. A minimum of 180 and a maximum of 200 patients with a deleterious *tBRCA* mutation will be enrolled. Enrollment of patients with a known deleterious *gBRCA* mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined.

6.2 Inclusion Criteria

All patients enrolling into the study must meet all of the following inclusion criteria:

1. Have signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Be ≥18 years of age at the time the informed consent form is signed
3. Have a histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer
   - For mixed histology, >50% of the primary tumor must be confirmed to be high-grade serous or endometrioid
4. Received prior platinum-based therapy and have platinum-sensitive disease (i.e., documented radiologic disease progression >6 months following the last dose of the penultimate platinum administered)
   - Received ≥2 prior platinum-based treatment regimens, including the platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to 1 non-platinum regimen is permitted.
     - There is no limit on the number of prior platinum-based regimens that may have been received; the patient must have been sensitive to the penultimate platinum-based regimen administered.
     - If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this will be considered 1 treatment regimen
     - Prior continuous (e.g. bevacizumab) or switch maintenance therapy following any prior treatment regimen is permitted
5. Achieved best response of either CR (defined as complete radiologic response by RECIST) or PR (defined as partial response by RECIST and/or a GCIG CA-125 response) to the most recent platinum-based regimen administered (4 cycles minimum) and maintained response through completion of chemotherapy
   - All responses require that CA-125 be <ULN. Response must have been maintained to permit entry into the study.

- All disease assessments performed prior to and during this chemotherapy regimen must be adequately documented in the patient's medical record

6. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 x 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 – 12 x 10 µm sections, or equivalent) available for planned analyses.
   - The most recently collected tumor tissue sample should be provided, if available.
   - Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample.
   - Sample must be received at the central laboratory at least 3 weeks prior to planned start of treatment in order to enable stratification for randomization.
7. Have CA-125 measurement that is < ULN
8. Have ECOG performance status of 0 to 1
9. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug:
   - Bone Marrow Function
     - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
     - Platelets $>100 \times 10^9$/L
     - Hemoglobin ≥9 g/dL
   - Hepatic Function
     - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN; if liver metastases, then ≤5 × ULN
     - Bilirubin ≤1.5 × ULN
   - Renal Function
     - Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate (GFR) ≥45 mL/min using the Cockcroft Gault formula

6.3 Exclusion Criteria

Patients will be excluded from participation if any of the following criteria apply:

1. History of a prior malignancy except:
   a. Curatively treated non-melanoma skin cancer
   b. Breast cancer treated curatively >3 years ago, or other solid tumor treated curatively >5 years ago, without evidence of recurrence
   c. Synchronous endometrioid endometrial cancer (Stage 1A G1/G2)
2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible.
3. Required drainage of ascites during the final 2 cycles of their last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomization to maintenance treatment in this study

4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
5. Prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with absorption of study drug
6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C
7. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test <3 days prior to first dose of study drug
8. Received treatment with chemotherapy, radiation, hormones, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > NCI CTCAE Grade 1
9. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of study drug or have on-going requirements for these medications (Appendix F)
10. Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration
11. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study

6.4 Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients who are more than 2 years postmenopausal or have had a hysterectomy and/or bilateral oophorectomy will not be considered of childbearing potential. Female patients of childbearing potential must have a negative serum pregnancy test result less than 3 days prior to administration of the first dose of study drug. A serum or urine pregnancy test (investigator's discretion) must be performed within 72 hours prior to Day 1 of every subsequent cycle during the treatment phase. A serum pregnancy test will be performed at the End of Treatment visit. All pregnancy testing will be performed by the local laboratory.

Female patients of reproductive potential must practice an effective method of contraception during treatment and for 6 months following the last dose of study drug. Adequate contraception is defined as double-barrier method (i.e., condom in combination with a diaphragm, cervical/vault cap, or intrauterine device). Oral, injectable, implant, or patch forms of contraception are not permitted as potential drug-drug interactions between oral rucaparib and these forms of birth control has not yet been evaluated.

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with study drug.

6.5 Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

7 DESCRIPTION OF STUDY TREATMENTS AND DOSE MODIFICATIONS

7.1 Description of Investigational Product

Rucaparib camsylate (also known as CO-338; previously known as PF-01367338-BW) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration and matched placebo tablets will be supplied to the study sites by the sponsor. A brief description of the investigational product is provided below.

Drug Name:	CO-338
rINN:	Rucaparib
Manufacturer:	[redacted]
Formulation:	Oval tablet; film coated; salmon pink
How Supplied:	120 mg (as free base) strength in high-density polyethylene bottles or equivalent with child-resistant caps and/or in Aclar foil blisters enclosed in card wallets
Storage Conditions:	15–30 °C

Placebo tablets will also be manufactured by [redacted], and will be identical in appearance to the rucaparib tablets.

Study drug containers containing rucaparib or placebo tablets will be labeled according to national regulations for investigational products. Where accepted, the expiry date will not appear on the labels, but will be controlled by the use of an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

7.2 Method of Assigning Patients to Treatment Groups

Following confirmation of eligibility in the screening phase, patients will be randomized 2:1 to receive rucaparib or placebo. Randomization will occur by a central randomization procedure using IVRS/IWRS. The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced:

- HRD classification (tBRCA, nbHRD, or biomarker negative) by the ICTA (Appendix A)
- Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 or >12 months) by radiologic assessment
- Best response (CR [defined as complete radiologic response by RECIST] or PR [defined as partial response by RECIST and/or a GCIG CA-125 response] to platinum regimen received immediately prior to initiation of maintenance therapy. All responses require that CA-125 be <ULN.

Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy. Study treatment must be initiated within 3 days of randomization.

7.3 Preparation and Administration of Protocol-Specified Treatment

The investigator or designee will be responsible for distributing study drug to all patients. Study drug will be assigned by the IVRS/IWRS according to the patient's randomization assignment. The system must be accessed at each dispensation in order to retrieve the bottle number appropriate to the patient's treatment. Study sites should follow local guidelines for the handling of oral cytotoxic drugs.

All patients will ingest study drug twice a day. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Each dose should be taken with at least 8 oz (240 mL) of room temperature water. Tablets should be swallowed whole.

Patients should take study drug doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (i.e., does not take it within 4 hours of the scheduled time), she should skip the missed dose and resume taking study drug with their next scheduled dose. Missed or vomited doses should not be made up.

A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken in an electronic dosing diary, and will be instructed to bring their study drug tablets, all containers (empty, partially used, and/or unopened), and electronic dosing diary to the next scheduled visit for reconciliation by site personnel. The electronic dosing diary is a Class 1 listed (i.e., approved) device.

7.3.1 Dietary Restrictions

All patients participating in the study should be instructed not to consume grapefruit, grapefruit juice, or any of the CYP1A2 or CYP3A4 inhibitors noted in Appendix F for 7 days prior to their first scheduled dose of oral rucaparib or placebo and for the duration of their participation on the study.

7.4 Starting Dose and Dose Modifications of Protocol-Specified Treatment

7.4.1 Starting Dose

The starting dose in this study will be 600 mg rucaparib or matched placebo, bid.

7.4.2 Dose Modification Criteria

The dose of study drug should be reduced if any of the following are observed:

- Grade 3 or 4 hematologic toxicity

- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines)
- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

Treatment with study drug should be held until the toxicity resolves to ≤CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, the dose should be reduced following resolution of the event to ≤CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted. If a patient continues to experience toxicity despite two dose reduction steps (i.e., to a dose of 360 mg BID rucaparib or placebo), or if dosing with study drug is interrupted for >14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the sponsor.

Dose reduction steps are presented in Table 3.

Dose re-escalation upon resolution of toxicity to ≤CTCAE Grade 1 is permitted upon agreement between the investigator and Sponsor.

Table 3. Dose Reduction Steps

Starting Dose	**600 mg BID**
Dose Level -1	480 mg BID
Dose Level -2	360 mg BID

7.4.3 Criteria for Re-Treatment

A new cycle of treatment may begin if:

- ANC ≥1.0 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Non-hematologic toxicities have returned to baseline or ≤CTCAE Grade 1 severity (or, at the investigator's discretion, ≤CTCAE Grade 2 severity if not considered a safety risk for the patient)

7.5 Accountability of Protocol-Specified Treatment

Study personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation. An IVRS/IWRS will be used to manage study drug inventory at all sites. In order to function properly, and to ensure patients receive the correct study drug according to the treatment assigned at randomization, the system will require real-time entry of study drug receipt, dispensation, or destruction, etc. by study personnel at the study center.

The site is responsible for the return or destruction of study drug as required. Any study drug accidentally or deliberately destroyed must be accounted for. All study drug containers must be accounted for prior to their destruction at the study center, according to institutional procedures for disposal of cytotoxic drugs. Unused study drug containers should be destroyed on-site if possible. Destruction of damaged or expired study drug at the site requires prior approval by the sponsor. If destruction on site is not possible, supply should be returned to the drug depot.

During the course of the study and at completion of the study, the number of study drug containers received, dispensed, returned, and destroyed must be reconciled.

7.6 Blinding/Masking of Treatment

Active and placebo tablets will be identical in appearance and supplied in identical containers. The medication labeling will ensure that no staff member or patient will be able to identify whether the tablets are placebo or contain active medication.

Patients will take the equivalent number of active or placebo tablets according to the treatment assignment and scheduled dose.

In the event of a medical emergency, an individual patient's treatment assignment may be unblinded using IVRS/IWRS. The module to unblind treatment assignment is accessible only to specific authorized study personnel. AEs per se are not a reason to break the treatment code. Unblinding should only occur for medical emergencies that require explicit knowledge of the treatment administered in order to determine the next course of action. The IVRS/IWRS vendor operates a 24-hour/365-day helpline as a back-up in the rare event the electronic system in unavailable when unblinding is required.

The study will not be unblinded for overall safety evaluation.

7.7 Treatment Compliance

Documentation of dosing will be recorded in a study specific electronic dosing diary provided by the sponsor (or designee). Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose. Patients (or legally authorized representative) will be instructed to record dosing information for study drug taken at home in the electronic dosing diary and to bring the electronic dosing diary and all unused tablets with them to scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits. Every effort should be made to ensure patients complete the electronic dosing diary and return their study drug containers at the end of each cycle of treatment.

8 PRIOR AND CONCOMITANT THERAPIES

Patients who have received prior treatment with a PARP inhibito,r including IV or oral rucaparib, are not eligible to participate in this study. Patients having received prior treatment with iniparib are eligible.

During the study, supportive care (e.g., antiemetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures.

All procedures performed (e.g., thoracentesis, etc.) and medications used during the study must be documented on the eCRF.

8.1 Anticancer or Experimental Therapy

No other anticancer therapies (including chemotherapy, radiation, hormonal treatment, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study. Prior treatment with such therapies between the completion of platinum-based therapies and the initiation of maintenance treatment is not permitted.

8.2 Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

8.3 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

The plasma concentrations of rucaparib may be increased in the presence of co-administered potent CYP1A2 or CYP3A4 inhibitors. Therefore, strong CYP1A2 and CYP3A4 inhibitors are excluded. Moderate inhibitors are permitted at the discretion of the Investigator in the event a suitable alternative cannot be found.

The plasma concentrations of rucaparib may be reduced in the presence of co-administered potent CYP1A2 or CYP3A4 inducers. Therefore, strong CYP1A2 and CYP3A4 inducers are excluded. Moderate inducers are permitted at the discretion of the Investigator in the event a suitable alternative cannot be found.

In addition, CYP1A2 is known to be induced in chronic smokers. Smokers are not excluded from the study; however, smoking status should be assessed and recorded in the source documents and eCRF.

A list of CYP1A2 and CYP3A4 inhibition / induction medications to be avoided or used with caution is provided in Appendix F.

Because rucaparib was shown to be a moderate inhibitor of CYP1A2, CYP2C8, CYP2C9, and CYP2C19 in vitro, caution should also be exercised in patients receiving rucaparib and requiring concomitant medication with CYP substrates that have a narrow therapeutic range, such as

phenytoin, *S*-mephenytoin, theophylline, tizanidine, and warfarin (Coumadin), as rucaparib doses ≥480 mg might increase the plasma concentrations of these medication. Other susceptible medications should be used with caution and plasma levels and/or pharmacodynamic surrogates monitored as appropriate.

8.4 Bisphosphonates

Bisphosphonates are permitted.

8.5 Anticoagulants

Caution should be exercised in patients receiving oral rucaparib and concomitant warfarin (Coumadin) as rucaparib showed a mixed inhibition of CYP2C9 in vitro. If appropriate, low molecular weight heparin should be considered as an alternative treatment. Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

8.6 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

Because rucaparib is a P-gp inhibitor in vitro, caution should be exercised in patients receiving rucaparib and requiring concomitant treatment with digoxin. Patients taking digoxin should have their digoxin levels monitored regularly according to standard institutional practices.

Oral, injectable, implant, or patch forms of contraception are not permitted as potential drug-drug interactions between oral rucaparib and these forms of birth control has not yet been evaluated.

9 STUDY PROCEDURES

9.1 Schedule of Assessments

Table 4 summarizes the procedures and assessments to be performed for all patients.

All procedures and assessments are to be completed within ±3 day of the scheduled time point.

Table 4. Schedule of Assessments

Procedure[a]	Pre-Randomization Phase			Randomization	Blinded Treatment Phase			Post-Treatment Phase		
	Screening				Cycles 1 & 2		Cycles 3+			
	Day -90 to Day-1	Day -28 to Day -1	Day -14 to Day -1		Day 1[b]	Day 15	Day 1	Treatment Discontinuation	28-day Follow-up	Long-term Follow-up
Informed Consent	X									
Medical/Oncology History[c]	X									
Archival Tumor Tissue Sample[d]	X									
Physical Examination, Height[e], Weight		X			X		X	X		
Vital Signs[f]		X			X		X	X		
12-lead ECG[g]		X						X		
Prior/Concomitant Medications		X			X	X	X	X		
Disease Assessment/Tumor Scans[h]		X					X[i]	X	X[j]	X[j]
Patient-reported outcome (FOSI-18, EQ-5D)[k]		X			X		X	X	X	
ECOG Performance Status		X			X		X	X		
Hematology[l]			X		X	X	X	X		
Serum Chemistry[m]			X		X	X	X	X		
Serum/Urine Pregnancy (WOCBP only)[n]			X		X		X			
Urinalysis[o]			X							
CA-125 Measurement[p]			X		X		X	X	X[j]	X[j]
Randomization to Study Treatment				X[q]						
Blood Sample for Storage (required)					X					
Study Drug Dispensation					X		X			
Adverse Events[r]					X	X	X	X[s]	X[s]	
Plasma PK Sample					X[t]	X[t]	X[t]			
Serum AAG Sample					X[u]	X[u]	X[u]			
Tumor Tissue Biopsy (optional)								X[v]		

Table 4. Schedule of Assessments

Subsequent Treatments, Secondary Malignancy Monitoring, and Overall Survival[w]									X	X

AAG = alpha-1 acid glycoprotein, ALP = alkaline phosphatase, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, *gBRCA* = germline breast cancer gene, BUN = blood urea nitrogen, CA-125 = cancer antigen 125, CO_2 = bicarbonate, CR = complete response, CT = computer tomography, CYP = cytochrome P450, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EQ-5D = Euro-QoL 5D, FOSI-18 = Functional Assessment of Cancer Therapy-Ovarian Symptom Index 18, QoL= quality of life, HRD = homologous recombination deficiency, INR = international normalized ratio, IVRS = interactive voice response system, GCIG = gynecologic cancer intergroup, MRI = magnetic resonance imaging, nbHRD = non-*BRCA* HRD, PET = positron emission tomography, PK = pharmacokinetic, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SAE = serious adverse event, WBC = white blood cell, WOCBP = women of child bearing potential

[a] = The study visit window in the double-blind treatment phase is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the subject's investigational product supply. Only 1 cycle of study drug will be dispensed to the subject on Day 1 of each cycle.

[b] = First dose of study drug in Cycle 1 should be administered within 3 days of randomization.

[c] = Patient's medical record must include prior treatments received, dates of administration, date of progression and how assessed, and radiology reports. *gBRCA* mutation status, if known, will also be recorded on the appropriate case report form.

[d] = Adequate archival tumor tissue samples must be provided to enable determination of HRD status for randomization, determination of HRD status prior to final analysis (if required), and storage for potential bridging to the final companion diagnostic test.

[e] = Height at screening only.

[f] = Vital signs (blood pressure, pulse, and temperature) to be taken predose on drug administration days, after the patient has been resting for at least 5 min.

[g] = Heart rate, PR, QRS, QT, QTc, and rhythm. Investigator to review results and assess as normal or abnormal (clinically significant or not clinically significant). ECGs to be repeated as clinically indicated.

[h] = Disease assessments to consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

[i] = Tumor scans to be performed within 7 days prior to end of every 3rd cycle of treatment. Disease progression will only be determined by RECIST. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST per the protocol schedule of assessments. If a patient who had residual disease at study entry is noted to have a best response of CR or PR during the blinded treatment phase, a confirmatory scan should be done 4 weeks after the response was first noted/documented.

[j] = To be performed every 12 (± 2) weeks through to investigator-assessed disease progression for any patient who discontinued from study treatment for reason other than disease progression or death.

[k] = The FOSI-18 and EQ-5D instruments must be completed prior to other scheduled study procedures and dosing (if applicable) at Screening, on Day 1 of each treatment cycle, at treatment discontinuation, and at the 28-day post-treatment discontinuation follow-up visit for all patients.

Table 4. Schedule of Assessments

[l] = Includes hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a central laboratory. A duplicate sample may be collected and analyzed by the local laboratory for immediate treatment decisions.

[m] = Includes total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, ALP, ALT, AST, total cholesterol, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus. Blood will be analyzed by a central laboratory. A duplicate sample may be collected and analyzed by the local laboratory for immediate treatment decisions.

[n] = Women of childbearing potential must have a negative serum pregnancy test result <3 days prior to the first dose of study drug. A serum or urine pregnancy test (investigator's discretion) must be performed <3 days prior to Day 1 of every cycle during the treatment phase. A serum pregnancy test must be performed at the treatment discontinuation visit. All tests will be performed by a local laboratory.

[o] = Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings abnormal, perform microscopic evaluation to assess abnormal findings. Urinalysis to be repeated as clinically indicated.

[p] = CA-125 measurement should be performed at Screening, on Cycle 1, Day 1, at the same time disease assessment scans are performed, and as clinically indicated. All CA-125 measurements will be performed by a central laboratory.

[q] = Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy. Randomization will occur by a central randomization procedure using an IVRS/IWRS. Patients will be stratified based on HRD classification (tBRCA, nbHRD or biomarker negative), interval between completion of penultimate platinum regimen and disease progression (6 to 12 or > 12 months) by radiologic assessment, and best response (RECIST CR, RECIST PR, or GCIG CA-125 response) to most recent platinum regimen. All responses require that CA-125 be <ULN.

[r] = AEs that occur after first dose through to 28 days after last dose of study drug will be recorded.

[s] = Ongoing SAEs will be followed to resolution.

[t] = PK samples to be collected on Day 15 of Cycle 1 (in morning or afternoon, after dose taken earlier in day), on Day 1 of Cycle 2 (prior to dosing), on Day 15 of Cycle 2 (in morning or afternoon, after dose taken earlier in day), and on Day 1 of Cycle 4 and Cycle 7 (prior to dosing). At least one morning post-dose sample and one afternoon post-dose sample must be taken for each patient.

[u] = Serum AAG sample to be collected on the same day as the PK sample. Sample should be collected at the same time as the hematology and serum chemistry samples for central laboratory testing.

[v] = An optional tumor biopsy may be collected from patients at time of disease progression. Additional consent is required. Refer to the Pathology Charter for detailed sample handling instructions.

[w] = All patients discontinued from treatment, regardless of reason, should be followed for subsequent treatments, secondary malignancy, and survival every 12 weeks until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (i.e., laboratory and/or pathology reports).

9.2 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to randomization. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care.

Up to 90 days prior to randomization:

- Medical history, including demographic information (birth date, race, gender, etc.) and smoking status, and oncology history, including date of diagnosis for ovarian, primary peritoneal, or fallopian tube cancer (and other malignancy, if applicable), prior treatments received, dates of administration, best response achieved, date of progression and how assessed, radiology reports, and *gBRCA* mutation status (if known)
- FFPE archival tumor tissue sample. Sufficient archival FFPE tumor tissue (enough for 1 x 4 µm section for H&E and approximately 8 to 12 x 10 µm sections, or equivalent) for planned analyses should be provided. Refer to the Pathology Charter for detailed sample handling instructions.
    - The most recently collected tumor tissue sample should be provided, if available.
    - Submission of a tumor block preferred; if sections are provided, these must all be from the same tumor sample.
    - Sample must be submitted to the central laboratory at least 3 weeks prior to planned start of treatment in order to enable stratification for randomization

Up to 28 days prior to randomization:

- PRO collected using the FOSI-18 and EQ-5D instruments
- Physical examination by body system, including height and weight
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG
- Prior and concomitant medications and any surgical procedures
- Disease assessment/tumor scans: tumor assessments should consist of clinical examination and appropriate imaging techniques (including CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST; other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment.
- ECOG performance status (Appendix D)

Up to 14 days prior to randomization:

- Hematology (hemoglobin, hematocrit, white blood cell [WBC] and differential [with ANC], and platelet count

- Serum chemistry (total protein, albumin, creatinine, or estimated GFR using the Cockcroft Gault formula, blood urea nitrogen [BUN] or urea, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus) and total cholesterol
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones) ≤14 days prior to the first dose of study drug. If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings
- CA-125 measurement

Up to 3 days prior to first dose of study drug:

- Serum pregnancy test for women of childbearing potential

9.3 Treatment Phase

9.3.1 Day 1 of Cycles 1 and 2

The following procedures/assessments will be completed before study drug is administered:

- PRO using the FOSI-18 and EQ-5D instruments
- Physical examination
- Weight
- Vital Signs
- Concomitant medications and procedures
- ECOG performance status (Appendix D)
- Hematology
- Serum chemistry
- Urine or serum pregnancy for women of childbearing potential (Cycle 2 only)
- CA-125 measurement
- Blood sample for storage (Cycle 1 only)
- Study drug dispensation
- AE monitoring
- Plasma PK sample (prior to first dose taken that day) (Cycle 2 only; see Section 9.5.1)
- Serum sample for AAG sample (Cycle 2 only)

Study drug will be dispensed to the patient in sufficient quantity to last until the next treatment cycle. Patients will ingest study drug twice daily at about the same times every day, as close to 12 hours apart as possible. Each dose of study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food

(with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their electronic dosing diary.

Patients will be instructed to refrain from taking their first dose of study drug at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

9.3.2 Day 15 of Cycles 1 and 2

The following procedures will be completed:

- Concomitant medications and procedures
- Hematology
- Serum chemistry
- AE monitoring
- Plasma PK sample (in morning or afternoon following the first dose of study drug taken this day; see Section 9.5.1)
- Serum sample for AAG analysis *(note: sample can be collected at the same time as hematology and serum chemistry)*

Patients will ingest study drug twice daily at about the same times every day, at close to 12 hours apart as possible. Each dose of study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their electronic dosing diary.

9.3.3 Day 1 of Cycles 3 and Beyond

The following procedures will be completed before study drug is administered:

- PRO using the FOSI-18 and EQ-5D instruments
- Physical examination
- Weight
- Vital signs
- Concomitant medications and procedures
- Disease assessment/tumor scans at the end of every 3rd cycle of treatment (within 7 days prior to the start of the next cycle)
- ECOG performance status (Appendix D)
- Hematology
- Serum chemistry
- Urine or serum pregnancy for women of childbearing potential

- CA-125 measurement
- AE monitoring
- Plasma PK sampling (prior to the first dose of study drug taken this day; Cycles 4 and 7 only; see Section 9.5.1)
- Serum sample for AAG analysis *(note: sample can be collected at the same time as hematology and serum chemistry)* (Cycles 4 and 7 only)

Study drug will be dispensed to the patient in sufficient quantity to last until the next clinic visit. A single dose of study drug will be administered during the current clinic visit with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Patient will record dosing information in their electronic dosing diary.

Patients will continue dosing with study drug at home on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal), taking doses twice daily at about the same times every day. Study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients will record dosing information in their electronic dosing diary.

9.4 Post-Treatment Phase

9.4.1 Treatment Discontinuation

Upon treatment discontinuation, regardless of the reason, patients will have a Treatment Discontinuation visit. The following procedures will be performed:

- PRO using the FOSI-18 and EQ-5D instruments
- Physical examination
- Weight
- Vital signs
- 12-lead ECG
- Concomitant medications and procedures
- Tumor scans (using the same methodology as was used at screening) if reason for treatment discontinuation was other than disease progression based on radiologic assessment
- ECOG performance status (Appendix D)
- Hematology
- Serum chemistry
- Serum pregnancy test for women of childbearing potential
- CA-125 measurement
- AE monitoring

- Optional tumor tissue biopsy collection at time of disease progression/treatment discontinuation (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

9.4.2 28-day Follow-up

The following procedures will be performed for all patients at 28 (±3) days after the last dose of study drug:

- PRO collected using the FOSI-18 and EQ-5D instruments
- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans and CA-125 measurement should continue to be performed at 12 (±2) week intervals until disease progression, as assessed by the investigator.
- CA-125 measurement
- AE monitoring

9.4.3 Long-term Follow-up

- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans and CA-125 measurement should continue to be performed at 12 (±2) week intervals until disease progression, as assessed by the investigator.
- Subsequent treatments, secondary malignancy monitoring, and overall survival information will be collected for all patients every 12 weeks until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (i.e., laboratory and/or pathology reports).

9.5 Methods of Data Collection

Hematology, serum chemistry, urinalysis, and assays described below will be performed centrally. Serum and/or urine pregnancy, if applicable, will be performed locally. Please refer to the Pathology Charter and/or Laboratory Manual for details on collecting and processing all samples that will be sent to central/core laboratories.

9.5.1 Pharmacokinetic Evaluations and AAG Measurement

For all patients, 4 mL blood samples for rucaparib population PK analysis will be drawn at the following time points:

- Day 15 of Cycle 1 (in morning or afternoon, after dose taken earlier in the day)
- Day 1 of Cycle 2 (before first dose taken that day)
- Day 15 of Cycle 2 (in morning or afternoon, after dose taken earlier in the day)
- Day 1 of Cycle 4 and 7 (before first dose taken that day)

At least one morning post-dose sample and one afternoon post-dose sample must be taken for each patient.

Serum samples for AAG analysis will be collected on the same day as PK samples.

Central laboratories will be used for bioanalysis of plasma rucaparib levels and AAG measurement. Please refer to the laboratory manual for details on collection and processing of blood PK samples.

9.5.2 Biomarker Analysis – FFPE Tumor Tissue

Archival tumor tissue must be located during the screening process and submitted to the central laboratory as soon as possible for determination of HRD status. Archival tumor tissue is required for HRD stratification for randomization and for storage for potential bridging to a validated companion diagnostic test.

9.5.3 Biomarker Analysis – Blood

A blood sample collected prior to first dose of study drug will be stored. Prior to final analysis, genomic DNA may be analyzed in an exploratory fashion in order to determine whether the mutation is germline or somatic.

9.5.4 Safety Evaluations

9.5.4.1 Adverse Event Assessment

The investigator is responsible for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs during study participation, beginning after the first dose of study drug and until 28 days after the last dose of study drug. Any ongoing serious adverse events (SAEs) will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (Version 4.0) and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 10.

9.5.4.2 Prior and concomitant medications

Prior concomitant medications will be recorded during screening and concomitant medications will be collected from study entry until the Treatment Discontinuation visit.

9.5.4.3 Clinical Laboratory Investigations

With the exception of samples for serum pregnancy, all other samples collected will be analyzed by a central laboratory; a duplicate sample may be collected and analyzed by the local laboratory for immediate treatment decisions. The panels of laboratory tests to be performed are shown below:

Hematology: Hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count at screening (to be performed ≤14 days prior to the first dose of study drug), at clinic visits during treatment, and at the Treatment Discontinuation visit. Hematology results must be reviewed by the investigator prior to the start of treatment with oral rucaparib or placebo.

Clinical Chemistry: Total protein, albumin, creatinine, or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, total cholesterol, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus at screening (to be performed ≤14 days prior to the first dose of study drug), on Day 1 of each cycle during treatment, and at the Treatment Discontinuation visit. Clinical chemistry results must be reviewed by the Investigator prior to the start of initial treatment with study drug.

Urinalysis: Performed on freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones per the schedule of evaluations. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening only, but may be repeated if clinically indicated.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE per the criteria specified in Section 10.4.

9.5.4.4 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature. Vital signs will be performed at most study visits.

9.5.4.5 12-Lead Electrocardiograms

For all patients, 12-lead ECGs will be taken at screening (within 28 days prior to first rucaparib dose) and at Treatment Discontinuation

The following will be measured or calculated: heart rate, PR, QRS, QT, QTc, and rhythm. The investigator will analyze the ECGs locally and assess the results as normal or abnormal (clinically significant or not clinically significant).

ECGs will be repeated as clinically indicated.

9.5.4.6 Body Weight and Height

Height will be measured during the Screening visit only. Weight will be measured per institutional guidelines at Screening, on Day 1 of each cycle, and at the End of Treatment visit.

9.5.4.7 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Physical examinations will be performed at screening (complete) and at most study visits (limited as appropriate).

9.5.4.8 ECOG Performance Status

ECOG performance status (Appendix D) will be assessed at screening, on Day 1 of each cycle, and at the Treatment Discontinuation visit. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

9.5.5 Efficacy Evaluations

9.5.5.1 Disease Assessments

Tumor assessment measurements will be performed at screening, at the end of every 12 weeks of treatment, at discontinuation of treatment, and as clinically indicated.

Disease assessment will comprise clinical examination and appropriate imaging techniques (CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. If a patient has known brain metastases, this disease should be evaluated at each required assessment. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Investigators should perform scans of the anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status.

Tumor response will be interpreted using RECIST v1.1 (Appendix B). Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST per the protocol schedule of assessments.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans and CA-125 measurement performed at 12 (± 2) week intervals until disease progression, as assessed by the investigator.

9.5.5.2 Tumor Markers

CA-125 measurement will be performed at screening, on Day 1 of Cycle 1, at the end of every 12 weeks of treatment (i.e. at the same time as disease assessment scans are performed), at discontinuation of treatment, and as clinically indicated. All CA-125 measurements will be performed by a central laboratory.

9.5.6 Patient-Reported Outcomes

PRO utilizing the FOSI-18 and EQ-5D instruments (see Appendix E) will be assessed at screening, on Day 1 of every treatment cycle, at treatment discontinuation, and at the 28-day follow-up visit. Patients will complete the instruments on an electronic device before any other scheduled study procedures are performed and dosing occurs (if applicable). The electronic device is a Class 1 listed (i.e. approved) device.

9.5.7 Appropriateness of Measurements

The assessments planned in the protocol are widely used and recognized as reliable, accurate and relevant.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered a pharmaceutical product. The pharmaceutical product does not necessarily have a causal relationship with the AE. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

For the purposes of this study, disease progression of the patient's tumor with new or worsening symptoms must be documented as an AE. However, disease progression documented solely by radiographic evidence with no new or worsening symptoms will not require reporting as an AE.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a nonleading question (e.g., "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). AEs will be reported on the AE eCRF. Symptoms reported spontaneously by the patient during the physical examination will also be documented on the AE eCRF.

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (including after informed consent is given and prior to dosing) that:

- Results in death.
- Is immediately life-threatening (i.e., the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly or birth defect.
- Is an important medical event based upon appropriate medical judgment; it may jeopardize the patient or may require intervention to prevent one of the other outcomes noted above.

10.3 Exceptions to Serious Adverse Event Reporting

The following are not considered SAEs and therefore are not required to be reported to the Sponsor:

- Pre-planned or elective hospitalization, including social and/or convenience situations (e.g., respite care).

- Overdose of study drug or concomitant medication, unless there is an AE that meets SAE criteria (e.g., hospitalization), as a direct consequence of the overdose. This should be entered as Overdose - followed by the appropriate AE/SAE term.

- Progression of the patient's underlying cancer (disease progression) documented solely on radiographic evidence with no new or worsening symptoms. (Note: disease progression manifested with clinical signs/symptoms should be documented as an AE on the eCRF).

10.4 Clinical Laboratory Assessments and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the list of reference ranges from the local laboratory. In some cases, significant change in laboratory values within the normal range may require similar assessment.

An abnormal value that is not already associated with an AE is to be recorded as an AE only if one of the following criteria is met:

- It resulted in treatment modification (reduction of dose, interruption of dosing, or permanent discontinuation of study drug)
- It required intervention / management
- It is suggestive of organ toxicity
- The Investigator considers it to be clinically significant

10.5 Pregnancy

If a patient becomes pregnant during the course of the study, study drug dosing should be held immediately.

Pregnancy is not considered to be an AE or SAE; however, all pregnancies must be reported to the Sponsor using the Clinical Pregnancy Report form within the same timelines as for as SAE.

All pregnancies should be followed through to outcome whenever possible. Once the outcome of a pregnancy is known, the Clinical Pregnancy Outcome Report form should be completed and submitted to the Sponsor.

10.6 Recording of Adverse Events and Serious Adverse Events

All AEs, serious and non-serious, will be fully documented on the appropriate eCRF. For each AE, the Investigator must provide duration (start and end dates or ongoing), intensity, relationship to study drug, and indicate whether specific action or therapy was required.

Any AE/SAE that occurs from the time informed consent is obtained until 28 days after last dose of study drug administration will be collected, documented and reported to the Sponsor by the Investigator according to the specific definitions and instructions detailed within this protocol,

whether dosing has occurred or not. After the 28-day window, only SAEs assessed as related to study drug should be reported. If a patient is determined to be a screen failure, no further AEs/ SAEs are required to be reported once that determination has been made, with the exception of AEs/SAEs deemed related to a protocol-specified procedure.

All SAEs, regardless of relationship to study drug, must be reported to the Sponsor/designee within 24 hours of the Investigator's knowledge. This should be done by faxing or emailing the completed SAE report to the Sponsor/designee contact provided on the SAE report form.

Investigators must follow patients with SAEs until the event has resolved or the condition has stabilized. If the patient is lost to follow-up with an ongoing SAE, this should be captured accordingly on a follow-up SAE report.

10.6.1 Intensity of Adverse Events

Severity refers to the intensity of an AE. The severity of each AE will be categorized using the NCI CTCAE, Version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf).[48]

For any term that is not specifically listed in the CTCAE, intensity should be assigned a grade of 1-5 using the following CTCAE guidelines:

- Mild (Grade 1): mild or asymptomatic symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (Grade 2): limiting age-appropriate instrumental activities of daily living; minimal, local or noninvasive intervention indicated
- Severe (Grade 3): limiting self-care activities of daily living; hospitalization indicated
- Life threatening (Grade 4): life-threatening consequences; urgent intervention indicated
- Fatal (Grade 5): results in death

10.6.2 Causal Relationship of Adverse Events to Investigational Medicinal Products

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as but not limited to: the disease under study, concurrent disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge.

Not Related To Study Drug	An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medication, disease under study, etc.) An AE that does not follow a reasonable temporal sequence from administration of the study drug. An AE that does not reappear or worsen when study drug is restarted. An AE for which an alternative explanation is likely, but not clearly identifiable.

Related to Study Drug	An AE that is difficult to assign to alternative causes. An AE that follows a strong or reasonable temporal sequence from administration of study drug. An AE that could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. An AE that is confirmed with a positive rechallenge or supporting laboratory data.

10.6.3 Outcome

The investigator will record the outcome for each AE according to the following criteria:

Outcome

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Ongoing
- Death
- Unknown/Lost to follow-up

10.7 Regulatory Aspects of Adverse Event Reporting

SAEs and pregnancy must be reported to the safety contract research organization (CRO) within 24 hours of knowledge of the event, according to the procedures below. It is important that the investigator provide an assessment of relationship of the SAE to study treatment at the time of the initial report. The SAE Report form must be used for reporting SAEs, the Clinical Pregnancy Report form must be used for reporting pregnancies, and the Clinical Pregnancy Outcome Report form must be used for reporting the outcome of any pregnancy.

All SAEs, irrespective of relationship to study treatment, and pregnancies must be reported within 24 hours of knowledge of the event by facsimile (fax) or email to:

PRA International

Region(s)	**Fax Number**	**Email Address**
North America:	[redacted]	[redacted]
All Other Regions:	[redacted]	[redacted]

Additional information should be reported via email or fax to the appropriate contact above. Further details on SAE/pregnancy reporting can be found in the investigator's file.

For urgent SAE-related questions, or when guidance is required from a safety specialist, investigational sites should call the following telephone numbers:

PRA International

Region(s)	Telephone Number
North America	[redacted]
All Other Regions:	[redacted]

Clovis Oncology, Inc. (Clovis Oncology), or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA, according to 21 Code of Federal Regulations (CFR) 312.32, to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), Clovis Oncology or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

Clovis Oncology or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

10.8 Independent Data Monitoring Committee

No formal efficacy interim analyses are planned.

An Independent Data Monitoring Committee (IDMC) will be established to review safety and efficacy data in compliance with a prospective charter. The IDMC will be comprised of medical oncologists with experience in treating women with ovarian cancer and a statistician, all of whom are not otherwise involved in the study as investigators. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC charter, which will be endorsed and signed by the IDMC prior to the first data review meeting.

The IDMC will:

- Review safety and efficacy of rucaparib compared with placebo to ensure the study is beneficial to patients
- Ensure the study is conducted in a high quality manner
- Monitor the size of the tBRCA subgroup and the known *gBRCA* group

Following data review, the IDMC will recommend continuation, revision, or termination of the study and/or continuing or halting enrollment into a particular subgroup. The IDMC will meet at least semi-annually after sufficient data has been collected. The IDMC chairperson may convene formal IDMC meeting if there are safety concerns. The Sponsor can also request an IDMC review of safety data.

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

Safety Table Population – The safety population will consist of all patients who received at least one dose of protocol-specified treatment.

Intent-to-treat (ITT) Population – The ITT population will consist of all randomized patients.

Response Evaluable Population – The response evaluable population will consist of all patients evaluable for response by RECIST (Appendix B). Patients evaluable for a RECIST response must have at least one measureable target lesion at baseline and at least one post-baseline tumor assessment.

11.2 Statistical Methods

11.2.1 General Considerations

Variables registered on a continuous scale will be presented using the following descriptive statistics: N, mean, standard deviation, median, minimum and maximum. Continuous variables may also be presented using frequencies and percentages among appropriate categorizations. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. The number of patients with events and the number of censored patients will also be presented. The stratified logrank test will be used to compare the time-to-event distributions between the randomized treatment groups. In addition, the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

The primary and key secondary endpoints will be tested among the tBRCA and all HRD subgroups, and all randomized patients, using an ordered step-down multiple comparisons procedure. Investigator determined PFS (invPFS) in the tBRCA subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the tBRCA subgroup is statistically significant then irrPFS in the tBRCA subgroup will be tested at a one-sided 0.025 significance level and if significant, invPFS and irrPFS will be tested in the all HRD subgroup followed by invPFS and irrPFS in all randomized patients. Continuing in an ordered step-down manner, the PRO of disease symptoms utilizing the FOSI-18 DRS-P subscale will be tested at the one-sided 0.025 significance level in the tBRCA, all HRD, and all randomized patients subgroups and then for the remaining key secondary endpoints of PRO utilizing the FOSI-18 total score and OS. Once statistical significance is not achieved for one test the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure.

All data will be used to their maximum possible extent but without any imputations for missing data.

All statistical analyses will be conducted with the SAS® System, version 9.1 or higher.

Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

11.2.2 Patient Disposition

Patient disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency counts, and the corresponding percentages.

11.2.3 Baseline Characteristics

All demographic and baseline characteristics will be summarized for the safety population.

The following variables will be summarized with frequency tabulations:

- Time since diagnosis of HGSOC (months): > 12-24, > 24
- Baseline laboratory parameters: graded based on CTCAE
- HRD status for stratification at randomization: tBRCA, nbHRD, biomarker negative
- Interval between completion of penultimate platinum regimen and disease progression (6 to 12 months of >12 months) by radiologic assessment
- Best response to most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST with normalization of CA-125] or PR [defined as partial radiologic response by RECIST and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN.

Descriptive statistics may also be used to summarize the continuous variables.

11.2.4 Efficacy Analyses

All efficacy evaluations will be conducted using the ITT population.

11.2.4.1 Primary Efficacy Analysis

The primary efficacy endpoint for the study is invPFS by RECIST. Investigator-determined PFS is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria (Appendix B), as assessed by the investigator, or death due to any cause, in molecularly defined subgroups. The stratification factors included in the primary analysis of invPFS will be as follows:

- HRD classification (tBRCA or nbHRD or biomarker negative)
- Interval between completion of penultimate platinum regimen and disease progression (6 to 12 months or >12 months) by radiologic assessment
- Best response to the most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST with normalization of CA-125] or PR [defined as partial

response by RECIST and/or a GCIG CA-125 response]). All responses required that CA-125 be <ULN.

Tumor HRD status by the FCTA will be determined after randomization, but before the final efficacy analysis, so that the primary endpoint (PFS in molecularly defined subgroups) can be assessed prospectively.

11.2.4.2 Secondary Efficacy Analyses

Secondary efficacy endpoints are:

- Disease progression according to RECIST v1.1, as assessed by IRR, or death from any cause (irrPFS), in molecularly defined subgroups
- Time to a 4-point decrease in the FOSI-18 DSR–P subscale
- Time to an 8-point decrease in the FOSI-18 total score
- OS

irrPFS

PFS for secondary efficacy analysis is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by IRR, or death due to any cause, whichever occurs first.

PRO of disease-related symptoms as measured by the FOSI-18 DRS–P subscale

The time to an event in PRO of worsening of disease symptoms will be defined as the time from randomization to a 4-point reduction in the FOSI-18 DRS-P subscale. Patients without a 4-point reduction will be censored on the date of their last PRO evaluation.

PRO as measured by the total score of the FOSI-18

An event in worsening of PRO utilizing the complete FOSI-18 instrument will be defined as the time from randomization to an 8-point reduction in the total score. Patients without an 8-point reduction will be censored on the date of their last PRO evaluation.

Overall survival

Overall survival (OS) is defined as the number of days from the date of randomization to the date of death (due to any cause). Patients without a known date of death will be censored on the date the patient was last known to be alive.

11.2.5 Safety Analyses

Safety endpoints are incidence of AEs, clinical laboratory abnormalities, and dose modifications.

Data from all patients who receive at least one dose of study drug will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized.

11.2.5.1 Adverse Events

AEs will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE whenever possible. Only treatment-emergent adverse events (TEAEs) will be collected: TEAEs are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days.

The number and percentage of patients who experienced TEAEs for each system organ class (SOC) and preferred term will be presented. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

Separate tables will be presented as follows:

- All TEAEs
- TEAEs by CTCAE grade
- Grade 3 or greater TEAEs
- Serious TEAEs
- TEAEs with an outcome of death
- TEAEs leading to discontinuation of study medication
- TEAEs resulting in interruption/delay of study medication
- TEAEs resulting in dose reduction of study medication

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least one TEAE of the given grade will be summarized.

11.2.5.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will be presented in SI units. The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include shift tables based on CTCAE for shifts in grade from baseline to maximum, minimum and last value during the on-treatment period.

Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings. Separate listings will be produced for clinically significant laboratory abnormalities (i.e., those that meet Grade 3 or 4 criteria according to CTCAE).

11.2.5.3 Vital Sign Measurements

The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign data will include descriptive statistics (N, mean, SD, minimum, median, third quartile and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, SD, minimum, median and maximum) of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

11.2.6 Population PK Analysis

The PK endpoint is individual model parameter estimates of rucaparib and covariates identification.

A specific population PK data analysis plan will be developed that will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques.

11.2.7 Exploratory Analyses

The endpoints for the exploratory analyses are:

- Change from baseline in CA-125 measurements by the central laboratory
- PFS2 (PFS on the subsequent line of treatment) defined as the time from randomization to the second event of disease progression or death, as assessed by the investigator
- ORR per RECIST v1.1, as assessed by both investigator and IRR, in patients with measureable disease at study entry
- DOR per RECIST Version 1.1, as assessed by both investigator and IRR
- PRO as measured by the EQ-5D total score
- Rucaparib PK, invPFS, irrPFS, CA-125, AEs, clinical laboratory abnormalities, and dose modifications

11.2.7.1 Change from Baseline in CA-125

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled pos-tbaseline visit and for the final visit for the CA-125 measurements from the central laboratory. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

The association between the change from baseline to the end of Cycle 2 in CA-125 measurements and invPFS will be evaluated using a Cox proportional hazards model. A measure of CA-125 kinetics such as the rate of change from baseline in CA-125 may also be associated with invPFS using a Cox model.

11.2.7.2 Progression Free Survival 2 (PFS2)

The second event of PFS, PFS2, is defined as the time from randomization to the second event of disease progression as assessed by the investigator, or death due to any cause. The first event of disease progression will be captured as the primary endpoint in this study and thus the second event will be the next event of disease progression as assessed by the investigator. This second event of PFS may be a documented event per RECIST guidelines or may be an event of symptomatic progression.

11.2.7.3 Overall Response Rate

ORR is defined as a best response of CR or PR using the RECIST v1.1 criteria (Appendix B), as assessed by both investigator and IRR, in patients with measurable disease at study entry. ORR will be summarized with frequencies and percentages in the safety population. Patients who are not evaluable for a RECIST response will be considered to have experienced disease progression.

11.2.7.4 Duration of Response

The DOR is measured from the time measurement criteria are met for CR/PR per RECIST v1.1 criteria (Appendix B), as assessed by both investigator and IRR, until the first date that recurrent or PD is objectively documented. The DOR will be summarized with descriptive statistics. Only patients with a response will be included in the summary.

11.2.7.5 Patient Reported Outcome EQ-5D

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled postbaseline visit and for the final visit for the EQ-5D instrument and the EQ VAS. Patients that do not have both a baseline measurement and at least one postbaseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

11.2.7.6 Relationship between Rucaparib Exposure and Efficacy and Safety

The primary endpoint of invPFS will be presented for subgroups of patients defined by levels of rucaparib exposure. These analyses are exploratory in nature so the definition of relevant subgroups may be data-driven.

11.3 Interim Analysis

No formal interim efficacy analyses will be performed.

11.4 Sample Size Considerations

The total enrollment planned is 540 patients. A minimum of 180 and a maximum of 200 patients with a deleterious *tBRCA* mutation will be enrolled. Enrollment of patients with a known deleterious *gBRCA* mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined. Prior to final efficacy analysis, HRD classification will be determined by the FCTA, which will evaluate homologous recombination gene mutations and/or extent of genomic scarring in tumor tissue.

Table 5 below provides estimated sample sizes and power calculations.

Table 5. Estimated Sample Sizes and Power Calculations

Group	Hazard Ratio	Cumulative N	Minimum Number of Events (70%)	Median PFS Placebo vs Rucaparib (months)	Power	One-sided Alpha
BRCA HRD	0.50	180	126	6 vs 12	90%	0.025
All HRD (BRCA + nbHRD)	0.60	300	210	6 vs 10	90%	0.025
ITT Population (BRCA + nbHRD + Biomarker Negative)	0.70	540	378	6 vs 8.5	90%	0.025

The study will end after 70% of the patients in the tBRCA subgroup have an observed event of investigator-determined disease progression or death. If the minimum number of tBRCA patients are enrolled, then the study will end following the 126th event of investigator-determined disease progression or death. Similarly, if the maximum number of tBRCA patients are enrolled, then the study will end following the 140th event of investigator-determined disease progression or death. The IDMC will inform the Sponsor when the required number of PFS events have been observed in order to ensure the Sponsor remains blinded to which patients are in the tBRCA subgroup. If the nbHRD and/or biomarker negative subgroups have observed events of invPFS in fewer than 60% of the patients, the IDMC may recommend that the study continue for up to 6 more months if it is likely that the nbHRD and biomarker negative subgroups will observe enough additional events of PFS to reach 60%.

Following the collection of the required number of PFS events, the outstanding queries for all visits and events prior to the data cutoff date will be resolved and the database will be locked before the blind break and subsequent primary analysis.

12 PATIENT DISPOSITION

12.1 Removal of patients from therapy or assessment

A patient must be discontinued from treatment with study drug if any of the following apply:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative
- Progression of patient's underlying disease by RECIST as assessed by the investigator
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy

The sponsor may discontinue the trial early for any of the reasons noted in Section 13.6.

12.2 Procedures for discontinuation

The sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of study drug must be documented in the eCRF and source documents. To the extent possible, end-of-study procedures should be performed on all patients who receive study drug. The Treatment Discontinuation visit should occur 28 (±3) days following the last dose of study drug. Patients will be followed for 28 days after the last dose of study drug for safety; those with ongoing SAEs will be followed until either resolution or stabilization has been determined.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; Food and Drug Administration (FDA) regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki.

13.1.1 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to concerned regulatory agencies for approval prior to the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 (or equivalent) and provide the completed form according to written instructions to the sponsor (or designee). Each investigator must submit to the sponsor (or designee) financial disclosure information according to national law and/or local regulations.

U.S.-generated data will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The trial will be registered at www.clinicaltrials.gov, EudraCT, and other applicable trial registry systems as appropriate.

13.1.2 Independent Ethics Committee/Institutional Review Board

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, drug dosing diaries, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IEC/IRB. This also applies to protocol amendments.

Clovis Oncology will supply relevant data for the investigator to submit the study protocol and additional study documents to the IEC/IRB. The principal investigator will submit the study protocol for review and approval by an IEC/IRB, according to national law and/or local regulations, and will provide the IEC/IRB with all appropriate materials.

Verification of the IEC's/IRB's unconditional approval of the study protocol and the written informed consent form will be transmitted to Clovis Oncology. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IEC/IRB approval of the study protocol has been received, the investigator has obtained the signed and dated informed consent form, and the sponsor is notified.

The principal investigator will submit appropriate reports on the progress of the study to the IEC/IRB at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IEC/IRB and sponsor.

The IEC/IRB must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

13.2 Confidentiality of Information

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient initials and an identification code (i.e., not names) should be recorded on any form submitted to the sponsor and the IRB. The investigator must record all screened and enrolled patients in the eCRF. The investigator must have a list where the identity of all treated patients can be found.

The investigator agrees that all information received from Clovis Oncology, including, but not limited to, the Investigator's Brochure, this protocol, eCRFs, the protocol-specified treatment, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

13.3 Patient Informed Consent

All information about the clinical study, including the patient information and the informed consent form, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed informed consent forms from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

The informed consent form, prepared by the investigator with the assistance of the sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the sponsor.

The patient must be provided with the patient information and informed consent form consistent with the study protocol version used and approved by the relevant IEC/IRB. The informed consent form must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the informed consent form. A copy of the signed informed consent form will be retained by the patient and the original will be filed in the investigator file unless otherwise agreed.

13.4 Study Monitoring

On behalf of Clovis Oncology, a CRO monitor will contact and visit the investigator at the study center prior to the entry of the first patient (unless Clovis or the CRO has worked with the center recently in which case this initial visit maybe waived) and at predetermined appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit. Visits may also be conducted by Clovis Oncology personnel.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (i.e., the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (i.e., source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the investigator file. Representatives from Clovis Oncology may also contact and visit the investigators and monitor data during the study.

13.5 Case Report Form

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Prior to study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

For each patient enrolled, an eCRF should be completed and reviewed by the principal investigator or co-investigator within a reasonable time period (<2 weeks) after data collection. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

Full information regarding electronic data capture and completing eCRFs is included in the investigator files. All questions or comments related to electronic capture should be directed to the assigned monitor.

13.6 Study Termination and Site Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, Clovis Oncology and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Clovis Oncology reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30 day written notification will be given.

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical
- The stated objectives of the study are achieved
- The sponsor discontinues the development of oral rucaparib

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

13.7 Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of Clovis Oncology. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

13.8 Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, drug accountability records, correspondence with the IEC/IRB and Clovis Oncology, and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, copies of all eCRFs,

query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and Clovis Oncology or its designees.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by Clovis Oncology. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of Clovis Oncology. Should the investigator wish to assign the study records to another party or move them to another location, Clovis Oncology must be notified in writing of the new responsible person and/or the new location. Clovis Oncology will inform the investigator, in writing, when the trial-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

13.9 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of Clovis Oncology and signed by the sponsor's chief medical officer, thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

13.10 Study Publication

The results of this study will be published and/or presented at scientific meetings in a timely manner. Any formal publication of study results will be a collaborative effort between the sponsor and the investigator(s). All data generated from this study are the property of Clovis Oncology and shall be held in strict confidence along with all information furnished by Clovis Oncology. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of Clovis Oncology. Written permission to the investigator will be contingent on the review by Clovis Oncology of the statistical analysis and manuscript, and will provide for nondisclosure of Clovis Oncology confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties. The sponsor may request a delay in publication if there are important intellectual property concerns relating to publication, but does not have the right to suppress publication of the study results indefinitely.

Result of this pivotal study will also be posted to www.clinicaltrials.gov within 30 days of marketing approval for rucaparib in the US and to EudraCT within one year of the end of the trial.

13.11 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by Clovis Oncology. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, standard operating procedures (SOPs), ICH GCPs, and the applicable regulatory requirements. The investigator and the sponsor may also be subject to an inspection by FDA, European Regulatory authorities, or other applicable regulatory authorities at any time. The auditor and regulatory authorities will require authorization from the investigator to have direct access to the patients' medical records. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

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15 APPENDICES

Appendix A. List of Homologous Recombination Genes for HRD Stratification by the ICTA

Appendix B. Response Evaluation Criteria in Solid Tumors Criteria

Appendix C. Gynecological Cancer Intergroup (GCIG) Guidelines

Appendix D. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Appendix E. Quality of Life Questionnaires

Appendix F. Inhibitors and Inducers of CYP1A2 and CYP3A

15.1 Appendix A

List of Homologous Recombination Genes for HRD Stratification by the ICTA

tBRCA	nbHRD		Biomarker-negative
BRCA1	*ATM*	*FANCI*	Genes not included in the tBRCA or nbHRD groups
BRCA2	*ATR*	*FANCL*	
	ATRX	*FANCM*	
	BARD1	*MRE11A*	
	BLM	*NBN*	
	BRIP1	*PALB2*	
	CHEK1	*RAD50*	
	CHEK2	*RAD51*	
	FANCA	*RAD51B*	
	FANCC	*RAD51C*	
	FANCD2	*RAD51D*	
	FANCE	*RAD52*	
	FANCF	*RAD54L*	
	FANCG	*RPA1*	

15.2 Appendix B

Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[31] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded n millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non target Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE = Not evaluable.			

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation

CT scans are required at screening and at the end of every 3rd cycle of treatment.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

15.3 Appendix C

Gynecological Cancer Intergroup (GCIG) Guidelines

GCIG Guidelines for Response Using CA-125[32]

GCIG CA 125 definitions are available at http://gcig.igcs.org/CA-125.html.

To be evaluable for response by CA-125 requires two pretreatment samples at least twice the upper limit of normal and at least two additional samples after the start of treatment.

A response to CA-125 has occurred if after two elevated levels before therapy there is at least a 50% decrease that is confirmed by a fourth sample. The four samples must satisfy the following criteria:

1. The two pretreatment samples must both be at least twice the upper limit of normal and at least 1 day but not more than 3 months apart;
2. At least one of the two pretreatment samples should be within 1 week of starting treatment;
3. The third sample must be ≤ 50% of the second sample;
4. The confirmatory fourth sample must be ≥ 21 days after sample 3 and ≤ 110% of sample 3;
5. Any intervening samples between samples 2 and 3 and between samples 3 and 4 must be ≤ 110% of the previous sample unless considered to be increasing because of tumor lysis.

Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical or surgical interference with their peritoneum or pleura during the previous 28 days.

15.4 Appendix D

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status	
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work or office work).
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead.

In the event performance status is assessed by the Karnofsky Performance Status scale, the following conversion chart applies.

Karnofsky Performance Status			**ECOG Performance Status**
General Description	**Score**	**Specific Description**	**Score**
Able to carry on normal activity and to work; no special care needed	100	Normal; no complaints; no evidence of disease	0
	90	Able to carry on normal activity; minor signs or symptoms of disease	1
	80	Normal activity with effort; some signs or symptoms of disease	
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work	2
	60	Requires occasional assistance, but is able to care for most of personal needs	
	50	Requires considerable assistance and frequent medical care	3
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance	
	30	Severely disabled; hospital admission is indicated although death not imminent	4
	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

15.5 Appendix E

National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy (NCCN-FACT) FACT - Ovarian Symptom Index (FOSI-18) instrument (NCCN-FACT FOSI-18) – English Version

Sample form and background available at: http://www.facit.org/FACITOrg/Questionnaires .

Patients will complete the instrument on an electronic device. This device is a Class 1 listed (i.e., approved) device.

Below is a list of statements that other people with your illness have said are important.

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy.....	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	O3	I have cramps in my stomach area	0	1	2	3	4
	HI7	I feel fatigued.....	0	1	2	3	4
	Cx6	I am bothered by constipation	0	1	2	3	4
	O1	I have swelling in my stomach area	0	1	2	3	4
	C3	I have control of my bowels	0	1	2	3	4
	GF5	I am sleeping well.....	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
TSE	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	O2	I have been vomiting	0	1	2	3	4
	BMT15	I am bothered by skin problems	0	1	2	3	4
	BMT5	I am able to get around by myself	0	1	2	3	4
	GF3	I am able to enjoy life.....	0	1	2	3	4
FWB	GF7	I am content with the quality of my life right now.....	0	1	2	3	4

Euro-QoL5D (EQ-5D) – English Version for the US

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

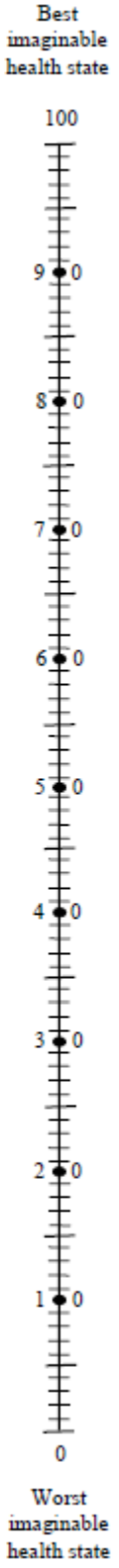
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



3

15.6 Appendix F

Inhibitors and Inducers of CYP1A2 and CYP3A

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit

CYP Enzyme	Strong Inhibitor (Avoid)	Moderate Inhibitor (Caution)
CYP1A2	Ciprofloxacin Enoxacin Fluvoxamine	Methoxsalen Mexiletine Phenylpropanolamine Thiabendazole Zileuton
CYP3A	Boceprevir Clarithromycin Conivaptan Grapefruit juice Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Voriconazole	Amprenavir Aprepitant Atazanavir Ciprofloxacin Darunavir/Ritonavir Diltiazem Erythromycin Fluconazole Fosamprenavir Grapefruit juice* Imatinib Verapamil

* The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Patients should be instructed to avoid grapefruit juice in this study.

CYP Enzyme	Strong Inducer (Avoid)	Moderate Inducer (Caution)
CYP1A2	N/A	Montelukast Phenytoin Smoking
CYP3A	Avasimibe Carbamazepine Phenytoin Rifampin St. John’s Wort	Bosentan Efavirenz Etravirine Modafinil Nafcillin

CONFIDENTIAL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or escriptiFallopian Tube Cancer

Protocol Number:	CO-338-014
Investigational Product:	Rucaparib (CO-338)
Eudra CT Number:	2013-000518-39
IND Number:	106,289
Development Phase:	Phase 3
Indications Studied:	Platinum-sensitive, high-grade serous and endometrioid epithelial ovarian, primary peritoneal, and fallopian tube cancer
Sponsor Name and Address:	Clovis Oncology, Inc. 5500 Flatiron Parkway Suite 100 Boulder, CO 80301 USA Phone Number: 303-625-5000 Facsimile Number: 303-245-0360
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and ICH GCP Guidelines. Essential study documents will be archived in accordance with applicable regulations.
Protocol Date:	9 September 2013
Amendment 1 Date:	4 November 2014
Amendment 2 Date:	9 March 2015
Amendment 3 Date:	7 July 2016

CONFIDENTIALITY STATEMENT

The information in this document contains commercial information and trade secrets that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable laws and regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

Coordinating Investigators for the Study

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Protocol Approval Signature Page

Protocol: CO-338-014

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Date: 7 July 2016

Amendment: 3

Reviewed and Approved by:

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

Protocol Acceptance Form

Protocol:	CO-338-014
Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer
Date:	7 July 2016
Amendment:	3

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature _____ Date _____

Name (printed) _____

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1 SYNOPSIS

Protocol Number	CO-338-014
Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rucaparib as Switch Maintenance Following Platinum-Based Chemotherapy in Patients with Platinum-Sensitive, High-Grade Serous or Endometrioid Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer
Study Phase	Phase 3
Introduction	Rucaparib is an orally available, small molecule inhibitor of poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1, PARP-2, and PARP-3 and is being developed for treatment of ovarian cancer associated with homologous recombination deoxyribonucleic acid (DNA) repair deficiency. The safety and efficacy of rucaparib has been evaluated in several Phase 1 and Phase 2 studies. Normal cells repair single-strand breaks (SSBs) in DNA primarily through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP-1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by homologous recombination DNA repair, a complex process involving multiple proteins, including those encoded by breast cancer susceptibility gene 1 and 2 (*BRCA1* and *BRCA2*), as well as many others. Homologous recombination pathway defects, either as an initiating event or late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. An analysis of the Cancer Genome Atlas (TCGA), which examined molecular changes in high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patients with HGSOC have homologous recombination deficiency (HRD).[1] Drivers of HRD include: 1. Germline mutations in the *BRCA1* and *BRCA2* genes (*gBRCA*). These are the strongest known hereditary factors for epithelial ovarian cancer (EOC), accounting for up to 15% of all EOC.[2, 3] These patients carry heterozygous deleterious mutations in their germline DNA and develop tumors when the remaining wild-type functional allele is inactivated (i.e. “second hit”). 2. Somatic *BRCA1/2* mutations (*sBRCA*) (6 – 8% of HGSOC patients)[1, 4] 3. Mutation in a homologous recombination gene other than *BRCA1/2* (approximately 16% of HGSOC patients).[1] Nonclinical studies by several groups have identified RAD proteins (eg, RAD51, RAD51C, RAD52, RAD54L),[5-8] Fanconi Anemia proteins (eg, FANCA, FANCC, FANCD2),[9-11] and many others (eg, ATM, ATR, CHEK1, CHEK2)[12-15] as being involved in homologous recombination. 4. Functional silencing of homologous recombination genes, such as through *BRCA* promoter methylation (approximately 10% of HGSOC patients)[1] or other mechanisms Inhibition of DNA damage repair in cancer cells, which are intrinsically genetically unstable, represents an attractive opportunity for the development of new therapies. Given the overlap in various DNA repair pathways, inhibition of a single pathway is unlikely to have a significant effect, whereas inhibition of multiple DNA repair pathways may lead to cell death, a concept known as synthetic lethality. Normal cells, with only one DNA repair pathway affected

Introduction (cont)	by inhibition of PARP, still have an intact DNA repair pathway that can compensate, whereas cancer cells with pre-existing HRD that are treated with a PARP inhibitor develop critically DNA repair deficiency and enter apoptosis. This concept of synthetic lethality has been demonstrated in landmark in vitro and in vivo studies[16, 17] as well as in several clinical trials that evaluated a single agent PARP inhibitor for the treatment of relapsed ovarian cancer and metastatic breast cancer with or without an associated germline *BRCA* mutation.[18-24] In vitro studies have also shown that cells deficient in or depleted of homologous recombination proteins other than BRCA1/2 have been associated with PARP inhibitor sensitivity.[25-28] It is possible that the 24% ORR observed in olaparib-treated ovarian cancer patients without evidence of a *gBRCA1/2* mutation[21] was due to HRD driven by a *sBRCA1/2* mutation or by an alteration in another key homologous recombination gene. Clinical activity in HGSOC has also been observed with switch maintenance PARP inhibitor therapy following response to platinum-based chemotherapy. Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median PFS (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio (HR) of 0.35 (95% CI, 0.25 – 0.49).[29] Patients with a *BRCA* mutation derived the most benefit (median PFS 11.2 vs 4.3 months; HR=0.18; 95% CI 0.11-0.31; $P<0.00001$).[30] It should be noted that the outcomes of *sBRCA* + *gBRCA* mutant patients were the same as *gBRCA* mutant patients alone, suggesting that, for stratification and analysis purposes in the present study, it is appropriate to not differentiate between germline and somatic mutations. Patients without a *BRCA* mutation also experienced significant benefit from treatment with olaparib (HR=0.53; 95% CI 0.33-0.84; $P=0.007$), suggesting that patients with DNA repair defects in genes other than *BRCA* are likely contributing to the overall PFS result.[30] The purpose of this study is to evaluate progression-free survival (PFS) of patients with platinum-sensitive, relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy. Prior to final analysis, patients will be placed into molecularly defined subgroups of HRD based on the Final Clinical Trial Assay (FCTA). It is anticipated that rucaparib will provide therapeutic benefit and increase PFS in patients with HRD.
Study Overview	This is a randomized, international, double-blind, placebo-controlled Phase 3 study evaluating rucaparib maintenance therapy in advanced ovarian cancer. The primary endpoint is PFS by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1[31] as assessed by the investigator. Risk/benefit will be assessed regularly by an Independent Data Monitoring Committee that will have access to unblinded datasets. This study will enroll patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer who achieved either a complete response (CR) by RECIST v1.1 or a partial response (PR), defined as either a RECIST v1.1 PR or a cancer antigen 125 (CA-125) response by Gynecologic Cancer Intergroup (GCIG) criteria,[32] to their last platinum-based regimen. All responses will require CA-125 that is within the

Study Overview (cont)	upper limit of normal (ULN). During the screening phase, each patient will have archival tumor tissue analyzed for mutations in homologous recombination pathway genes. Genes of interest will be sequenced using Foundation Medicine's next generation sequencing (NGS) test, which examines a panel of cancer-related genes, including *BRCA1/2* and other homologous recombination pathway genes. Patients will be stratified into one of three HRD subgroups (*BRCA1/2* mutation in tumor tissue [tBRCA], HRD due to mutation in a homologous recombination gene other than *BRCA1/2* [nonBRCA HRD (nbHRD)], or biomarker negative) for randomization based on the results obtained with Foundation Medicine's Initial Clinical Trial Assay (ICTA) (Appendix A). Enrollment of patients known *a priori* to harbor a *gBRCA* mutation classified as deleterious (pathogenic), suspected deleterious, or equivalent, on the most recent assessment, will be limited to 150. Enrollment of patients with a *BRCA* gene mutation detected in tumor tissue (tBRCA), including those known to harbor a *gBRCA* mutation, will be limited to 200. Once this cap is reached, newly screened patients identified as having a *BRCA* mutation in tumor tissue will be offered treatment in another study. The complete results of the Foundation Medicine NGS test, which examines exons of 287 genes as well as introns of 19 genes, will be provided to all patients who opt to receive this information and provide appropriate consent. Tumor tissue results for the *BRCA* genes will be provided to patients who consent to receive this information upon availability. Results for the remainder of the gene panel will be provided to consenting patients upon study treatment discontinuation. Results are to be disclosed to consenting patients by the study physician as part of an overall clinical discussion. In the event a mutation associated with hereditary cancer or other syndrome is detected in tumor tissue, the patient will be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline *BRCA* testing, this result will be entered into the clinical trial database. Mutations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether any mutation identified is of germline or somatic origin. Tumor DNA will also be assessed by the NGS test to detect the presence of genomic scars.[33-36] Analysis of specific genomic scarring patterns may identify tumors with HRD regardless of the underlying mechanism(s). The extent of genomic scarring and its utility in predicting clinical outcome with rucaparib will be assessed in a Phase 2 study (CO-338-017) that will be initiated in parallel with this Phase 3 study, but will be completed earlier. The insights from study CO-338-017 will be applied prospectively to the analysis of this Phase 3 study. The FCTA analysis plan (gene mutation and/or genomic scarring) and classification of HRD subgroups will be finalized and locked down prior to the completion of the Phase 3 study and applied prospectively to the primary efficacy analysis. The Sponsor will remain blinded to all tumor tissue and germline test results until the primary efficacy analysis is conducted.

Number of Patients	Approximately 540 patients will be enrolled. A minimum of 180 and a maximum of 200 patients with a deleterious *tBRCA* mutation will be enrolled. Enrollment of patients with a known deleterious *gBRCA* mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined.
Number of Sites	This is a multicenter, multinational study. Patients will be enrolled from approximately 90 – 100 study sites.
Study Duration	Q4 2013 – Q2 2017
Study Objectives	The primary objective of this study is: • To evaluate PFS by RECIST, as assessed by the investigator, in molecularly-defined HRD subgroups The secondary objectives of this study are: • To evaluate patient-reported outcome (PRO) of disease-related symptoms utilizing the disease-related symptoms – physical (DRS–P) subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Ovarian Symptom Index 18 (FOSI-18) • To evaluate PRO utilizing the complete FOSI-18 • To evaluate survival benefit • To evaluate PFS by RECIST, as assessed by independent radiology review (IRR), in molecularly-defined HRD subgroups • To evaluate safety • To determine the population pharmacokinetics (PK) of rucaparib The exploratory objectives of this study are: • To evaluate the relationship between cancer antigen 125 (CA-125) levels and invPFS • To evaluate PFS2 (PFS on the subsequent line of treatment) • To evaluate overall response rate (ORR) • To evaluate duration of response (DOR) • To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D) • To explore the relationship between rucaparib exposure, efficacy, and safety
Study Population	**Inclusion Criteria** All patients enrolling into the study must meet all of the following inclusion criteria: 1. Have signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation 2. Be ≥18 years of age at the time the informed consent form is signed 3. Have a histologically confirmed diagnosis of high-grade (Grade 2 or 3) serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer – For mixed histology, >50% of the primary tumor must be confirmed to be high-grade serous or endometrioid – Grade 2 tumors classified under a 3-tier system should be re-reviewed by local pathology and confirmed as high-grade under the 2-tier system

Study Population (cont)	4. Received prior platinum-based therapy and have platinum-sensitive disease (i.e. documented radiologic disease progression >6 months following the last dose of the penultimate platinum administered) – Received ≥2 prior platinum-based treatment regimens, including platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to 1 non-platinum chemotherapy regimen is permitted. Prior hormonal therapy is permitted; this treatment will not be counted as a non-platinum regimen. – There is no upper limit on the number of prior platinum-based regimens that may have been received, but the patient must have been sensitive to the penultimate platinum-based regimen administered. – If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this will be considered 1 treatment regimen – Prior maintenance therapy following a prior treatment regimen is permitted, with the exception of the regimen received immediately prior to maintenance in this study. No anticancer therapy is permitted to be administered as maintenance treatment in the interval period between completion of the most recent platinum-based therapy and initiation of study drug in this trial. 5. Achieved best response of either CR or PR to the most recent platinum-based regimen administered and is randomized to study treatment within 8 weeks of the last dose of platinum received. – The most recent platinum-based regimen must have been a chemotherapy doublet. The choice of the platinum and the 2nd chemotherapy agent is per Investigator's discretion. – A minimum of 4 cycles of platinum chemotherapy must have been administered. There is no cap on the maximum number of cycles; however, additional cycles of treatment administered following completion of therapy for the specific purpose of enabling patient eligibility and randomization within 8 weeks of the last platinum dose is not permitted. – A CR is defined as a complete radiologic response per RECIST v1.1, i.e. absence of any detectable disease and CA-125 <ULN.* – A PR is defined as either a partial response per RECIST v1.1 (if disease was measurable prior to chemotherapy) or a serologic response per GCIG CA-125 response criteria (if disease was not measurable according to RECIST v1.1).* o CA-125 must also be <ULN for all responses classified as a PR – R0 surgery (no visible tumor) or R1 surgery (residual disease <1 cm) as a component of the most recent treatment regimen is not permitted. The response assessment must be determined solely in relation to the chemotherapy regimen administered. The presence of measurable disease or CA-125 > 2 x ULN immediately prior to the chemotherapy regimen is required.

Study Population (cont)	– Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study. – All disease assessments performed prior to and during this chemotherapy regimen must be adequately documented in the patient's medical record 6. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 x 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 to 12 x 10 µm sections, or equivalent) available for planned analyses. – The <u>most recently</u> collected tumor tissue should be provided, if available – Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample. – Sample must be received at the central laboratory **<u>at least 3 weeks prior to start of treatment</u>** in order to enable stratification for randomization 7. Have CA-125 measurement that is < ULN 8. Have ECOG performance status of 0 to 1 9. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug: – Bone Marrow Function o Absolute neutrophil count (ANC) ≥ 1.5×10^9/L o Platelets > 100×10^9/L o Hemoglobin ≥ 9 g/dL – Hepatic Function o Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN o Bilirubin ≤ 1.5 × ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome) – Renal Function o Serum creatinine ≤ 1.5 × ULN or estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft Gault formula * <u>Note</u>: It is acceptable for sites to utilize local and contemporaneous clinical imaging reports to record lesion measurement history and define a burden of disease according to RECIST; it is not a requirement to re-read radiological scans to collect this data. **Exclusion Criteria** Patients will be excluded from participation if any of the following criteria apply: 1. History of a prior malignancy except: – Curatively treated non-melanoma skin cancer – Breast cancer treated curatively > 3 years ago, or other solid tumor treated curatively > 5 years ago, without evidence of recurrence – Synchronous endometrioid endometrial cancer (Stage 1A G1/G2) 2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible.

Study Population (cont)	3. Required drainage of ascites during the final 2 cycles of their last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomization to maintenance treatment in this study 4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks. 5. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of study drug 6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C 7. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to first dose of study drug. 8. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤14 days prior to first dose of study drug and/or ongoing adverse effects from such treatment > NCI CTCAE Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug – Ongoing hormonal treatment for previously treated breast cancer is permitted – Refer also to inclusion criteria #4 for guidelines pertaining to prior maintenance therapy 9. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤ 7 days prior to first dose of study drug or have on-going requirements for these medications (Appendix F) 10. Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration 11. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients of reproductive potential must practice a highly effective method of contraception (failure rate < 1% per year) with their male partners during treatment and for 6 months following the last study drug dose. No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolled into the study.

Study Treatment	Eligible patients will be randomized 2:1 to receive rucaparib (600 mg bid) or placebo. Randomization will occur by a central randomization procedure using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced: • HRD classification (tBRCA, nbHRD, or biomarker negative) by the ICTA (Appendix A). • Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 or >12 months) by radiologic assessment • Best response to the most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST or PR [defined as partial response by RECIST and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN. Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy. Study drug will be taken orally twice daily (12 hours apart) with at least 8 oz (240 mL) of water. Study drug may be taken with an empty stomach or with food. Patients will take study drug twice daily for continuous 28-day cycles until disease progression by RECIST as assessed by the investigator, or other reason for discontinuation. Treatment interruptions and/or dose reductions are permitted in the event of unacceptable toxicity.
Withdrawal Criteria	A patient must be discontinued from treatment with study drug if any of the following apply: • Consent withdrawal at the patient's own request or at the request of their legally authorized representative • Progression of patient's underlying disease by RECIST as assessed by the investigator • Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient • An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy • A positive pregnancy test at any time during the study
Disease Assessments for Efficacy	Efficacy measures will include clinical examination, CA-125 measurement, and appropriate imaging (CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. Disease assessment will be performed at screening, at the end of every 12 calendar weeks after start of treatment on Day 1 of Cycle 1, at discontinuation of treatment, and as clinically indicated. Disease progression will be determined by RECIST (Appendix B). Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria (Appendix C) for disease progression should have a radiologic assessment by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST per the protocol schedule.

<table>
<tr><td>Disease Assessments for Efficacy (cont)</td><td>Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals (up to 1 week prior is permitted) until disease progression, as assessed by the investigator.</td></tr>
<tr><td>Safety Assessments</td><td>Safety assessments will include adverse events (AEs), hematology, serum chemistry, vital signs, body weight, concomitant medications/procedures, ECOG performance status (Appendix D), and study drug modifications.</td></tr>
<tr><td>Statistical Procedures</td><td>
Sample Size Justification
The total enrollment planned is 540 patients. A minimum of 180 and a maximum of 200 patients with a deleterious tBRCA mutation will be enrolled. Enrollment of patients with a known deleterious gBRCA mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined. Prior to final efficacy analysis, HRD classification will be determined by the FCTA that will evaluate homologous recombination gene mutations and/or extent of genomic scarring in tumor tissue.
The table below provides estimated sample sizes and power calculations.
<table>
<tr><th>Group</th><th>Hazard Ratio</th><th>Cumulative N</th><th>Minimum Number of Events (70%)</th><th>Median PFS Placebo vs Rucaparib (months)</th><th>Power</th><th>One-sided Alpha</th></tr>
<tr><td>tBRCA</td><td>0.50</td><td>180</td><td>126</td><td>6 vs 12</td><td>90%</td><td>0.025</td></tr>
<tr><td>All HRD (tBRCA + nbHRD)</td><td>0.60</td><td>300</td><td>210</td><td>6 vs 10</td><td>90%</td><td>0.025</td></tr>
<tr><td>ITT Population (tBRCA + nbHRD + Biomarker Negative)</td><td>0.70</td><td>540</td><td>378</td><td>6 vs 8.5</td><td>90%</td><td>0.025</td></tr>
</table>
Analysis Populations
Safety: The safety population will consist of all patients who received at least one dose of protocol-specified treatment.
Intent-to-treat (ITT): The ITT population will consist of all randomized patients.
Response evaluable: The response evaluable population will consist of all patients who have measurable or evaluable disease at study entry, received at least one dose of study drug, and who had at least one post-baseline disease assessment.
General Statistical Considerations
Quantitative variables will be summarized using descriptive statistics. For variables registered on a continuous scale, the following will be presented: N, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. The stratified hazard ratio from the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups. The primary and key secondary endpoints will be tested among the tBRCA subgroup, all HRD subgroup, and all randomized patients, using an ordered step-down multiple comparisons procedure.
</td></tr>
</table>

Statistical Procedures (cont)	Investigator determined PFS (invPFS) in the tBRCA subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the tBRCA subgroup is statistically significant, then invPFS will be tested in the all HRD subgroup followed by invPFS in all randomized patients. Continuing in an ordered step-down manner, the PRO of disease symptoms utilizing the DRS-P subscale of the FOSI-18 will be tested at the one-sided 0.025 significance level in the tBRCA, all HRD, and all randomized patients subgroups and then for the remaining key secondary endpoints of PRO utilizing the FOSI-18 total score and OS. Once statistical significance is not achieved for one test the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure. PFS by IRR will be evaluated as a stand-alone secondary endpoint. Primary Efficacy Analysis The primary efficacy analysis for the study is investigator-determined PFS (invPFS) by RECIST. Investigator-determined PFS is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by the investigator, or death due to any cause, whichever occurs first. The stratification factors included in the primary analysis of invPFS will be HRD classification (tBRCA, nbHRD or biomarker negative), interval between completion of penultimate platinum regimen and disease progression (6 to 12 months or >12 months) by radiologic assessment, and best response to the most recent platinum-based regimen (either CR [defined as complete radiologic response by RECIST] or PR [defined as partial response by RECIST and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN. Tumor HRD status by the FCTA will be determined after randomization, but before the final efficacy analysis, so that the primary endpoint (PFS in molecularly defined subgroups) can be assessed prospectively. Secondary Efficacy Analyses Secondary efficacy endpoints include: • PRO of disease-related symptoms as measured by the DRS-P subscale score of the FOSI-18 • PRO as measured by the total score of the FOSI-18 • OS • PFS by RECIST v1.1 as assessed by IRR The time to an event in PRO of worsening of disease symptoms will be defined as the time from randomization to a 4-point reduction in the FOSI-18 DRS–P subscale score. Similarly, an event in worsening of PRO utilizing the FOSI-18 total score will be defined as the time from randomization to an 8-point reduction in the total score. OS, time to death from any cause, is defined as the number of days from the date of randomization to the date of death (due to any cause). Patients without a known date of death will be censored on the date the patient was last known to be alive. PFS for secondary efficacy analysis is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by IRR, or death due to any cause, whichever occurs first.

Statistical Procedures (cont)	Safety Analysis Data from all patients who receive at least one dose of study drug will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, and concomitant medications / procedures will be tabulated and summarized. AEs will be summarized overall, with separate summaries for serious AEs, AEs leading to treatment discontinuation or death, and CTCAE Grade 3 or higher AEs. **Independent Data Monitoring Committee (IDMC)** No formal efficacy interim analyses for early stopping are planned. An IDMC will meet to review the efficacy and safety data from this study. The IDMC will: • Review efficacy and safety of rucaparib compared to placebo to ensure the study is beneficial to patients; • Ensure the study is conducted in a high quality manner; and • Monitor the size of the tBRCA subgroup and known gBRCA subgroup

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha-1 acid glycoprotein
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
AUCR	ratio of the area under the curve
BCRP	breast cancer resistance protein
BER	base excision repair
BID	twice a day
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BUN	blood urea nitrogen
CA-125	cancer antigen 125
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events (version 4.03)
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-strand break
DRS–P	disease-related symptoms–physical
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOC	epithelial ovarian cancer

EQ-5D	Euro-Quality of Life 5D
FCTA	Final Clinical Trial Assay
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOSI-18	FACT-Ovarian Symptom Index 18
GALT	gut-associated lymphoid tissue
gBRCA	germline *BRCA*
GCIG	Gynecologic Cancer InterGroup
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
h	hour
Hct	hematocrit
HDL	high-density lipoprotein
hERG	human ether-a-go-go-related gene
Hgb	hemoglobin
HGSOC	high grade serous ovarian cancer
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
ICH	International Conference on Harmonization
ICTA	Initial Clinical Trial Assay
IC_{xx}	concentration where maximum response is inhibited by XX%
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
invPFS	disease progression according to RECIST v1.1 as assessed by the investigator, or death from any cause
IRB	Institutional Review Board
IRR	independent radiology review
irrPFS	disease progression according to RECIST v1.1 as assessed by independent radiology review, or death from any cause
ITT	Intent-to-treat
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDL	low-density lipoprotein
LOH	loss of heterozygosity
MATE	multidrug and toxin extrusion transporter
MCV	mean corpuscular volume

MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	minute
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mut	mutant
nbHRD	non-BRCA homologous recombination deficiency
NCCN-FACT	National Comprehensive Cancer Network-Functional Assessment of Cancer
NCI	National Cancer Institute
NGS	next generation sequencing
NOAEL	no-observed-adverse-effect level
OCT	organic cation transporter
ORR	overall response rate
OS	overall survival
PARP	poly (adenosine diphosphate [ADP]-ribose) polymerase
PD	progressive disease
PET	positron emission tomography
PLD	PEGylated liposomal doxorubicin
PFS	progression-free survival
PFS2	second event of progression-free survival
P-gp	P-glycoprotein
PID	poly (adenosine diphosphate [ADP]-ribose) polymerase inhibiting dose
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PS	performance status
QD	once a day
QoL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	serious adverse event
SAS	statistical analysis software
sBRCA	somatic breast cancer gene 1 or 2 mutation
SD	stable disease
SNP	single-nucleotide polymorphism
SOC	system organ class

SOP	Standard operating procedure
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
tBRCA	tumor tissue alteration in *BRCA1* or *BRCA2*, includes *gBRCA* and *sBRCA*
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse events
T_{max}	time to maximum concentration
TMZ	temozolomide
UGT	uridinediphosphate-glucuronosyletransferase
ULN	upper limit of normal
unk	unknown
UV	ultraviolet
WBC	white blood cell
WOCBP	women of child-bearing potential
WT	wild type

3 INTRODUCTION

3.1 Ovarian Cancer

3.1.1 General Overview

Ovarian cancer is the second most common gynecologic malignancy worldwide and the leading cause of death attributed to gynecological cancer.[37, 38] After initial therapy, most women will have a progression-free interval of approximately 1.5 to 2 years, depending on the extent of post-operative residual disease and response to chemotherapy.[39] Relapse still occurs, however, in the majority of cases, and only 10–30% of women experience long-term survival.[39] Advanced stage disease is associated with a 5-year survival rate of only 30–40%.[37]

Approximately 90% of ovarian tumors are surface epithelial in origin, and the papillary serous histology subtype accounts for approximately 75%, of which the large majority (70%) is high-grade.[39] The site of origin of epithelial ovarian cancer (EOC) remains unclear. Some studies suggest that serous EOC and primary peritoneal cancer (PPC) arise from the fallopian tube epithelium;[40, 41] however, other studies suggest an origin within stem cells of the ovarian surface epithelium.[39, 42] EOC, PPC and fallopian tube cancer behave very similarly, and are therefore treated in the same way.

The median age at presentation of EOC is 60 years. Many women present with advanced disease and therefore have a poor prognosis.

3.1.2 Treatment of Ovarian Cancer

The standard approach to treatment of advanced ovarian cancer is cytoreductive surgery (either at time of diagnosis or interval debulking following 2 – 3 cycles of neoadjuvant chemotherapy), with the goal of minimizing residual tumor to no visible residual disease, a major prognostic indicator for improved survival. Six to eight cycles of platinum- and taxane-based chemotherapy is the global standard of care. If initial cytoreduction is not performed, interval debulking surgery is considered. This surgery may be carried out after three or four cycles of primary chemotherapy, followed by three further cycles of chemotherapy. Platinum analogues, such as carboplatin and cisplatin, are the most active agents, mediating their effects through the formation of inter- and intra-strand cross-links with deoxyribonucleic acid (DNA).[43, 44]

The choice of treatment for relapsed disease is based on the treatment-free interval relative to last therapy administered and chemotherapy agents used. As many patients experience multiple relapses, prognosis and response to therapy decreases as the interval between last chemotherapy exposure and disease relapse shortens. The treatment-free, or specifically the platinum-free interval, provides further prognostic information for patients, as therapeutic options lessen and survival shortens as a patient's tumor becomes less responsive to platinum-based therapy.

Platinum-based regimens dominate ovarian cancer therapy and define treatment groups.[44] In general, patients whose disease progresses during treatment with a platinum-based regimen are considered to have platinum-refractory disease; patients whose disease relapses within 6 months after the last platinum agent was administered are considered to have platinum-resistant disease;

and patients whose disease relapses more than 6 months after the last platinum-based therapy was administered are considered to have platinum-sensitive disease. These classifications are clinical, and not based on a mechanistic definition of platinum sensitivity or resistance.

PARP inhibitor monotherapy has elicited objective responses in patients with platinum-sensitive disease as well as in patients with platinum-resistant disease, although response rates are higher in the former population.[21-23] This indicates that using platinum-sensitivity alone as a selection marker for PARP inhibitor therapy is not a very effective tool, although it is a reasonable place to begin predictive biomarker development.

Maintenance therapy following a response to standard treatment provides an opportunity to extend the disease-free period. Maintenance strategies evaluated to date for ovarian cancer have focused on the prolonged use of single-agent chemotherapy, antiangiogenesis agents, hormonal therapy, vaccines, and intraperitoneal chemotherapy. The OCEANS study evaluated carboplatin and gemcitabine with or without bevacizumab as part of the initial treatment and then as maintenance in women with platinum-sensitive ovarian, primary peritoneal, or fallopian tube cancer who were in their first relapse following primary chemotherapy. The addition of bevacizumab resulted in a statistically significant improvement in PFS (median 12.4 vs 8.4 months; HR=0.484 [95% CI, 0.388 to 0.605; log-rank $P<0.00001$]).[45] The PFS benefit of bevacizumab administered together with chemotherapy followed by single agent bevacizumab maintenance treatment compared to chemotherapy alone and placebo maintenance was further established in two front-line Phase 3 studies, GOG-218 (HR=0.717 [95% CI, 0.625 to 0.824; log-rank $P<0.001$])[46] and ICON-7 (HR=0.81 [95% CI, 0.70 to 0.94; log-rank $P<0.04$]).[47] Based on these trials, the European Medicines Agency approved bevacizumab, in combination with carboplatin and paclitaxel, for front-line treatment of advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian-tube, or primary peritoneal cancer, and, in combination with carboplatin and gemcitabine, for treatment of first recurrence of platinum-sensitive epithelial ovarian, fallopian-tube or primary peritoneal cancer in women who have not received prior therapy with bevacizumab or other vascular-endothelial-growth-factor (VEGF) inhibitors or VEGF-receptor-targeted agents.

3.1.3 Homologous Recombination Deficiency

DNA is constantly damaged by both endogenous and exogenous (environmental) assaults. A common type of DNA damage is the formation of DNA single-strand breaks (SSBs). During normal cell cycling, DNA is replicated and replication forks are eventually stalled by persistent SSBs. If stalled replication forks are not rapidly repaired, they can often degenerate and form DNA double-strand breaks (DSBs), which are highly likely to be lethal to the cell.

Normal cells repair single-strand breaks (SSBs) in DNA primarily through base excision repair (BER). While there are several variations of BER, all pathways rely on PARP enzymes, of which PARP1 is the best characterized. SSBs that are not repaired result in stalled replication forks and the development of double-strand breaks (DSBs), which are in turn primarily repaired by homologous recombination DNA repair, a complex process involving multiple proteins, including those encoded by breast cancer susceptibility gene 1 and 2 (*BRCA1* and *BRCA2*), among others.

If either the BER or homologous recombination pathway is rendered non-functional, the remaining functional pathway can compensate to ensure ongoing DNA repair and cell cycling. For example, when the BRCA-associated homologous recombination pathway is lost or dysfunctional, repair shifts towards the BER repair pathway that is dependent on PARP enzymes. In contrast, in the setting in which both repair pathways (BER and homologous recombination) are rendered non-functional, the cell dies. This concept, where a defect in either of two pathways can be withstood by a cell, but defects in both are lethal, is referred to as synthetic lethality. This type of lethality can arise from a variety of different interactions. In the case of DNA damage repair, dual non-functionality can be achieved by enzymatic inhibition of PARP in the context of a genetic mutation in the *BRCA1* or *BRCA2* genes.

Synthetic lethality has been demonstrated in landmark in vitro and in vivo studies as well as in several clinical trials that evaluated a single agent PARP inhibitor for the treatment of relapsed ovarian cancer and metastatic breast cancer. Bryant and colleagues showed that cell lines and a tumor xenograft deficient in homologous recombination (via a defect in a *BRCA* or other homologous recombination gene) were highly sensitive to PARP inhibition.[16] This study also showed that synthetic lethality could be achieved regardless of whether the mutation was in *BRCA1* or *BRCA2*. In a parallel set of experiments, Farmer and colleagues illustrated that chemical inhibition of PARP1 was more potent in homozygous *BRCA*-deficient cell lines than in heterozygous mutant or wild-type cell lines.[17] These findings were also supported by a *BRCA2*-deficient murine model. Taken together, these studies provided support for the treatment of patients with a *BRCA*-deficient tumor with a PARP inhibitor.

3.1.4 Role of HRD in Ovarian Cancer

Homologous recombination pathway defects, either as an initiating event or late event in the carcinogenetic process, may be responsible for the genetic instability observed in many cancers. An analysis of the Cancer Genome Atlas (TCGA), which examined molecular changes associated with high-grade serous ovarian cancer (HGSOC), estimated that approximately 50% of patient with HGSOC have homologous recombination deficiency (HRD).[1] Drivers of HRD in ovarian cancer include:

1. Germline mutations in the *BRCA1* and *BRCA2* genes (*gBRCA*). These are the strongest known hereditary factors for epithelial ovarian cancer (EOC), accounting for up to 15% of all EOC.[2, 3] These patients carry heterozygous deleterious mutations in their germline DNA and develop tumors when the remaining wild-type functional allele is inactivated (i.e. “second hit”).
2. Somatic *BRCA1/2* mutations (*sBRCA*) (approximately 6 – 8% of HGSOC patients)[1, 4]
3. Mutation in a homologous recombination gene other than *BRCA1/2* (approximately 16% of HGSOC patients).[1] Nonclinical studies by several groups have identified RAD proteins (eg, RAD51, RAD51C, RAD52, RAD54L),[5-8] Fanconi Anemia proteins (eg, FANCA, FANCC, FANCD2),[9-11] and many others (eg, ATM, ATR, CHEK1, CHEK2)[12-15] as being involved in homologous recombination.
4. Functional silencing of homologous recombination genes, such as through *BRCA* promoter methylation (approximately 10% of HGSOC patients)[1] or other mechanisms

Mutations in the BRCA genes in the tumor can be detected through next-generation sequencing (NGS). A possible approach to identify non-*BRCA* patients with HRD is to detect genomic scars within the tumor, which arise from the use of error-prone DNA repair pathways when HRR is compromised. Through a series of experiments and data analyses, the Sponsor has determined that a potential method for identifying patients who may be sensitive to rucaparib is to assess genomic scarring by quantifying the extent of loss of heterozygosity across the tumor genome (tumor genomic LOH). One of the main advantages of detecting tumor genomic LOH is that it can identify HRD tumors regardless of the underlying mechanisms, which include both known (i.e. *BRCA* mutations) and unknown genomic mechanisms.[33, 36]

3.2 PARP Inhibitors

PARP inhibitors have been evaluated in the clinic for the past decade. Olaparib (AZD-2281), the most advanced investigational PARP inhibitor, has demonstrated compelling Phase 2 clinical activity, both in treatment and maintenance settings, in relapsed, HGSOC patients (both germline *BRCA* mutant and wild-type) and in metastatic breast cancer patients with a *gBRCA* mutation. The concept of synthetic lethality was exploited in two proof-of-concept clinical studies with olaparib in patients with *BRCA*-associated tumor types. These studies evaluated the efficacy and safety of continuous oral dosing with olaparib in women with either relapsed ovarian cancer or advanced breast cancer and a *gBRCA* mutation.[19, 20] In these patients, who had received a median of three prior chemotherapy regimens, encouraging overall response rates of 33% and 41%, were observed, in *gBRCA* ovarian and *gBRCA* breast cancer, respectively. In a third study, olaparib treatment was associated with a greater overall response rate (ORR) in patients with *gBRCA*-associated ovarian cancer compared with the patients in the non-*gBRCA* associated cohort (41% vs 24%, respectively).[21] In a fourth study that evaluated olaparib versus PEGylated liposomal doxorubicin (PLD) in patients with a *gBRCA* mutation and relapsed ovarian cancer, the efficacy of olaparib was consistent with that observed in previous studies.[22]

Activity in HGSOC has also been observed with PARP inhibitor switch maintenance therapy following response to platinum-based chemotherapy.[29, 30] Patients with platinum-sensitive relapsed ovarian cancer who achieved a response to another regimen of platinum-based chemotherapy followed by olaparib as switch maintenance treatment experienced a statistically significant improvement in median PFS (8.3 months) compared to patients who received placebo as maintenance therapy (4.8 months); hazard ratio of 0.35 (95% CI, 0.25 – 0.49).[29] Patients with a *BRCA* mutation derived the most benefit (median PFS 11.2 vs 4.3 months; HR=0.18; 95% CI 0.11-0.31; $P<0.00001$).[30] It should be noted that the outcomes of *sBRCA* + *gBRCA* mutant patients were the same as *gBRCA* mutant patients alone, suggesting that, for stratification and analysis purposes in the present study, it is appropriate to not differentiate between germline and somatic mutations. Patients without a *BRCA* mutation also experienced significant benefit from treatment with olaparib (HR=0.53; 95% CI 0.33-0.84; $P=0.007$).[30]

Niraparib (MK-4827) has exhibited clinical activity in a Phase 1 study in both *BRCA*-mutated ovarian cancer (8 RECIST PRs) and sporadic ovarian cancer (5 RECIST PRs and/or GCIG CA-125 responses).[23] In a Phase 1 evaluation of BMN 673, 11 of 17 *BRCA*-mutated ovarian cancer patients treated at doses ≥100 µg/day exhibited a RECIST and/or CA-125 response.[24]

Taken together, these data support the potential role for the PARP inhibitor rucaparib in the treatment of patients with *BRCA*-associated ovarian cancer. Furthermore, the 24% ORR and HR of 0.53 in the non-*BRCA* cohorts described above[21, 30] suggests that the clinical utility of PARP inhibitors can be extended to a larger patient group. Patients with HRD due to defects in homologous recombination genes other than *BRCA*, i.e. nbHRD, may be part of this larger group.

3.3 Rucaparib

Rucaparib (formerly known as AG-014447 and PF-01367338) refers to the free base. The camphorsulfonic acid salt form (also referred to as camsylate salt) CO-338 (formerly known as PF-01367338-BW) will be used in this clinical trial.

Rucaparib is a small molecule inhibitor of PARP-1, PARP-2, and PARP-3. Nonclinical evaluation has demonstrated exquisite sensitivity of *BRCA1* and *BRCA2* homozygous mutant cell lines to rucaparib and provides a rationale for the clinical assessment of rucaparib as monotherapy in patients with hereditary deficiencies of *BRCA1* and/or *BRCA2*. Rucaparib has also shown antitumor activity as a single agent in the MDA-MB-436 (*BRCA1* mutant) xenograft mouse model. The activity of rucaparib in these nonclinical experiments was similar to that of olaparib.

The details of these and other nonclinical experiments are provided in the Investigator's Brochure.

3.3.1 Nonclinical Experience

3.3.1.1 Rucaparib Absorption, Distribution, Metabolism, and Excretion

The pharmacokinetics (PK) and toxicokinetics of rucaparib (as camsylate salt) following oral administration, the intended route of administration in humans, was evaluated in the mouse, rat, and dog. The time at which the peak plasma concentrations were observed (T_{max}) occurred at 1–3 hours post dose in the mouse and dog, with the rat generally exhibiting a later T_{max} (4–8 hours). The oral bioavailability was 17%, 36%, and 62%, respectively, in the mouse (50 mg/kg), rat (100 mg/kg), and dog (20 mg/kg). In the rat and dog, there were no marked gender-related differences and no accumulation after repeat oral administration. A less than dose-proportional increase in exposure was observed in the rat and dog when rucaparib was administered as a suspension in 0.5% methylcellulose; however, a greater than dose-proportional increase in exposure was observed in the 1-month dog toxicity study when rucaparib was administered in capsules.

In vitro plasma protein binding studies in mouse, rat, and dog plasma showed moderate binding and ranged from 49.5% to 73%. Plasma protein binding in humans ranged from 55% to 75%.

Recombinant cytochrome P450 (CYP) studies indicated that CYP2D6, and to a lesser extent, CYP1A2 and CYP3A4, have the ability to metabolize rucaparib.

In vitro studies indicated that rucaparib reversibly inhibited (in order of decreasing potency) CYP1A2, CYP2C19, CYP2C9, CYP3A, CYP2C8, and CYP2D6. Rucaparib demonstrated

concentration-dependent induction of CYP1A2 and down-regulation of CYP3A4 and CYP2B6 at clinically relevant concentrations in a hepatocyte incubation study. No time-dependent CYP inhibition was observed. Rucaparib also moderately inhibited uridinediphosphate-glucuronosyletransferase (UGT)1A1. Based on in vitro CYP interaction data, the drug-drug interaction (DDI) potential of rucaparib as a CYP inhibitor and/ or inducer was assessed by calculating the ratio of AUC (AUCR) of CYP substrate drugs in the presence and absence of rucaparib at target clinical exposures (600 mg BID) using the mechanistic static modeling.[48, 49] AUCR allows a conservative estimation of the magnitude of DDIs. Based on this analysis, the DDI potential for rucaparib was estimated to be moderate (AUCR 2 to 5) for CYP3A (AUCR=5.0), CYP1A2 (AUCR=2.9), CYP2C8 (AUCR=2.6), and CYP2D6 (AUCR=2.3); but appeared to be strong (AUCR > 5) for CYP2C19 (AUCR=11) and CYP2C9 (AUCR=5.2). Clinical implication of CYP3A downregulation was unknown and thus not considered in the modeling; however, downregulation could further increase AUCR for CYP3A and result in elevated exposures of drugs that are CYP3A substrates.

Rucaparib is a substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In vitro data indicate rucaparib is a potent inhibitor of multidrug and toxin extrusion transporter (MATE)-1 and MATE2-K (efflux transporters on renal tubule cells), and moderate inhibitor of organic cation transporter (OCT)1, BCRP, and P-gp.

Quantitative whole body autoradiography studies in Long Evans rats showed [^{14}C] rucaparib radioequivalents were rapidly and widely distributed to tissues following IV administration, consistent with a large volume of distribution. At 2 minutes after dosing, highest concentrations were found in kidney, lung, thyroid gland, heart, stomach mucosa, liver adrenal glands, spleen, and blood. Little radioactivity was present in brain; levels were undetectable at 15 minutes after dosing. Activity was undetectable in most tissues by 96 hours after dosing, however levels in the choroid/retina declined more slowly, and persistent radioactivity was also found in hair follicles through 192 hours, indicating that drug equivalents have high affinity and long half-life in pigmented tissues. High levels of radioactivity were observed in ureters, bladder, and bile ducts, indicating both renal and biliary routes eliminated drug equivalents.

3.3.1.2 Multiple-Dose Toxicity Studies

Rucaparib was evaluated in both rat and dog in oral and IV infusion toxicity studies. Only the multiple-dose toxicity studies utilizing the oral formulation are summarized below. Details of all other toxicity studies are provided in the Investigator's Brochure.

Target organs identified in studies where rucaparib was administered orally include the hematopoietic system and gastrointestinal tract. No cardiovascular findings were noted in any of the oral toxicity studies.

Multiple-Dose Oral Toxicity in Rats

Administration of rucaparib camsylate salt via oral gavage was generally well-tolerated in the rat up to 1000 mg/kg/day for 7 days and up to 150 mg/kg/day for 28 days. Decreases in body weight gain and food consumption were noted in both studies. In the 7-day study, target organs identified microscopically were bone marrow, spleen, and thymus. Minimal to mild bone

marrow hypocellularity was noted in all dose groups. The no-observed-adverse-effect-level (NOAEL) was established at 500 mg/kg/day.

In the 28-day study, there were 3 rucaparib-related deaths at 500 mg/kg/day immediately after blood collection on Day 28 (n=1) or Day 29 (first day of recovery phase (n=2). These deaths likely resulted from the marked anemia identified hematologically. Other rucaparib-related clinical signs at 500 mg/kg/day included thinning haircoat and pale eyes. Identified target organs included bone marrow, spleen, lymphoid tissue (thymus, gut-associated-lymphoid tissue [GALT], and lymph nodes), and cecum (at 500 mg/kg/day only). Following cessation of rucaparib dosing, most findings reversed. In this study, the severe toxic dose in 10% of the animals (STD10) was 500 mg/kg/day and the NOAEL was 50 mg/kg/day.

Rucaparib camsylate in capsules was also given orally to rats at doses of 10, 40, and 100 mg/kg/day for 91 consecutive days with a 28-day recovery period. Decreased body weight and body weight gain were observed for animals given ≥40 mg/kg/day. At the end of the recovery phase, mean body weight was still lower for males given 100 mg/kg/day and females given ≥40 mg/kg/day. Hematological findings included decreases in red blood cell mass parameters in animals given ≥40 mg/kg/day (which correlated with decreased bone marrow hypocellularity), and decreases in reticulocytes, white blood cells (WBC) and absolute lymphocytes at ≥40 mg/kg/day. The latter changes correlated with the microscopic findings of decreased lymphocytes in the mandibular lymph nodes and gut-associated lymphoid tissue. All effects were reversible. Microscopically, bone marrow hypocellularity at 100 mg/kg/day and minimally decreased lymphocytes in lymphoid tissues at ≥40 mg/kg/day were noted and were completely reversed at the end of the recovery period. The NOAEL was established to be 100 mg/kg/day.

Multiple-Dose Oral Toxicity in Dogs

Oral gavage administration of the camsylate salt form of rucaparib to dogs for 7 days resulted in gastrointestinal clinical signs at the 80 mg/kg/day high-dose group. Hematopoietic effects of decreased reticulocytes were noted in mid- to high-dose groups and leukopenia was exhibited in all treatment groups. Lymphoid atrophy occurred in both sexes and in all treatment groups. Decreased bone marrow cellularity was seen in both sexes (males at all doses; females at 80 mg/kg/day). A 7-day repeat-dose toxicity study using oral capsules in dogs was repeated in order to characterize the toxicity of a new lot of rucaparib camsylate. Similar to the results of the prior 7-day study in dog, gastrointestinal clinical findings were noted at 80 mg/kg/day. Vomiting was observed throughout the dosing phase for males as well as liquid and/or mucoid feces in both genders. Decreased food consumption was observed at 80 mg/kg/day that correlated with the body weight loss that was considered adverse. Decreases in erythroid, platelet, and leukocyte parameters were observed primarily at 80 mg/kg/day and occasionally at 20 or 5 mg/kg/day. These data indicated that the drug targeted multiple bone marrow lineages in a dose-related pattern.

Rucaparib camsylate salt in capsules was administered orally to dogs for 30 consecutive days with a 29-day recovery. Gastrointestinal clinical signs were noted at ≥5 mg/kg/day, with decrease in food consumption at 75 mg/kg/day. Adverse hematological changes (decrease in

erythroid, myeloid, and megokaryocytic lineages) occurred at ≥20 mg/kg/day. Effects were fully reversible. The NOAEL in this study was 5 mg/kg/day.

Rucaparib camsylate in capsules was also given orally to dogs at doses of 3, 15/10, 40/30/20 mg/kg/day for 91 consecutive days with a 29-day recovery period. Body weight losses and inappetance observed at the high dose in both sexes during the first quarter of the dosing phase were considered adverse and resulted in dose reductions (40 to 30 to 20 mg/kg/day for toxicity and 15 to 10 mg/kg day in order to maintain multiples of exposures for optimal testing of dose response) for the remainder of the study. Clinical pathology findings were indicative of bone marrow toxicity; these changes were non-progressive over time suggesting potential adaptation to these initial effects. Hematological findings at 40/30/20 mg/kg/day correlated with erythroid atrophy of the bone marrow detected microscopically. By Day 29 of recovery, most effects reversed. The highest non-severely toxic dose (HNSTD) for this study was 20 mg/kg/day for male dogs. No HNSTD was established for female dogs. The NOAEL was 10 and 20 mg/kg/day for male and female dogs, respectively.

3.3.1.3 Additional Observations

In vitro genetic toxicology assays demonstrated oral rucaparib to be clastogenic. Bacterial mutagenicity data for rucaparib were clearly negative in four microbial tester strains, both with and without metabolic activation, and equivocal in a fifth tester strain.

In an in vitro assay for human ether-a-go-go-related gene (hERG) activity, the IC_{50} and IC_{20} for the inhibitory effects of rucaparib (50% inhibitory concentration and 20% inhibitory concentration) on hERG potassium currents were 24 µM (7761 ng/mL) and 7 µM (2264 ng/mL), respectively. These values are 9-fold and 2.6-fold higher, respectively, than the mean unbound steady state plasma concentration (858 ng/mL) observed to date in humans at a dose of 600 mg BID rucaparib administered orally.

Effects on appearance and behavior, motor activity, body temperature, and a number of neurofunctional tests and reflexes were evaluated in rats. A dose of 50 mg/kg of rucaparib administered via IV infusion (mean C_{max}=13629 ng/mL) resulted in a significant reduction in motor activity compared with vehicle-treated animals; however, there were no effects on neurofunctional or reflex testing at this dose. The plasma concentration measured at this dose is 4.7-fold above the mean steady state plasma concentration (2880 ng/mL) observed to date in humans at a dose of 600 mg BID rucaparib administered orally.

Administration of rucaparib to Long-Evans rats orally at doses up to 750 mg/kg/dose, followed by a single exposure to solar-simulated ultraviolet radiation approximately 4 hours after the final dose elicited no skin or ocular reactions indicative of phototoxicity. The no-observed-effect-level (NOEL) for phototoxicity was >750 mg/kg/day.

3.3.2 Clinical Experience

The early clinical program assessed safety and efficacy of rucaparib in patients with malignancies commonly treated with chemotherapeutic agents. Initially, the IV formulation of rucaparib was administered in combination with a variety of chemotherapies; later, the oral

formulation of rucaparib was administered in combination with chemotherapy and as a monotherapy. The oral formulation as monotherapy is the focus of current development efforts.

More information regarding the studies conducted in the rucaparib clinical program may be found in the Investigator's Brochure.

3.3.2.1 Rucaparib Monotherapy

3.3.2.1.1 Study CO-338-010

Clovis-sponsored study CO-338-010 is a 2-part, open-label, safety, PK, and preliminary efficacy study of oral rucaparib administered daily for continuous 21-day cycles. Part 1 is a Phase 1 portion in patients with any solid tumor, including lymphoma, who have progressed on standard treatment. The primary objective of Part 1 is to determine the optimal monotherapy dose for orally administered rucaparib. Part 2 is a Phase 2 portion in patients with platinum-sensitive relapsed ovarian cancer with evidence of a *gBRCA* mutation who have received at least 2, but no more than 4, prior regimens. The primary objective of Part 2 is to assess the overall objective response rate by RECIST v1.1.

Study CO-338-010 was initiated in Q4 2011. As of 27 June 2014, 56 patients (median age 50 yrs [range 21–71]; 51 female; 27 breast cancer, 20 ovarian/peritoneal cancer, 9 other tumor) were treated at dose levels of 40, 80, 160, 300, and 500 mg once daily (QD), and 240, 360, 480, 600, and 840 mg twice daily (BID) rucaparib administered continuously in the Phase 1 portion of the study. A total of 50 patients discontinued rucaparib; n=46 due to disease progression; n=2 due to an adverse event (unrelated to rucaparib); n=1 due to consent withdrawal; and n=1 due to an eligibility criteria violation. One of 6 patients treated with 360 mg BID rucaparib experienced a dose-limiting toxicity (DLT) of Common Toxicity Criteria for Adverse Events (CTCAE) Grade 3 nausea despite maximal intervention in Cycle 1 of treatment. No DLTs were observed during Cycle 1 in the 480 (n=9), 600 (n=5), and 840 mg BID (n=3) cohorts; however, similar to other PARP inhibitors, non-DLT myelosuppression was observed beyond Cycle 1. The dose of 600 mg BID rucaparib was selected as the recommended dose for Phase 2 and Phase 3 studies based on the overall safety & tolerability, PK, and clinical activity profile. As of June 27, 2014, 15 patients (median age=58 [range=45-84]; 9 ECOG PS=0) with platinum-sensitive, relapsed ovarian cancer associated with a deleterious *BRCA1/2* mutation have been enrolled in the Phase 2 portion of the study. One patient has discontinued rucaparib due to disease progression.

Treatment-related adverse events (all grades) reported in ≥15% of patients treated with 600 mg bid rucaparib include gastrointestinal and related symptoms (nausea, vomiting, dysgeusia, diarrhea, abdominal pain, and decreased appetite), anemia, fatigue/asthenia, and headache. Elevations of ALT and/or AST have been reported. The ALT/AST elevations occur early (within first 2-4 weeks of treatment), were generally mild to moderate (Gr 1-2), not accompanied by any changes in bilirubin levels, and often transient and resolved to within normal ranges, or stabilize. No patient met the laboratory criteria for Hy's Law.[50] As has been observed with rucaparib and other PARP inhibitors, myelosuppression may be delayed and observed after a period of continuous dosing. All treatment-related adverse events were successfully managed with concomitant medication, supportive care, treatment interruption and/or dose reduction. No patient discontinued rucaparib treatment due to a treatment-related adverse event. A total of five

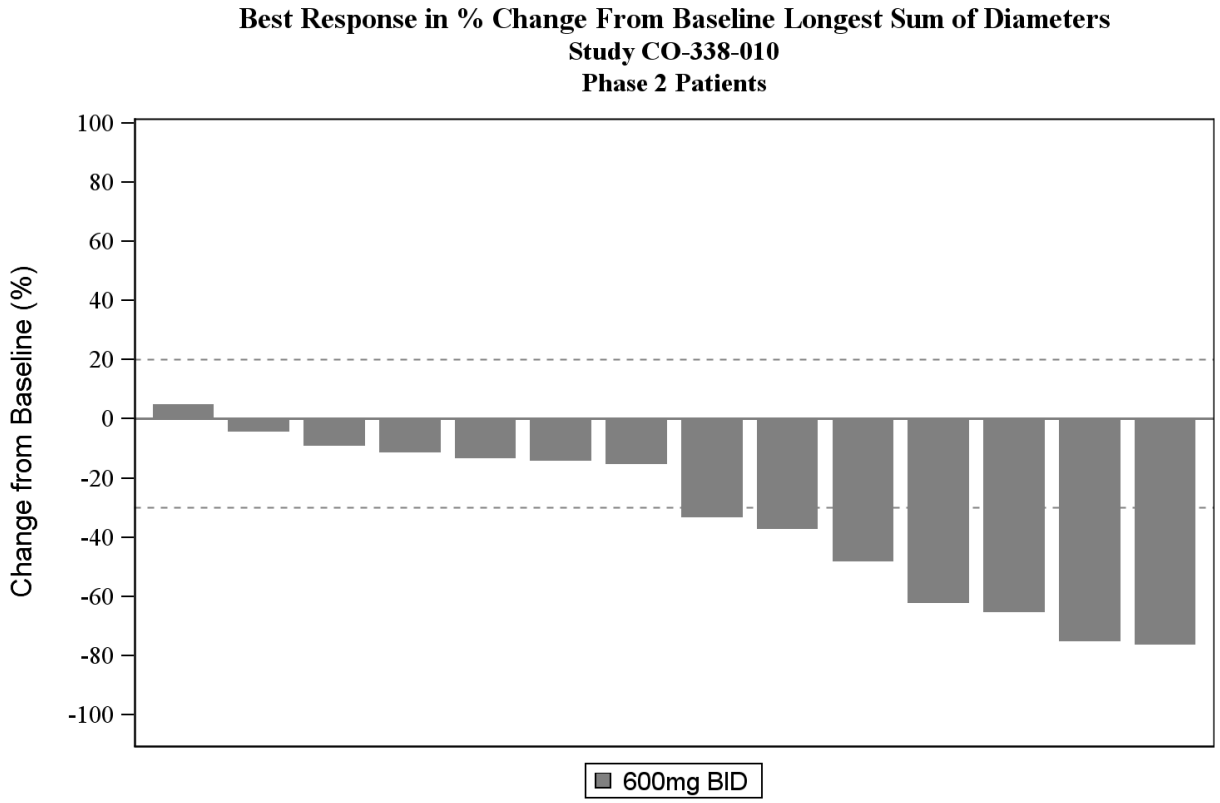
patients have died on study or within 30 days of last dose of rucaparib; all deaths were due to disease progression and were assessed as not related to rucaparib.

Extensive centrally-reviewed electrocardiogram (ECG) monitoring was conducted in the Phase I portion of Study CO-338-010. ECG results (as triplicate reads) are available for all 56 treated patients. No patient had a QTcF measurement ≥500 msec at any time during study participation. Only one patient had a QTcF measurement ≥480 msec. This measurement occurred in a patient receiving 480 mg BID rucaparib and concomitant administration of citalopram, a medication with known potential to cause QT prolongation. This patient has continued to receive monotherapy rucaparib at a dose of 480 mg BID with no further QTcF measurement ≥480 msec. No patient experienced a ≥60 msec increase in QTcF over baseline. The data suggest no relationship between QTcF increase and dose or exposure. In addition, there were no adverse events suggestive of cardiac arrhythmia (eg, presyncope, syncope, sudden death) in any patient. ECG and adverse event data as of the cutoff date in patients receiving monotherapy rucaparib at doses up to 840 mg BID suggest there is a minimal risk of QTc prolongation.

In the Phase 1 portion, 2 patients (1 breast cancer, 1 ovarian cancer, both gBRCAmut) achieved a RECIST CR and 7 patients (2 ovarian cancer, 4 breast cancer, 1 pancreatic cancer; all gBRCA mut) achieved a RECIST PR (n=2 at 300 mg QD; n=2 at 360 mg BID; n=3 at 480 mg BID; and n=2 at 600 mg BID). In addition, 3 patients with ovarian cancer achieved a cancer antigen 125 (CA-125) response as defined by Gynecologic Cancer InterGroup (GCIG) criteria. The disease control rate (CR, PR, or SD>12 wks at doses ≥360 mg BID in evaluable ovarian cancer patients is 92% (11/12). Responses have been durable across tumor types.

Preliminary efficacy data are available for 16 patients in the Phase 2 portion of Study CO-338-010. Currently, 12 of 16 (75%) patients have achieved a RECIST PR. Response to treatment occurs rapidly; the majority of these patients achieved a PR by the first disease assessment (week 6). All responses are ongoing, with several patients in Cycle 5 of treatment or beyond. The vast majority of patients had some level of target lesion measurement reduction as shown in Figure 1.

Figure 1 Best Response in Target Lesions – Phase 2 Portion of Study CO-338-010



After once daily oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. T_{max} and $t_{1/2}$ were independent of dose. Steady state exposure increased by an average of 89%, consistent with accumulation expected for a compound exhibiting a $t_{1/2}$ of approximately 17 hours administered once daily. Following BID oral administration of rucaparib for 15 days, steady state C_{max} and AUC_{0-24} generally increased dose proportionally. Moreover, BID dosing delivered a lower C_{max} with a low peak to trough plasma concentration variation. The target trough level of 2 µM was achieved in 100% of patients (n=14) at ≥240 mg BID with low inter-patient variability (<4-fold) within each dose group. Steady state trough levels also exhibited low intra-patient variability (24% CV). No sporadically high exposures were observed. The effect of food on rucaparib PK was evaluated at 40 mg (n=3) and 300 mg (n=6) doses administered once daily. There was no food effect; patients may take rucaparib on an empty stomach or with food.

Updates of study information may be found in the Investigator's Brochure.

3.3.2.1.2 Study CO-338-017

Study CO-338-017 (ARIEL2) is a Phase 2 study of rucaparib as monotherapy treatment for relapsed, platinum-sensitive high-grade ovarian, fallopian tube or primary peritoneal cancer. The purpose of this study is to define a tumor-based molecular signature of HRD in ovarian cancer that correlates with response to rucaparib and enables selection of appropriate ovarian cancer

patients for treatment with rucaparib. The trial is enrolling patients with and without a *BRCA1/2* mutation in order to enable identification of this response signature, which will then be prospectively applied to the primary analysis of study CO -338-014 (ARIEL3). Tumor HRD status is assessed using next generation sequencing, with an algorithm for HRD status based on the presence of a BRCA mutation (germline or somatic) and/or degree of tumor genomic loss of heterozygosity (LOH), a phenotypic consequence of HRD.

All patients enrolled into Clinical Study CO-338-017 (ARIEL2) must have received at least 1 prior platinum-based treatment regimen, received a platinum-based regimen as their last course of treatment and have platinum-sensitive disease, defined as disease progression >6 months after the last dose of platinum. In addition, all patients must have disease that can be biopsied and is measurable by RECIST v1.1. Rucaparib 600 mg BID is administered continuously until disease progression.

Clinical Study CO-338-017 (ARIEL2) was initiated in October 2013. As of 27 June 2014, 72 of 180 planned patients have been enrolled. The median age is 65.5 years (range 44 – 83) and the majority of patients (n= 54, 75%) had Eastern Cooperative Oncology Group (ECOG) performance status of 0.

The most frequent (reported in ≥15% of patients treatment-related adverse events (all grades) as of 27 June 2014 are gastrointestinal-related toxicities (nausea, constipation, vomiting, diarrhea, and abdominal pain), fatigue, elevations in ALT/AST, decreased appetite, and dysgeusia. Transaminase elevations occur early in treatment and are generally transient and resolve or stabilize. All patients who experienced adverse events related to rucaparib, including those with Grade 3 transaminase elevation, were successfully managed by treatment interruption and/or a dose reduction. No patient has discontinued rucaparib due to a treatment-related adverse event. No patients have died on study or within 30 days of last dose of rucaparib.

Response data are preliminary, yet indicate that rucaparib has activity in $BRCA^{wt}$ patients with high level of LOH as well as in $BRCA^{mut}$ patients.

Updates of study information may be found in the Investigator's Brochure.

3.3.2.1.3 Study A4991002, A4991005, and A4991014

Further details of these studies are provided in the Investigator's Brochure.

3.3.2.1.4 Safety: Events of Special Interest

The current list of adverse events of special interest (AESIs) is located in the rucaparib IB. As of 25 March 2016, there have been 3 events of Myelodysplastic Syndrome (MDS) and 2 events of Acute Myeloid Leukemia (AML) reported in patients participating in Clovis-sponsored clinical studies. The 2 events of AML were reported in this study (CO-338-014 [ARIEL3]). The 3 events of MDS were reported in open-label studies CO-338-017 (ARIEL2) (n=2) and CO-338-010 (n=1). One of these 5 events was fatal.

More than 900 patients have received oral rucaparib in Clovis-sponsored studies as of 25 March 2016, thus these events have been observed in < 0.6% of all patients treated in these

trials. All patients experiencing these events received prior treatment with chemotherapy. While the etiology of these events is confounded by prior treatments and the relationship to rucaparib is not clear, Clovis has added these potential risks to all informed consent forms and patient information sheets. Events of MDS and AML have also been reported with another PARP inhibitor.[51]

3.4 Rationale for Study

In vitro studies have shown that cells deficient in BRCA1/2 as well as cells deficient in or depleted of homologous recombination proteins other than BRCA1/2 have been associated with PARP inhibitor sensitivity in vitro.[16, 17, 25-28] Clinical data have shown that ovarian cancer patients with and without evidence of a *gBRCA* mutation benefit from treatment with a PARP inhibitor[18-22] and that maintenance treatment with a PARP inhibitor following a response to platinum-based treatment increases PFS in patients with ovarian cancer.[29, 30] While patients with a *BRCA* mutation derived the most benefit, patients without evidence of a BRCA mutation also derived significant benefit.[21, 30] The purpose of this study is to evaluate PFS of patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy in order to identify the patients most likely to benefit from treatment with rucaparib. It is anticipated that rucaparib will provide therapeutic benefit and increase PFS in patients with HRD associated with a *BRCA* gene mutation or other HR gene alteration.

Patients will be stratified into one of 3 HRD subgroups (tBRCA, nbHRD, and biomarker negative) (Appendix A) by Foundation Medicine's ICTA, which will determine HRD status through analysis of homologous recombination gene mutations in tumor tissue. Tumor DNA will also be assessed to detect the presence of genomic scars.[33-36] Analysis of specific genomic scarring patterns may identify tumors with HRD regardless of the underlying mechanism(s). Homologous recombination gene mutation analysis and genomic scarring will also be assessed in a Phase 2 study (CO-338-017) that will be initiated in parallel with this Phase 3 study. The insights from study CO-338-017 will be applied prospectively to the analysis of this Phase 3 trial. The FCTA analysis plan (gene mutation and/or genomic scarring) and classification of HRD subgroups will be finalized and locked down prior to the completion of the Phase 3 study and applied prospectively to the analysis of this Phase 3 study.

4 STUDY OBJECTIVES

4.1 Objectives and Endpoints

This is a double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, relapsed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy.

Primary, secondary, and exploratory objectives and endpoints are shown in Table 1.

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints

Primary Objectives	**Primary Endpoints**
1. To evaluate PFS by RECIST, as assessed by the investigator, in molecularly-defined HRD subgroups	1. Disease progression according to RECIST Version 1.1 (v1.1), as assessed by the investigator, or death from any cause (invPFS), in molecularly defined subgroups
Secondary Objectives	**Secondary Endpoints**
1. To evaluate patient-reported outcome (PRO) of disease related symptoms utilizing the disease-related symptoms – physical (DRS−P) subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy (NCCN-FACT) FACT-Ovarian Symptom Index 18 (FOSI-18)	1. Time to a 4-point decrease in the DSR−P subscale of the FOSI-18
2. To evaluate PRO utilizing the complete FOSI-18	2. Time to an 8-point decrease in the total score of the FOSI-18
3. To evaluate survival benefit	3. OS
4. To evaluate PFS by RECIST, as assessed by independent radiology review (IRR), in molecularly-defined HRD subgroups	4. Disease progression according to RECIST v1.1, as assessed by IRR, or death from any cause (irrPFS), in molecularly defined subgroups
5. To evaluate safety	5. Incidence of AEs, clinical laboratory abnormalities, and dose modifications
6. To determine the population PK of rucaparib	6. Individual model parameter estimates of rucaparib and covariates identification

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints (continued)

Exploratory Objectives	Exploratory Endpoints
1. To evaluate the relationship between cancer antigen 125 (CA-125) levels and invPFS	1. Association between the change from baseline in CA-125 measurements and invPFS
2. To evaluate PFS2 (PFS on the subsequent line of treatment)	2. Time to the next event of disease progression or death, as assessed by the investigator
3. To evaluate ORR	3. ORR per RECIST v1.1, as assessed by both investigator and IRR, in patients with measureable disease at study entry
4. To evaluate duration of response (DOR)	4. DOR per RECIST Version 1.1, as assessed by both investigator and IRR
5. To evaluate PRO utilizing the Euro-Quality of Life 5D (EQ-5D)	5. PRO as measured by the total score on the EQ-5D
6. To explore the relationship between rucaparib exposure, efficacy, and safety	6. Rucaparib PK, invPFS, irrPFS, CA-125, AEs, clinical laboratory abnormalities, and dose modifications

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who receive rucaparib or placebo as switch maintenance therapy following a response to platinum-based chemotherapy.

5.1.1 Screening Phase

All patients will undergo screening assessments within 120 days prior to randomization.

The study will enroll patients with platinum-sensitive (defined as disease with confirmed radiologic relapse > 6 months after the last dose of the penultimate platinum regimen received), high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who achieved a response to platinum-based chemotherapy administered for relapsed disease. Patients must have received ≥ 2 prior platinum-based treatment regimens, inclusive of the regimen that must have been administered immediately prior to maintenance therapy in this trial. There is no limit on the number of prior platinum-regimens that may have been received, but the patient must have been sensitive to the penultimate platinum regimen received. In addition, up to 1 prior non-platinum chemotherapy regimen is permitted. Prior hormonal therapy is permitted; this treatment will not be counted as a non-platinum regimen. Prior maintenance therapy may have been administered with any prior treatment, with the exception of the platinum regimen received immediately prior to maintenance in this study. For the last chemotherapy course prior to study entry, patients must have received a platinum-based doublet chemotherapy regimen (minimum 4 cycles) and have achieved a CR (defined as complete radiologic response by RECIST [Appendix B] or PR (defined as partial response by RECIST [Appendix B] and/or a GCIG CA-125 response [Appendix C]. All responses require that CA-125 be < ULN. The response must be maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study.

Screening assessments will include demographics and medical history, prior treatments for serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (and other malignancies, if applicable), prior and current medications and procedures, 12 lead electrocardiogram (ECG), ECOG performance status, central laboratory hematology, serum chemistry, and CA-125 measurement, serum pregnancy (for women of childbearing potential only), urinalysis, physical examination, height, weight, and vital signs measurements, adverse events, and radiologic assessment by CT or MRI. PRO will be collected using the FOSI-18 and EQ-5D instruments.

Germline *BRCA* mutation results should be obtained for all patients who are known to have been tested prior to enrollment in order to determine whether any mutation was reported and if so, whether the mutation was classified as deleterious / pathogenic or other. Enrollment of patients with a *gBRCA* mutation classified as deleterious (i.e. pathogenic), suspected deleterious, or the equivalent, on the most recent assessment by a testing laboratory will be limited to 150. Patients with a *BRCA* mutation detected in tumor tissue (tBRCA) will be limited to 200. Once this cap is

reached, newly screened patients identified as having a *BRCA* mutation in tumor tissue will be offered treatment in another study.

The complete results of the Foundation Medicine NGS test, which examines exons of 287 genes as well as introns of 19 genes, will be provided to all patients who opt to receive this information and provide appropriate consent. Results for the *BRCA* genes will be provided to patients who consent to receive this information upon availability. Results for the remainder of the gene panel will be provided to consenting patients upon treatment discontinuation. All results are to be disclosed to consenting patients by the study physician as part of an overall clinical discussion. In the event a mutation associated with hereditary cancer or other syndrome is detected in tumor tissue, the patient will be referred by the investigator for genetic counseling and potential germline testing per institutional guidelines. If the patient chooses to have germline *BRCA* testing, this result will be entered into the clinical trial database. The Sponsor will remain blinded to all NGS test results (including all *tBRCA* results), as well as existing *BRCA* data, until the primary efficacy analysis is conducted.

Mutations detected in tumor tissue may be somatic or germline; however, the NGS test will not distinguish between the two. A blood sample will therefore be collected for all patients and stored. Prior to final efficacy analysis, genomic DNA may be subjected to exploratory analysis in order to determine whether any mutation identified is of germline or somatic origin. This data will be generated in a research setting and will not be provided to the investigator or patient.

Enrollment will require Clovis (or designee) review of eligibility, including, but not limited to:

- The number of prior therapies and the details for the penultimate and most recent platinum-based regimens, including dates administered;
- documentation supporting platinum sensitivity;
- documentation supporting a RECIST or GCIG CA-125 response to most recent platinum-based treatment;
- confirmation if patient has had local *gBRCA* testing;
- confirmation that sufficient tumor tissue was submitted for HRD stratification for randomization and storage for potential bridging to a validated companion diagnostic test and analysis results were successfully transmitted to IXRS

5.1.2 Randomization

Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy, and is described in more detail in Section 7.2. Study treatment must be initiated within 3 days of randomization.

5.1.3 Double-Blind Treatment Phase

During the double-blind treatment phase (continuous 28-day treatment cycles), patients will be monitored for safety and efficacy. Assessments will include AEs, physical examination, vital signs and weight measurement, central laboratory hematology, serum chemistry, including alpha-1 acid glycoprotein (AAG) analysis on days where a blood sample is taken for PK, and

CA-125 measurement, serum pregnancy for women of childbearing potential, concomitant medications, therapies and procedures, disease status assessment, study drug administration and accountability, and PRO. ECGs and urinalysis will be performed as clinically indicated. Blood samples will also be collected for population PK. The purpose of AAG monitoring is to determine whether there is an association with rucaparib PK variability.

Patients will be assessed for disease status per RECIST v1.1 every 12 calendar weeks (up to 1 week prior is permitted) following initiation of study treatment on Day 1 of Cycle 1. Patients experiencing disease progression by RECIST v1.1, as assessed by the investigator, will be discontinued from treatment and enter follow-up. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and be assessed by RECIST v1.1 per the protocol schedule of assessments.

All CT scans (and other imaging, as appropriate) performed during the treatment period and at treatment discontinuation will be collected for IRR.

Patients will be continuously monitored for safety. An Independent Data Monitoring Committee (IDMC) with multidisciplinary representation will evaluate safety in compliance with a prospective charter.

5.1.4 Treatment Discontinuation

Upon treatment discontinuation, regardless of reason, patients will have a Treatment Discontinuation visit. Assessments will include AEs, physical examination, vital signs and weight measurements, central laboratory hematology, serum chemistry, and CA-125 measurement, serum pregnancy (for women of childbearing potential only), concomitant medications, therapies and procedures, disease status assessment, study drug accountability, and PRO. Additionally, all patients discontinued from treatment will be followed for 28 days following the last dose of study drug for the collection of AEs and PRO. An optional tumor biopsy will be collected from patients who experience disease progression and provide appropriate consent.

5.1.5 Follow-Up Phase

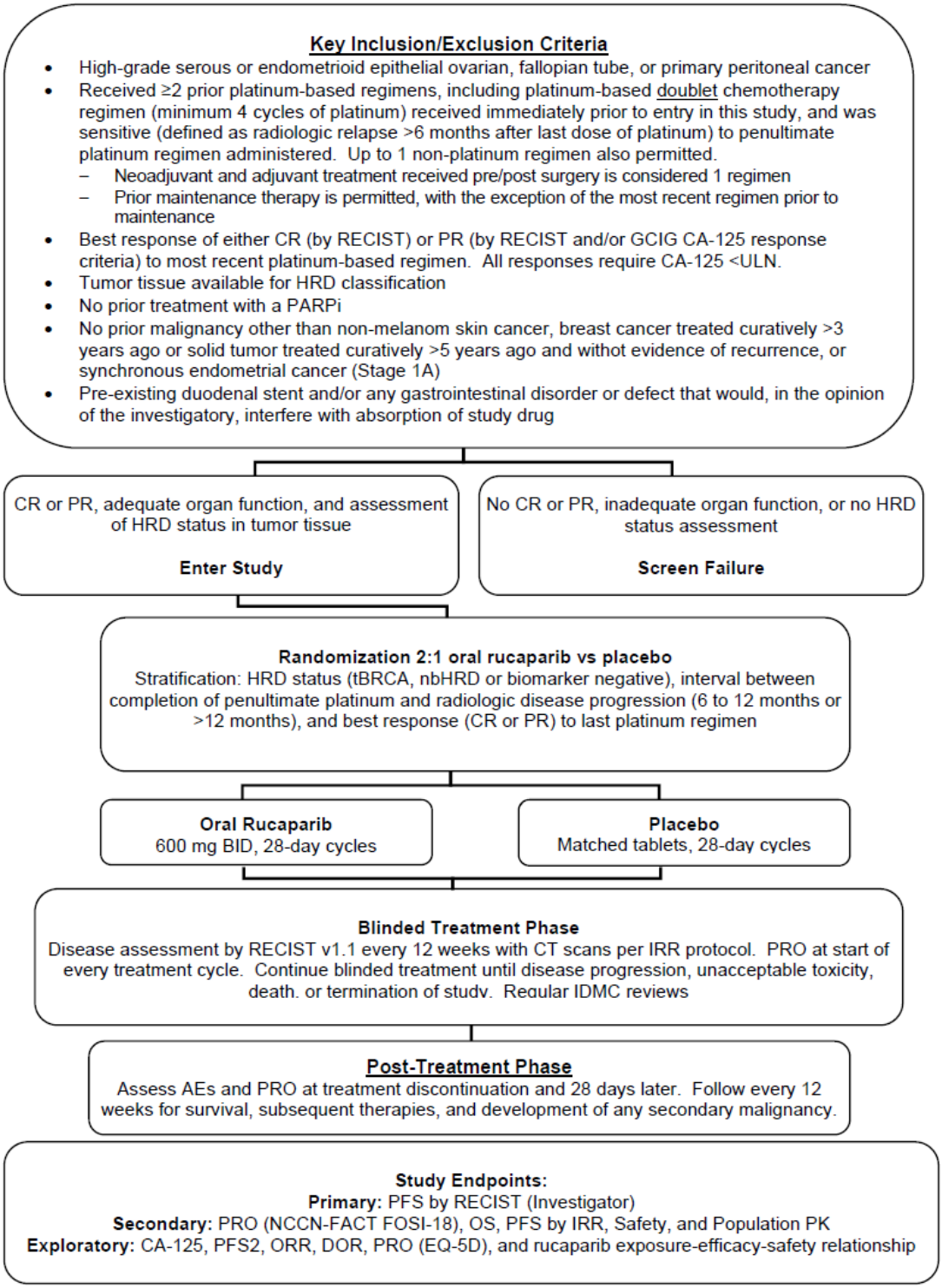
After the Treatment Discontinuation visit, all patients will be followed for AEs up to 28 days after last dose of study drug. Patients will also be followed for survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent, or study closure.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals from Cycle 1 Day 1 (a window of up to 7 days prior is permitted) until disease progression by RECIST v1.1, as assessed by the investigator.

5.2 Study Schema

An overview of the study design is provided in Figure 2.

Figure 2 Study Schema



5.3 End of Study

The trial is monitored on an ongoing basis by an IDMC for the number of PFS events required for the primary endpoint and for safety signals. An unblinding of treatment assignment might be performed when the study is still ongoing if the IDMC recommends it. However, the study is not anticipated to close until all patients are off treatment and sufficient OS follow up has occurred. Upon formal closure of the study, individual patients who are continuing to benefit from treatment with rucaparib at the time of study closure, and who do not meet any of the criteria for withdrawal, will have the option of entering an extension protocol in which they can continue to receive rucaparib.

The sponsor may discontinue the study early for any reason as noted in Section 13.6.

5.4 Discussion of Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study.

Sponsor personnel (with the exception of individuals responsible for clinical supply chain), investigator and clinical site staff, and patient will all be blinded to study treatment to avoid bias in the interpretation of the efficacy and safety results. To avoid bias between treatment groups, patients will be randomized to treatment with active drug or placebo with stratification according to HRD classification, interval between completion of penultimate platinum-based regimen and disease progression by radiologic assessment, and best response to platinum regimen received immediately before initiation of maintenance therapy.

PFS by RECIST will be assessed by the investigator for the primary endpoint (invPFS) and by a blinded independent radiologist for the secondary endpoint (irrPFS).

Ongoing benefit/risk will be assessed regularly by an IDMC that will have access to unblinded datasets.

6 STUDY POPULATION

6.1 Number of Patients and Sites

Approximately 540 patients with platinum-sensitive, relapsed, high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer will be enrolled at approximately 90 – 100 study sites. A minimum of 180 and a maximum of 200 patients with a deleterious *tBRCA* mutation will be enrolled. Enrollment of patients with a known deleterious *gBRCA* mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined.

6.2 Inclusion Criteria

All patients enrolling into the study must meet all of the following inclusion criteria:

1. Have signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Be ≥18 years of age at the time the informed consent form is signed
3. Have a histologically confirmed diagnosis of high-grade (Grade 2 or 3) serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer
   - For mixed histology, >50% of the primary tumor must be confirmed to be high-grade serous or endometrioid
   - Grade 2 tumors classified under a 3-tier system should be re-reviewed by local pathology and confirmed as high-grade under the 2-tier system
4. Received prior platinum-based therapy and have platinum-sensitive disease (i.e. documented radiologic disease progression >6 months following the last dose of the penultimate platinum administered)
   - Received ≥2 prior platinum-based treatment regimens, including platinum-based regimen that must have been administered immediately prior to maintenance therapy in this trial. In addition, up to 1 non-platinum chemotherapy regimen is permitted. Prior hormonal therapy is permitted; this treatment will not be counted as a non-platinum regimen.
   - There is no upper limit on the number of prior platinum-based regimens that may have been received, but the patient must have been sensitive to the penultimate platinum-based regimen administered.
   - If both neoadjuvant and adjuvant treatment were administered pre/post any debulking surgery, this will be considered 1 treatment regimen
   - Prior maintenance therapy following a prior treatment regimen is permitted, with the exception of the regimen received immediately prior to maintenance in this study. No anticancer therapy is permitted to be administered as maintenance treatment in the interval period between completion of the most recent platinum-based therapy and initiation of study drug in this trial.

5. Achieved best response of either CR or PR to the most recent platinum-based regimen administered and is randomized to study treatment within 8 weeks of the last dose of platinum received
   - The most recent platinum-based regimen must have been a chemotherapy doublet. The choice of the platinum and the 2nd chemotherapy agent is per Investigator' discretion.
   - A minimum of 4 cycles of platinum chemotherapy must have been administered. There is no cap on the maximum number of cycles; however, additional cycles of treatment administered following completion of therapy for the specific purpose of enabling patient eligibility and randomization within 8 weeks of the last platinum dose is not permitted.
   - A CR is defined as a complete radiologic response per RECIST v1.1, i.e. absence of any detectable disease and CA-125 <ULN*
   - A PR is defined as either a partial response per RECIST v1.1 (if disease was measurable prior to chemotherapy) or a serologic response per GCIG CA-125 response criteria (if disease was not measurable according to RECIST v1.1)*
     - CA-125 must also be <ULN for all responses classified as a PR
   - R0 surgery (no visible tumor) or R1 surgery (residual disease <1 cm) as a component of the most recent treatment regimen is not permitted. The response assessment must be determined solely in relation to the chemotherapy regimen administered. The presence of measurable disease or CA-125 >2 x ULN immediately prior to the chemotherapy regimen is required.
   - Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry in the study
   - All disease assessments performed prior to and during this chemotherapy regimen must be adequately documented in the patient's medical record
6. Have sufficient archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (1 x 4 µm section for hematoxylin and eosin [H&E] stain and approximately 8 – 12 x 10 µm sections, or equivalent) available for planned analyses.
   - The most recently collected tumor tissue sample should be provided, if available
   - Submission of a tumor block is preferred; if sections are provided, these must all be from the same tumor sample
   - Sample must be received at the central laboratory **at least 3 weeks prior to planned start of treatment** in order to enable stratification for randomization
7. Have CA-125 measurement that is < ULN
8. Have ECOG performance status of 0 to 1
9. Have adequate organ function confirmed by the following laboratory values obtained within 14 days of the first dose of study drug:
   - Bone Marrow Function
     - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L

- Platelets > 100×10^9/L
- Hemoglobin ≥ 9 g/dL

– Hepatic Function

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN; if liver metastases, then ≤ 5 × ULN
- Bilirubin ≤ 1.5 × ULN (< 2 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)

– Renal Function

- Serum creatinine ≤ 1.5 × ULN or estimated glomerular filtration rate (GFR) ≥ 45 mL/min using the Cockcroft Gault formula

* Note: It is acceptable for sites to utilize local and contemporaneous clinical imaging reports to record lesion measurement history and define a burden of disease according to RECIST; it is not a requirement to re-read radiological scans to collect this data.

6.3 Exclusion Criteria

Patients will be excluded from participation if any of the following criteria apply:

1. History of a prior malignancy except:
   – Curatively treated non-melanoma skin cancer
   – Breast cancer treated curatively >3 years ago, or other solid tumor treated curatively >5 years ago, without evidence of recurrence
   – Synchronous endometrioid endometrial cancer (Stage 1A G1/G2)
2. Prior treatment with any PARP inhibitor, including oral or intravenous rucaparib. Patients who previously received iniparib are eligible.
3. Required drainage of ascites during the final 2 cycles of their last platinum-based regimen and/or during the period between the last dose of chemotherapy of that regimen and randomization to maintenance treatment in this study
4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks.
5. Pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the Investigator, interfere with absorption of study drug
6. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C
7. Pregnant or breast feeding. Women of childbearing potential must have a negative serum pregnancy test ≤ 3 days prior to first dose of study drug
8. Received treatment with chemotherapy, radiation, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior

to first dose of study drug and/or ongoing adverse effects from such treatment > NCI CTCAE Grade 1, with the exception of Grade 2 non-hematologic toxicity such as alopecia, peripheral neuropathy, and related effects of prior chemotherapy that are unlikely to be exacerbated by treatment with study drug

  - Ongoing hormonal treatment for previously treated breast cancer is permitted
  - Refer also to inclusion criteria #4 for guidelines pertaining to prior maintenance therapy

9. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of study drug or have on-going requirements for these medications (Appendix F)
10. Non-study related minor surgical procedure ≤5 days, or major surgical procedure ≤21 days, prior to first dose of study drug; in all cases, the patient must be sufficiently recovered and stable before treatment administration
11. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the investigator, would make the patient inappropriate for entry into the study

6.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients are considered to be of childbearing potential unless 1 of the following applies:

- Postmenopausal, defined as no menses for at least 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state: or

- Considered to be permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy.

Female patients of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to administration of the first dose of study drug. In addition, a serum pregnancy test must be performed within ≤ 3 days prior to Day 1 of every subsequent cycle during the treatment phase and at the Treatment Discontinuation visit. All pregnancy testing will be performed by the local laboratory.

Female patients of reproductive potential must practice highly effective methods of contraception (failure rate < 1% per year) with their male partners during treatment and for 6 months following the last dose of study drug. Highly effective contraception includes:

- Ongoing use of progesterone-only injectable or implantable contraceptives (eg, Depo Provera, Implanon, Nexplanon);

- Placement of an intrauterine device (IUD) or intrauterine system (IUS);

- Bilateral tubal occlusion;
- Male sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate; or
- Sexual abstinence as defined as complete or true abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable.

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with study drug.

6.5 Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

7 DESCRIPTION OF STUDY TREATMENTS AND DOSE MODIFICATIONS

7.1 Description of Investigational Product

Rucaparib camsylate (also known as CO-338; previously known as PF-01367338-BW) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration and matched placebo tablets will be supplied to the study sites by the sponsor. A brief description of the investigational product is provided below.

Drug Name:	CO-338
rINN:	rucaparib
Formulation:	Oval tablet; film coated; salmon pink
How Supplied:	120 mg (as free base) strength in high-density polyethylene bottles or equivalent with child-resistant caps
Storage Conditions:	15–30 °C/ 59-86 ºF

Placebo tablets will be identical in appearance to the rucaparib tablets.

Study drug containers containing rucaparib or placebo tablets will be labeled according to national regulations for investigational products. Where accepted, the expiry date will not appear on the labels, but will be controlled by the use of an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

7.2 Method of Assigning Patients to Treatment Groups

Following confirmation of eligibility in the screening phase, patients will be randomized 2:1 to receive rucaparib or placebo. Randomization will occur by a central randomization procedure using IVRS/IWRS. The following will be included as randomization stratification factors at study entry to ensure treatment groups are balanced:

- HRD classification (tBRCA, nbHRD, or biomarker negative) by the ICTA (Appendix A)
- Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 or >12 months) by radiologic assessment
- Best response (CR [defined as complete radiologic response by RECIST] or PR [defined as partial response by RECIST and/or a GCIG CA-125 response] to platinum regimen received immediately prior to initiation of maintenance therapy. All responses require that CA-125 be <ULN.

Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy. Study treatment must be initiated within 3 days of randomization.

7.3 Preparation and Administration of Protocol-Specified Treatment

The investigator or designee will be responsible for distributing study drug to all patients. Study drug will be assigned by the IVRS/IWRS according to the patient's randomization assignment. The system must be accessed at each dispensation in order to retrieve the bottle number

appropriate to the patient's treatment. Study sites should follow local guidelines for the handling of oral cytotoxic drugs.

All patients will ingest study drug twice a day. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Each dose should be taken with at least 8 oz (240 mL) of room temperature water. Tablets should be swallowed whole.

Patients should take study drug doses as close to 12 hours apart as possible, preferably at the same times every day. If a patient misses a dose (i.e. does not take it within 4 hours of the scheduled time), she should skip the missed dose and resume taking study drug with their next scheduled dose. Missed or vomited doses should not be made up.

A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken in an electronic dosing diary, and will be instructed to bring their study drug tablets, all containers (empty, partially used, and/or unopened), and electronic dosing diary to the next scheduled visit for reconciliation by site personnel. The electronic dosing diary is a Class 1 listed (i.e. approved) device.

7.3.1 Dietary Restrictions

All patients participating in the study should be instructed not to consume any grapefruit products or any of the CYP1A2 or CYP3A4 inhibitors noted in Appendix F for 7 days prior to their first scheduled dose of oral rucaparib or placebo.

7.4 Starting Dose and Dose Modifications of Protocol-Specified Treatment

7.4.1 Starting Dose

The starting dose in this study will be 600 mg rucaparib or matched placebo, bid.

7.4.2 Dose Modification Criteria

Treatment with study drug should be held if any of the following are observed and a dose reduction should be considered or implemented:

- Grade 3 or 4 hematologic toxicity

  Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below.
- In addition, and at the discretion of the investigator, the dose of study drug may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

MANAGEMENT OF STUDY DRUG TREATMENT-EMERGENT ALT/AST ELEVATIONS

- Grade 4 ALT/AST elevations: hold study drug until values have returned to Grade 2 or better, then resume study drug with a dose reduction. Monitor liver function tests weekly for 3 weeks after study drug has been restarted.

- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:

  – Monitor liver function tests weekly until resolution to ≤ Grade 2.

  – Continuation of study drug with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.

  – If patient has Grade 3 ALT/AST and continues on study drug, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before study drug can be resumed, either at the current dose or at a reduced dose.

Treatment with study drug should be held until the toxicity resolves to ≤ CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient experiences the same toxicity, the dose should be reduced following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted; however, the Investigator should consult with the Sponsor's medical monitor before reducing to 240 mg BID. If a patient continues to experience toxicity despite two dose reduction steps (ie, to a dose of 360 mg BID rucaparib or placebo), or if dosing with study drug is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed between the investigator and the sponsor.

Dose reduction steps are presented in Table 2.

Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 is permitted at the discretion of the Investigator.

Table 2. Dose Reduction Steps

Starting Dose	**600 mg BID**
Dose Level -1	480 mg BID
Dose Level -2	360 mg BID
Dose Level -3*	240 mg BID

*Consult with medical monitor before reducing to this dose

7.4.3 Criteria for Re-Treatment

A new cycle of treatment may begin if:

- ANC $\geq 1.0 \times 10^9$/L
- Platelet count $\geq 100 \times 10^9$/L
- Non-hematologic toxicities have returned to baseline or ≤ CTCAE Grade 1 severity (or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient). Grade 3 or Grade 4 ALT/AST elevations should be managed as described above.

7.5 Accountability of Protocol-Specified Treatment

Study personnel will maintain accurate records of study drug receipt, dispensation, use, return, destruction, and reconciliation. An IVRS/IWRS will be used to manage study drug inventory at all sites. In order to function properly, and to ensure patients receive the correct study drug according to the treatment assigned at randomization, the system will require real-time entry of study drug receipt, dispensation, or destruction, etc. by study personnel at the study center.

The site is responsible for the return or destruction of study drug as required. Authorization to destroy study drug at the site that has not been dispensed to a patient (eg, expired study drug), must be requested from the Sponsor prior to destruction. Any study drug accidentally or deliberately destroyed must be accounted for. All study drug containers must be accounted for prior to their destruction at the study center, according to institutional procedures for disposal of cytotoxic drugs. Unused study drug containers should be destroyed on-site if possible. Destruction of damaged or expired study drug at the site requires prior approval by the sponsor. If destruction on site is not possible, supply should be returned to the drug depot.

During the course of the study and at completion of the study, the number of study drug containers received, dispensed, returned, and destroyed must be reconciled.

7.6 Blinding/Masking of Treatment

Active and placebo tablets will be identical in appearance and supplied in identical containers. The medication labeling will ensure that no staff member or patient will be able to identify whether the tablets are placebo or contain active medication.

Patients will take the equivalent number of active or placebo tablets according to the treatment assignment and scheduled dose.

In the event of a medical emergency, an individual patient's treatment assignment may be unblinded using IVRS/IWRS. The module to unblind treatment assignment is accessible only to specific authorized study personnel. AEs per se are not a reason to break the treatment code. Unblinding should only occur for medical emergencies that require explicit knowledge of the treatment administered in order to determine the next course of action. The IVRS/IWRS vendor

operates a 24-hour/365-day helpline as a back-up in the rare event the electronic system in unavailable when unblinding is required.

The study will not be unblinded for overall safety evaluation.

7.7 Treatment Compliance

Documentation of dosing will be recorded in a study specific electronic dosing diary provided by the sponsor (or designee). Study site personnel will review dosing information with the patient (or legally authorized representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets to be taken for each dose. Patients (or legally authorized representative) will be instructed to record dosing information for study drug taken at home in the electronic dosing diary and to bring the electronic dosing diary and all unused tablets with them to scheduled clinic visits. A compliance check and tablet count will be performed by study personnel during clinic visits. Every effort should be made to ensure patients complete the electronic dosing diary and return their study drug containers at the end of each cycle of treatment.

8 PRIOR AND CONCOMITANT THERAPIES

Patients who have received prior treatment with a PARP inhibitor including IV or oral rucaparib, are not eligible to participate in this study. Patients having received prior treatment with iniparib are eligible.

During the study, supportive care (eg, antiemetics; analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures.

All procedures performed (eg, thoracentesis, etc.) and medications used during the study must be documented on the eCRF.

8.1 Anticancer or Experimental Therapy

No anticancer therapy is permitted to have been administered as maintenance treatment in the interval period between completion of the most recent platinum-based chemotherapy and initiation of maintenance treatment in this study.

No other anticancer therapies (including chemotherapy, radiation, hormonal treatment, antibody or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or other experimental drugs) of any kind will be permitted while the patient is participating in the study, with the exception of ongoing hormonal treatment for previously treated breast cancer.

8.2 Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

8.3 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on *in vitro* CYP interaction studies (Please refer to current IB for details), caution should be used for concomitant medications with narrow therapeutic windows that are substrates of CYP2C19, CYP2C9, and/or CYP3A (Appendix F). Selection of an alternative concomitant medication is recommended.

8.4 Bisphosphonates

Bisphosphonates are permitted.

8.5 Anticoagulants

Caution should be exercised in patients receiving study drug and concomitant warfarin (Coumadin) as rucaparib showed a mixed inhibition of CYP2C9 in vitro. If appropriate, low molecular weight heparin should be considered as an alternative treatment. Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

8.6 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

Because rucaparib is a moderate inhibitor of P-gp *in vitro*, caution should be exercised for patients receiving study drug and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored after starting study drug and then regularly per standard clinical practice. Caution should also be exercised for concomitant use of certain statin drugs (eg, rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9.[52]

9 STUDY PROCEDURES

9.1 Schedule of Assessments

Table 3 summarizes the procedures and assessments to be performed for all patients.

All procedures and assessments are to be completed within ±3 days of the scheduled time point unless otherwise stated.

Imaging guidelines provided in the Bioclinica Site Manual should be followed for the collection of images and the radiological assessment of disease.

Table 3. Schedule of Assessments

Procedure[a]	Pre-Randomization Phase			Randomization	Blinded Treatment Phase			Post-Treatment Phase		
	Screening				Cycles 1 & 2		Cycles 3+			
	Day -120 to Day-1	Day -28 to Day -1	Day -14 to Day -1		Day 1[b]	Day 15	Day 1	Treatment Discontinuation	28-day Follow-up	Long-term Follow-up
Informed Consent	X									
Medical/Oncology History[c]	X									
Archival Tumor Tissue Sample[d]	X									
Physical Examination, Height[e], Weight		X			X		X	X		
Vital Signs[f]		X			X		X	X		
12-lead ECG[g]		X						X		
Prior/Concomitant Medications/Procedures		X			X	X	X	X	X	
Disease Assessment/Tumor Scans[h]		X					X[i]	X	X[j]	X[j]
Patient-reported outcome (FOSI-18, EQ-5D)[k]		X			X		X	X	X	
ECOG Performance Status		X			X		X	X		
Hematology[l]			X		X	X	X	X		
Serum Chemistry[m] (fasting not required)			X		X	X	X	X		
Serum Pregnancy Test (WOCBP only)[n]			X		X		X	X		
Urinalysis[o]			X							
CA-125 Measurement[p]			X		X		X	X		
Randomization to Study Treatment				X[q]						
Blood Sample for Storage (required)					X[r]					
Study Drug Dispensation					X		X			
Adverse Events[s]	(X)	(X)	(X)		X	X	X	X[t]	X[t]	
Plasma PK Sample					X[u]	X[u]	X[u]			
Serum AAG Sample					X[v]	X[v]	X[v]			
Tumor Tissue Biopsy (optional)								X[w]		

Table 3. Schedule of Assessments

Subsequent Treatments, Secondary Malignancy Monitoring, and Overall Survival[x]									X	X

AAG = alpha-1 acid glycoprotein, AESI = adverse event of special interest, ALP = alkaline phosphatase, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, *gBRCA* = germline breast cancer gene, BUN = blood urea nitrogen, CA-125 = cancer antigen 125, CO_2 = bicarbonate, CR = complete response, CT = computer tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EQ-5D = Euro-QoL 5D, FOSI-18 = Functional Assessment of Cancer Therapy-Ovarian Symptom Index 18, QoL= quality of life, Hct = hematocrit, HDL= high density lipoprotein, Hgb = hemoglobin, HRD = homologous recombination deficiency, INR = international normalized ratio, IVRS = interactive voice response system, GCIG = gynecologic cancer intergroup, GFR = glomerular filtration rate, LDL= low density lipoprotein, MCH = mean corpuscular hemoglobin, MCHC, = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MRI = magnetic resonance imaging, nbHRD = non-*BRCA* HRD, PET = positron emission tomography, PK = pharmacokinetic, PR = partial response, RBC= red blood cell count, RECIST = Response Evaluation Criteria in Solid Tumors, SAE = serious adverse event, WBC = white blood cell, WOCBP = women of child bearing potential

[a] = The study visit window in the double-blind treatment phase is ± 3 days, unless noted otherwise for a particular assessment. Study visits should take into account the subject's investigational product supply. Only 1 cycle of study drug will be dispensed to the subject on Day 1 of each cycle.

[b] = First dose of study drug in Cycle 1 should be administered within 3 days of randomization.

[c] = Patient's medical record must include prior treatments received, dates of administration, date of progression and how assessed, and radiology reports. *gBRCA* mutation status, if known, will also be recorded on the appropriate case report form.

[d] = Adequate archival tumor tissue samples must be provided to enable determination of HRD status for randomization, determination of HRD status prior to final analysis (if required), and storage for potential bridging to the final companion diagnostic test. The most recently collected sample should be provided, if available. Submission of a tumor block and tumor content ≥30% is strongly preferred. Sample must be submitted to the central laboratory **at least 3 weeks prior to planned start of treatment** in order to enable stratification for randomization

[e] = Height at screening only.

[f] = Vital signs (blood pressure, pulse, and temperature) to be taken predose on drug administration days, after the patient has been resting for at least 5 min.

[g] = Heart rate, PR, QRS, QT, QTc, and rhythm. Investigator to review results and assess as normal or abnormal (clinically significant or not clinically significant). ECGs to be repeated as clinically indicated.

[h] = Disease assessments to consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen and pelvis, with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT/ MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline.

[i] = Tumor scans to be performed every 12 calendar weeks (a 7-day window prior is permitted) after start of treatment on Day 1 of Cycle 1. Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST v1.1. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

[j] = To be performed every 12 calendar weeks (up to 7 days prior is permitted) through to investigator-assessed radiologic disease progression by RECIST v1.1 for any patient who discontinued from study treatment for reason other than disease progression or death.

Table 3. Schedule of Assessments

[k] = The FOSI-18 and EQ-5D instruments must be completed prior to other scheduled study procedures and dosing (if applicable) at Screening, on Day 1 of each treatment cycle, at treatment discontinuation, and at the 28-day post-treatment discontinuation follow-up visit for all patients. If a patient has known brain metastases, this disease should be evaluated at each required assessment.

[l] = Includes RBC and parameters (Hgb, Hct, MCV, MCH, MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a central laboratory. A duplicate sample may be collected and analyzed by the local laboratory for immediate eligibility/treatment decisions.

[m] = Includes total protein, albumin, creatinine or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, ALP, ALT, AST, lipid panel (total cholesterol, LDL, HDL, and triglycerides), glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus. Blood will be analyzed by a central laboratory. A duplicate sample may be collected and analyzed by the local laboratory for immediate eligibility/treatment decisions.

[n] = Women of childbearing potential must have a negative serum pregnancy test result ≤ 3 days prior to the first dose of study drug. A serum pregnancy test must also be performed ≤ 3 days prior to Day 1 of every cycle during the treatment phase and at the treatment discontinuation visit. All tests will be performed by a local laboratory.

[o] = Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings abnormal based on Investigator's judgment, perform microscopic evaluation to assess abnormal findings. Urinalysis to be repeated as clinically indicated.

[p] = CA-125 measurement should be performed at Screening, on Cycle 1, Day 1, at the start of every 3rd cycle thereafter (i.e. Day 1 of Cycles 4, 7, 10, etc.), at treatment discontinuation, and as clinically indicated. All CA-125 measurements will be performed by a central laboratory.

[q] = Randomization to study treatment must occur within 8 weeks following a patient's last dose of platinum-based chemotherapy and study treatment must begin within 3 days of randomization. Randomization will occur by a central randomization procedure using an IVRS/IWRS. Patients will be stratified based on HRD classification (tBRCA, nbHRD or biomarker negative), interval between completion of penultimate platinum regimen and disease progression (6 to 12 or > 12 months) by radiologic assessment, and best response (RECIST CR, RECIST PR, or GCIG CA-125 response) to most recent platinum regimen. All responses require that CA-125 be <ULN.

[r] = If sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter.

[s] = AEs, SAEs, and AESIs that occur after first administration of study drug through to 28 days after last dose of study drug will be recorded. In addition, AEs that were related to a screening procedure will also be recorded. Section 10 includes the details of reporting AEs, SAEs, and AESIs.

[t] = Ongoing SAEs/ AESIs will be followed to resolution or stabilization.

[u] = PK samples to be collected on Day 15 of Cycle 1 (in morning or afternoon, after dose taken earlier in day), on Day 1 of Cycle 2 (prior to dosing), on Day 15 of Cycle 2 (in morning or afternoon, after dose taken earlier in day), and on Day 1 of Cycle 4 and Cycle 7 (prior to dosing). At least one morning post-dose sample and one afternoon post-dose sample must be taken for each patient. For example, if on Day 15 of Cycle 1 a PK sample is collected in the morning, then on Day 15 of Cycle 2, the PK sample should be collected in the afternoon. Conversely, if on Day 15 of Cycle 1 a PK sample is collected in the afternoon, then on Day 15 of Cycle 2, the PK sample should be collected in the morning. There is no requirement for either of these 2 samples to be collected at a specific time following the first dose taken on these days (Cycle 1 Day 15 and Cycle 2 Day 15).

[v] = Serum AAG sample to be collected on the same day as the PK sample. Sample should be collected at the same time as the hematology and serum chemistry samples for central laboratory testing.

[w] = An optional tumor biopsy may be collected from patients at time of disease progression. Additional consent is required. Refer to the Pathology Charter for detailed sample handling instructions.

Table 3. Schedule of Assessments

[x]	= All patients discontinued from treatment, regardless of reason, should be followed for subsequent treatments, secondary malignancy, and survival every 12 weeks (± 14 days) from Cycle 1 Day 1 until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (i.e. laboratory and/or pathology reports) and should be reported a specified in Section 10.8.

9.2 Screening Phase

Following written informed consent, and unless otherwise specified, the following assessments will be performed prior to randomization. Assessments performed within the specified windows, but prior to patient signing informed consent, are acceptable only if confirmed to have been standard of care.

Up to 120 days prior to randomization:

- Medical history, including demographic information (birth date, race, gender, etc.) and smoking status, and oncology history, including date of diagnosis for ovarian, primary peritoneal, or fallopian tube cancer (and other malignancy, if applicable), prior treatments received, dates of administration, best response achieved, date of progression and how assessed, radiology reports, and *gBRCA* mutation status (if known)
- FFPE archival tumor tissue sample. Sufficient archival FFPE tumor tissue (enough for 1 x 4 µm section for H&E and approximately 8 to 12 x 10 µm sections, or equivalent) for planned analyses should be provided. Refer to the Pathology Charter for detailed sample handling instructions.
    - The most recently collected tumor tissue sample should be provided, if available.
    - Submission of a tumor block preferred; if sections are provided, these must all be from the same tumor sample.
    - Tumor content ≥30% is strongly preferred for successful genomic scarring / LOH analysis
    - Sample must be submitted to the central laboratory **at least 3 weeks prior to planned start of treatment** in order to enable stratification for randomization
- AE monitoring (only if related to screening procedure)

Up to 28 days prior to randomization:

- PRO collected using the FOSI-18 and EQ-5D instruments
- Physical examination by body system, including height and weight
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG
- Prior and concomitant medications and any surgical procedures
- Disease assessment/tumor scans: tumor assessments should consist of clinical examination and appropriate imaging techniques (including CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST; other studies (magnetic resonance imaging [MRI], X-ray, positron emission tomography [PET], and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment. CT/ MRI scans of the chest, abdomen, and pelvis

performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline.

- ECOG performance status (Appendix D)
- AE monitoring (only if related to screening procedure)

Up to 14 days prior to randomization:

- Hematology (RBC and parameters [Hgb, Hct, MCH, MCV, and MCHC] and reticulocyte count, white blood cell [WBC] and differential [with ANC], and platelet count
- Serum chemistry (total protein, albumin, creatinine, or estimated GFR using the Cockcroft Gault formula, blood urea nitrogen [BUN] or urea, total bilirubin, ALP, ALT, AST, glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus) and lipid panel (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL], and triglycerides). *Note: fasting is not required.*
- Urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones) ≤14 days prior to the first dose of study drug. If dipstick findings are abnormal based on investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings
- CA-125 measurement
- AE monitoring (only if related to screening procedure)

Up to 3 days prior to first dose of study drug:

- Serum pregnancy test for women of childbearing potential
- AE monitoring (only if related to screening procedure)

9.3 Treatment Phase

9.3.1 Day 1 of Cycles 1 and 2

The following procedures/assessments will be completed before study drug is administered:

- PRO using the FOSI-18 and EQ-5D instruments
- Physical examination
- Weight
- Vital Signs
- Concomitant medications and procedures
- ECOG performance status (Appendix D)
- Hematology
- Serum chemistry (fasting is not required)

- Serum pregnancy for women of childbearing potential (Cycle 2 only)
- CA-125 measurement (Cycle 1 only)
- Blood sample for storage (Cycle 1 only; if sample is not collected on Day 1 of Cycle 1, it should be collected as soon as possible thereafter)
- Study drug dispensation
- AE monitoring
- Plasma PK sample (prior to first dose taken that day) (Cycle 2 only; see Section 9.5.1)
- Serum sample for AAG sample (Cycle 2 only)

Study drug will be dispensed to the patient in sufficient quantity to last until the next treatment cycle. Patients will ingest study drug twice daily at about the same times every day, as close to 12 hours apart as possible. Each dose of study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their electronic dosing diary.

Patients will be instructed to refrain from taking their first dose of study drug at home on the day of their clinic visits because certain assessments must be performed prior to dosing.

9.3.2 Day 15 of Cycles 1 and 2

The following procedures will be completed:

- Concomitant medications and procedures
- Hematology
- Serum chemistry (fasting is not required)
- AE monitoring
- Plasma PK sample (in morning or afternoon following the first dose of study drug taken this day; see Section 9.5.1)
- Serum sample for AAG analysis *(note: sample can be collected at the same time as hematology and serum chemistry and/or with the PK sample)*

Patients will ingest study drug twice daily at about the same times every day, at close to 12 hours apart as possible. Each dose of study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Patients will record dosing information in their electronic dosing diary.

9.3.3 Day 1 of Cycles 3 and Beyond

The following procedures will be completed:

- PRO using the FOSI-18 and EQ-5D instruments
- Physical examination
- Weight
- Vital signs
- Concomitant medications and procedures
- Disease assessment/tumor scans every 12 calendar weeks (within 7 days prior is permitted) after start of treatment on Day 1 of Cycle 1
- ECOG performance status (Appendix D)
- Hematology
- Serum chemistry (fasting is not required)
- Serum pregnancy for women of childbearing potential
- CA-125 measurement (Day 1 of Cycles 4, 7, 10, etc.)
- AE monitoring
- Plasma PK sampling (prior to the first dose of study drug taken this day; Cycles 4 and 7 only; see Section 9.5.1)
- Serum sample for AAG analysis *(note: sample can be collected at the same time as hematology and serum chemistry and/or with the PK sample)* (Cycles 4 and 7 only)

Study drug will be dispensed to the patient in sufficient quantity to last until the next clinic visit. A single dose of study drug will be administered during the current clinic visit with at least 8 oz (240 mL) of room temperature water. Patients may take study drug on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal). Patient will record dosing information in their electronic dosing diary.

Patients will continue dosing with study drug at home on an empty stomach or with food (with a regular meal or within 30 minutes after a regular meal), taking doses twice daily at about the same times every day. Study drug should be taken with at least 8 oz (240 mL) of room temperature water. Patients will record dosing information in their electronic dosing diary.

9.4 Post-Treatment Phase

9.4.1 Treatment Discontinuation

Upon treatment discontinuation, regardless of the reason, patients will have a Treatment Discontinuation visit. The following procedures will be performed:

- PRO using the FOSI-18 and EQ-5D instruments
- Physical examination
- Weight

- Vital signs
- 12-lead ECG
- Concomitant medications and procedures
- Tumor scans (using the same methodology as was used at screening) if reason for treatment discontinuation was other than disease progression based on radiologic assessment
- ECOG performance status (Appendix D)
- Hematology
- Serum chemistry (fasting is not required)
- Serum pregnancy test for women of childbearing potential
- CA-125 measurement
- AE monitoring
- Optional tumor tissue biopsy collection at time of disease progression/treatment discontinuation (requires additional consent). Tumor tissue will be processed locally as FFPE tissue. Refer to the Pathology Charter for detailed sample handling instructions.

9.4.2 28-day Follow-up

The following procedures will be performed for all patients at 28 (±3) days after the last dose of study drug:

- PRO collected using the FOSI-18 and EQ-5D instruments
- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans should continue to be performed at 12-week intervals (up to 7 days prior permitted) until radiologic disease progression by RECIST v1.1, as assessed by the investigator.
- AE monitoring
- Concomitant medications and procedures

9.4.3 Long-term Follow-up

- Disease assessment for patients who discontinued treatment for reason other than disease progression or death. Tumor scans should continue to be performed at 12-week intervals (up to 7 days prior permitted) until radiologic disease progression by RECIST v1.1, as assessed by the investigator.
- Subsequent treatments, secondary malignancy monitoring, and overall survival information will be collected for all patients every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone. Diagnosis of any secondary malignancy requires appropriate documentation (i.e. laboratory and/or pathology reports) and should be reported as indicated in Section 10.8.

- SAEs related to study drug and all AESIs, irrespective of causality, are to be reported as specified in Section 10.8.

9.5 Methods of Data Collection

Hematology, serum chemistry, and assays described below will be performed centrally. Urinalysis and serum pregnancy, if applicable, will be performed locally. Please refer to the Pathology Charter and/or Laboratory Manual for details on collecting and processing all samples that will be sent to central/core laboratories.

9.5.1 Pharmacokinetic Evaluations and AAG Measurement

For all patients, 4 mL blood samples for rucaparib population PK analysis will be drawn at the following time points:

- Day 15 of Cycle 1 (in morning or afternoon, after dose taken earlier in the day)
- Day 1 of Cycle 2 (before first dose taken that day)
- Day 15 of Cycle 2 (in morning or afternoon, after dose taken earlier in the day)
- Day 1 of Cycle 4 and 7 (before first dose taken that day)

At least one morning post-dose sample and one afternoon post-dose sample must be taken for each patient.

Serum samples for AAG analysis will be collected on the same day as PK samples.

Central laboratories will be used for bioanalysis of plasma rucaparib levels and AAG measurement. Please refer to the laboratory manual for details on collection and processing of blood PK samples.

9.5.2 Biomarker Analysis – FFPE Tumor Tissue

Archival tumor tissue must be located during the screening process and submitted **to the central laboratory directly** as soon as possible for determination of HRD status. Archival tumor tissue is required for HRD stratification for randomization and for storage for potential bridging to a validated companion diagnostic test.

9.5.3 Biomarker Analysis – Blood

A blood sample will be collected from all patients and stored. Prior to final analysis, genomic DNA may be analyzed in an exploratory fashion in order to determine whether the mutation is germline or somatic.

9.5.4 Safety Evaluations

9.5.4.1 Adverse Event Assessment

The investigator is responsible for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs during study participation, beginning after the first dose of study drug and until 28 days after the last dose of study drug. Any ongoing serious adverse events (SAEs) and AESIs will be followed until resolution or stabilization. In addition, any AE/SAE that occurs after informed consent is obtained and that is deemed related to a screening procedure for the study should be entered on the eCRF. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (Version 4.03) and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 10.

9.5.4.2 Prior and concomitant medications

Prior concomitant medications will be recorded during screening and concomitant medications will be collected from study entry until the Treatment Discontinuation visit.

9.5.4.3 Clinical Laboratory Investigations

With the exception of samples for serum pregnancy and urinalysis, all other samples collected will be analyzed by a central laboratory; a duplicate sample may be collected and analyzed by the local laboratory for immediate eligibility/ treatment decisions. The panels of laboratory tests to be performed are shown below:

Hematology: RBC and parameters (Hgb, Hct, MCV, MCH, and MCHC) and reticulocyte count, WBC and differential (with ANC), and platelet count at screening (to be performed ≤14 days prior to the first dose of study drug), at clinic visits during treatment, and at the Treatment Discontinuation visit. Hematology results must be reviewed by the investigator prior to the start of treatment with oral rucaparib or placebo.

Clinical Chemistry: Total protein, albumin, creatinine, or estimated GFR using the Cockcroft Gault formula, BUN or urea, total bilirubin, alkaline phosphatase (ALP), ALT, AST, lipid panel (total cholesterol, LDL, HDL, and triglycerides), glucose, sodium, potassium, chloride, CO_2, calcium, and phosphorus at screening (to be performed ≤14 days prior to the first dose of study drug), on Day 1 of each cycle during treatment, and at the Treatment Discontinuation visit. Clinical chemistry results must be reviewed by the Investigator prior to the start of initial treatment with study drug.

Urinalysis: Performed on freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones per the schedule of evaluations. If dipstick findings are abnormal based on Investigator's judgment, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis will be performed at screening only, but may be repeated if clinically indicated.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow-up to the abnormalities, will be documented on the eCRF as an AE per the criteria specified in Section 10.5.

Serum Pregnancy: For women of childbearing potential only. Serum pregnancy testing is to be performed ≤ 3 days prior to first dose of study drug, ≤ 3 days prior to the start of every cycle during the treatment phase, and at the Treatment Discontinuation visit.

9.5.4.4 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature. Vital signs will be performed at most study visits.

9.5.4.5 12-Lead Electrocardiograms

For all patients, 12-lead ECGs will be taken at screening (within 28 days prior to first dose of study drug) and at Treatment Discontinuation.

The following will be measured or calculated: heart rate, PR, QRS, QT, QTc, and rhythm. The investigator will analyze the ECGs locally and assess the results as normal or abnormal (clinically significant or not clinically significant).

ECGs will be repeated as clinically indicated.

9.5.4.6 Body Weight and Height

Height will be measured during the Screening visit only. Weight will be measured per institutional guidelines at Screening, on Day 1 of each cycle, and at the End of Treatment visit.

9.5.4.7 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Physical examinations will be performed at screening (complete) and at most study visits (limited as appropriate).

9.5.4.8 ECOG Performance Status

ECOG performance status (Appendix D) will be assessed at screening, on Day 1 of each cycle, and at the Treatment Discontinuation visit. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

9.5.5 Efficacy Evaluations

9.5.5.1 Disease Assessments

Tumor assessment measurements will be performed at screening, at the end of every 12 weeks of treatment (up to 1 week prior permitted) relative to Cycle 1 Day 1, at discontinuation of treatment, and as clinically indicated.

Disease assessment will comprise clinical examination and appropriate imaging techniques (CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST); other studies (MRI, X-ray, PET, and ultrasound) may be performed if required. If a patient has known brain metastases, this disease should be evaluated at each required assessment. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT/ MRI scans of the chest, abdomen, and pelvis performed to determine the extent of disease at baseline should also be performed at each time of disease assessment, even if the scans were negative at baseline. Investigators should perform scans of other anatomical sites that, in their judgment, are appropriate to assess based on each patient's tumor status. Imaging guidelines provided in the Bioclinica Site Manual should be followed for the collection of images and the radiological assessment of disease.

Tumor response will be interpreted using RECIST v1.1 (Appendix B). Disease progression will only be determined by RECIST v1.1. Patients with a CR at study entry will only be considered to have disease progression if a new lesion is identified. Patients who meet GCIG CA-125 criteria for disease progression should have a radiologic assessment and be assessed by RECIST. If the radiologic assessment does not confirm disease progression, patients should continue on treatment and continue to be assessed by RECIST v1.1 per the protocol schedule of assessments.

Patients who discontinued treatment for reason other than disease progression or death should continue to have tumor scans performed at 12-week intervals (up to 7 days prior permitted) until radiologic disease progression by RECIST v1.1, as assessed by the investigator.

9.5.5.2 Tumor Markers

CA-125 measurement will be performed at screening, on Day 1 of Cycle 1, at the start of every 3rd cycle thereafter (i.e. Day 1 of Cycle 4, Cycle 7, Cycle 10, etc.), at discontinuation of treatment, and as clinically indicated. All CA-125 measurements will be performed by a central laboratory.

9.5.6 Patient-Reported Outcomes

PRO utilizing the FOSI-18 and EQ-5D instruments (see Appendix E) will be assessed at screening, on Day 1 of every treatment cycle, at treatment discontinuation, and at the 28-day follow-up visit. Patients will complete the instruments on an electronic device before any other scheduled study procedures are performed and dosing occurs (if applicable). The electronic device is a Class 1 listed (i.e. approved) device.

9.5.7 Appropriateness of Measurements

The assessments planned in the protocol are widely used and recognized as reliable, accurate and relevant.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered a pharmaceutical product. The pharmaceutical product does not necessarily have a causal relationship with the AE. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

For the purposes of this study, disease progression of the patient's tumor with new or worsening symptoms must be documented as an AE. However, disease progression documented solely by radiographic evidence with no new or worsening symptoms will not require reporting as an AE.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a nonleading question (eg, "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). AEs will be reported on the AE eCRF. Symptoms reported spontaneously by the patient during the physical examination will also be documented on the AE eCRF.

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose that:

- Results in death.
- Is immediately life-threatening (i.e. the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly or birth defect.
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or the development of drug dependency or drug abuse.

10.3 Definition of an Adverse Event of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, health authorities or ethics committees) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for rucaparib can be found in the current rucaparib IB. These AESIs are to be reported to the sponsor expeditiously (see Section 10.8 for reporting instructions).

10.4 Exceptions to Serious Adverse Event Reporting

The following are not considered SAEs and therefore are not required to be reported to the Sponsor:

- Pre-planned or elective hospitalization, including social and/or convenience situations (eg, respite care).
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward).
- Overdose of either study drug or concomitant medication, unless the event meets SAE criteria (eg, hospitalization) as a direct consequence of the overdose. If the event does not meet SAE criteria it should still be captured as a non-serious AE on the appropriate eCRF.
- Events of disease progression of the patient's underlying cancer as well as events clearly related to disease progression (i.e. signs and symptoms) should not be reported as a SAE unless the outcome is fatal and occurs during the safety reporting period. If the event has a fatal outcome during the safety reporting period, then the event of Progression of Disease must be recorded as an AE/SAE with CTC Grade 5 (fatal outcome) indicated.
- Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as a SAE.

10.5 Clinical Laboratory Assessments and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the list of reference ranges from the local laboratory. In some cases, significant change in laboratory values within the normal range may require similar assessment.

An abnormal value that is not already associated with an AE is to be recorded as an AE only if one of the following criteria is met:

- It resulted in treatment modification (reduction of dose, interruption of dosing, or permanent discontinuation of study drug)
- It required intervention / management
- It is suggestive of organ toxicity
- The Investigator considers it to be clinically significant

10.6 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the course of the study, study drug dosing should be held immediately.

Pregnancy is not considered to be an AE or SAE; however, all pregnancies occurring during study participation or within 6 months of last dosing must be reported to the Sponsor using the Clinical Pregnancy Report form within the same timelines as for as SAE.

All pregnancies should be followed through to outcome whenever possible. Once the outcome of a pregnancy is known, the Clinical Pregnancy Outcome Report form should be completed and submitted to the Sponsor.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/ AESI processes using the appropriate AE or SAE/ AESI forms.

10.7 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

All AEs, serious and non-serious, will be fully documented on the appropriate eCRF. For each AE, the Investigator must provide duration (start and end dates or ongoing), intensity, relationship to study drug, and indicate whether specific action or therapy was required.

Any AE/SAE that occurs after the first dose of study drug until 28 days after last dose of study drug administration will be collected, documented and reported to the Sponsor by the Investigator according to the specific definitions and instructions detailed within this protocol, whether dosing has occurred or not. In addition, any AE/SAE that occurs after informed consent is obtained and is deemed related to a screening procedure for the study should also be reported on the AE eCRF and, if applicable, the SAE report form. Events that occur after signing of informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, should be recorded on the Medical History eCRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

All SAEs/ AESIs that occur during the study or within 28 days after receiving the last dose of study drug, regardless of relationship to study drug, must be reported to the Sponsor/designated

safety contact immediately (ie, **within 24 hours** of the Investigator's knowledge of the event). This should be done by faxing or emailing the completed SAE/ AESI report to the Sponsor/designee contact provided on the SAE/ AESI report form. After the 28-day window after treatment discontinuation, only SAEs assessed as related to study drug and all AESIs, irrespective of causality, should be reported. If a patient is determined to be a screen failure, no further AEs/ SAEs are required to be reported once that determination has been made, with the exception of AEs/ SAEs deemed related to a protocol-specified procedure. Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 10.7.4.

10.7.1 Intensity of Adverse Events

Severity refers to the intensity of an AE. The severity of each AE will be categorized using the NCI CTCAE, Version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).[53]

For any term that is not specifically listed in the CTCAE, intensity should be assigned a grade of 1-5 using the following CTCAE guidelines:

- Mild (Grade 1): mild or asymptomatic symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (Grade 2): limiting age-appropriate instrumental activities of daily living; minimal, local or noninvasive intervention indicated
- Severe (Grade 3): limiting self-care activities of daily living; hospitalization indicated
- Life threatening (Grade 4): life-threatening consequences; urgent intervention indicated
- Fatal (Grade 5): results in death

10.7.2 Causal Relationship of Adverse Events to Study Drug

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as but not limited to: the disease under study, concurrent disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge with the study drug.

Not Related To Study Drug	An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medication, disease under study, etc.) An AE that does not follow a reasonable temporal sequence from administration of the study drug. An AE that does not follow a known pattern of response to study drug. An AE that does not reappear or worsen when study drug is restarted. An AE for which an alternative explanation is likely, but not clearly identifiable.

Related to Study Drug	An AE that is difficult to assign to alternative causes. An AE that follows a strong or reasonable temporal sequence from administration of study drug. An AE that could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. An AE that follows a known response pattern to study drug. An AE that is confirmed with a positive rechallenge or supporting laboratory data.

10.7.3 Outcome

The investigator will record the outcome for each AE according to the following criteria:

Outcome

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Improved
- Ongoing
- Death
- Unknown/Lost to follow-up

10.7.4 Follow-up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized until 28 days after the last dose of study treatment. Any SAE/ AESI must be followed until the event has resolved, the condition has stabilized, or the patient is lost to follow-up. If the patient is lost to follow-up with an ongoing SAE/ AESI, this should be captured accordingly on a follow-up SAE/ AESI report.

10.8 Regulatory Aspects of Adverse Event Reporting

All SAEs and AESIs, irrespective of relationship to study treatment, as well as all pregnancies, must be reported to the Sponsor's SAE designee **within 24 hours** of knowledge of the event, occurring during the study through 28 days after receiving the last dose of study treatment, according to the procedures below. After the 28-day specified window, SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported if occurring. Pregnancies that occur within 6 months of the last dose of study drug should be reported. It is important that the investigator provide an assessment of relationship of the SAE/ AESI to study treatment at the time of the initial report. The SAE/ AESI Report form must be used for reporting SAEs/ AESIs. The contact information for reporting of SAEs/ AESIs can be found on the SAE/ AESI Reporting Form and Pregnancy Report Forms.

Clovis Oncology, Inc. (Clovis Oncology), or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA, according to 21 Code of Federal Regulations (CFR) 312.32, to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), Clovis Oncology or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

Clovis Oncology or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

10.9 Independent Data Monitoring Committee

No formal efficacy interim analyses are planned.

An Independent Data Monitoring Committee (IDMC) will be established to review safety and efficacy data in compliance with a prospective charter. The IDMC will be comprised of medical oncologists with experience in treating women with ovarian cancer and a statistician, all of whom are not otherwise involved in the study as investigators. The IDMC responsibilities, authorities, and procedures will be documented in the IDMC charter, which will be endorsed and signed by the IDMC prior to the first data review meeting.

The IDMC will:

- Review safety and efficacy of rucaparib compared with placebo to ensure the study is beneficial to patients
- Ensure the study is conducted in a high quality manner
- Monitor the size of the tBRCA subgroup and the known gBRCA group

Following data review, the IDMC will recommend continuation, revision, or termination of the study and/or continuing or halting enrollment into a particular subgroup. The IDMC will meet at least semi-annually after sufficient data has been collected. The IDMC chairperson may convene formal IDMC meeting if there are safety concerns. The Sponsor can also request an IDMC review of safety data.

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

Safety Table Population – The safety population will consist of all patients who received at least one dose of protocol-specified treatment.

Intent-to-treat (ITT) Population – The ITT population will consist of all randomized patients.

Response Evaluable Population – The response evaluable population will consist of all patients evaluable for response by RECIST (Appendix B). Patients evaluable for a RECIST response must have at least one measureable target lesion at baseline and at least one post-baseline tumor assessment.

11.2 Statistical Methods

11.2.1 General Considerations

Variables registered on a continuous scale will be presented using the following descriptive statistics: N, mean, standard deviation, median, minimum and maximum. Continuous variables may also be presented using frequencies and percentages among appropriate categorizations. Categorical variables will be presented using frequencies and percentages. The Kaplan-Meier methodology will be used to summarize time-to-event variables. The number of patients with events and the number of censored patients will also be presented. The stratified logrank test will be used to compare the time-to-event distributions between the randomized treatment groups. In addition, the Cox proportional hazards model will be used to estimate the HR between the randomized treatment groups.

The primary and key secondary endpoints will be tested among the tBRCA and all HRD subgroups, and all randomized patients, using an ordered step-down multiple comparisons procedure. Investigator determined PFS (invPFS) in the tBRCA subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the tBRCA subgroup is statistically significant, then invPFS will be tested in the all HRD subgroup followed by invPFS in all randomized patients. Continuing in an ordered step-down manner, the PRO of disease symptoms utilizing the FOSI-18 DRS-P subscale will be tested at the one-sided 0.025 significance level in the tBRCA, all HRD, and all randomized patients subgroups and then for the remaining key secondary endpoints of PRO utilizing the FOSI-18 total score and OS. Once statistical significance is not achieved for one test the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure.

PFS by IRR will be evaluated as a stand-alone secondary endpoint.

All data will be used to their maximum possible extent but without any imputations for missing data.

All statistical analyses will be conducted with the SAS® System, version 9.1 or higher.

Unless otherwise specified, baseline is defined as the last measurement on or prior to the first day of study drug administration.

11.2.2 Patient Disposition

Patient disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency counts, and the corresponding percentages.

11.2.3 Baseline Characteristics

All demographic and baseline characteristics will be summarized for the safety population.

The following variables will be summarized with frequency tabulations:

- Time since diagnosis (months): > 12-24, > 24
- Baseline laboratory parameters: graded based on CTCAE
- HRD status for stratification at randomization: tBRCA, nbHRD, biomarker negative
- Interval between completion of penultimate platinum regimen and disease progression (6 to 12 months of >12 months) by radiologic assessment
- Best response to most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST v1.1 with normalization of CA-125] or PR [defined as partial radiologic response by RECIST v1.1 and/or a GCIG CA-125 response]). All responses require that CA-125 be <ULN.

Descriptive statistics may also be used to summarize the continuous variables.

11.2.4 Efficacy Analyses

All efficacy evaluations will be conducted using the ITT population.

11.2.4.1 Primary Efficacy Analysis

The primary efficacy endpoint for the study is invPFS by RECIST v1.1. Investigator-determined PFS is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria (Appendix B), as assessed by the investigator, or death due to any cause, in molecularly defined subgroups. The stratification factors included in the primary analysis of invPFS will be as follows:

- HRD classification (tBRCA or nbHRD or biomarker negative)
- Interval between completion of penultimate platinum regimen and disease progression (6 to 12 months or >12 months) by radiologic assessment

- Best response to the most recent platinum-based regimen (CR [defined as complete radiologic response by RECIST v1.1 with normalization of CA-125] or PR [defined as partial response by RECIST v1.1 and/or a GCIG CA-125 response]). All responses required that CA-125 be <ULN.

Tumor HRD status by the FCTA will be determined after randomization, but before the final efficacy analysis, so that the primary endpoint (PFS in molecularly-defined HRD subgroups) can be assessed prospectively.

11.2.4.2 Secondary Efficacy Analyses

Secondary efficacy endpoints are:

- Time to a 4-point decrease in the FOSI-18 DSR–P subscale
- Time to an 8-point decrease in the FOSI-18 total score
- OS
- PFS by RECIST v1.1 as assessed by IRR (irrPFS)

PRO of disease-related symptoms as measured by the FOSI-18 DRS–P subscale

The time to an event in PRO of worsening of disease symptoms will be defined as the time from randomization to a 4-point reduction in the FOSI-18 DRS-P subscale. Patients without a 4-point reduction will be censored on the date of their last PRO evaluation.

PRO as measured by the total score of the FOSI-18

An event in worsening of PRO utilizing the complete FOSI-18 instrument will be defined as the time from randomization to an 8-point reduction in the total score. Patients without an 8-point reduction will be censored on the date of their last PRO evaluation.

Overall survival

Overall survival (OS) is defined as the number of days from the date of randomization to the date of death (due to any cause). Patients without a known date of death will be censored on the date the patient was last known to be alive.

irrPFS

PFS for secondary efficacy analysis is defined as the time from randomization to disease progression, according to RECIST v1.1 criteria as assessed by IRR, or death due to any cause, whichever occurs first.

11.2.5 Safety Analyses

Safety endpoints are incidence of AEs, clinical laboratory abnormalities, and dose modifications.

Data from all patients who receive at least one dose of study drug will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECG results, ECOG performance status, body weight, and concomitant medications/procedures will be tabulated and summarized.

11.2.5.1 Adverse Events

AEs will be classified using the Medical Dictionary for Drug Regulatory Activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE whenever possible. Only treatment-emergent adverse events (TEAEs) will be collected: TEAEs are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days.

The number and percentage of patients who experienced TEAEs for each system organ class (SOC) and preferred term will be presented. Multiple instances of the TEAE in each SOC and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

Separate tables will be presented as follows:

- All TEAEs
- TEAEs by CTCAE grade
- Grade 3 or greater TEAEs
- Serious TEAEs
- TEAEs with an outcome of death
- TEAEs leading to discontinuation of study medication
- TEAEs resulting in interruption/delay of study medication
- TEAEs resulting in dose reduction of study medication

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of “Missing.” For each toxicity grade, the number and percentage of patients with at least one TEAE of the given grade will be summarized.

11.2.5.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. The laboratory values will be presented in SI units. The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

The summary of laboratory data will include shift tables based on CTCAE for shifts in grade from baseline to maximum, minimum and last value during the on-treatment period.

Supporting laboratory data including normal ranges and abnormal laboratory flags will be provided using by-patient listings. Separate listings will be produced for clinically significant laboratory abnormalities (i.e. those that meet Grade 3 or 4 criteria according to CTCAE).

11.2.5.3 Vital Sign Measurements

The on-treatment period will be defined as the time from the first dose of study drug to 28 days after the last dose of study drug. Vital sign measurements collected during the on-treatment period will be included in the summary tables. The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign data will include descriptive statistics (N, mean, SD, minimum, median, third quartile and maximum) of the maximum, minimum and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, SD, minimum, median and maximum) of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given.

11.2.6 Population PK Analysis

The PK endpoint is individual model parameter estimates of rucaparib and covariates identification.

A specific population PK data analysis plan will be developed that will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques.

11.2.7 Exploratory Analyses

The endpoints for the exploratory analyses are:

- Change from baseline in CA-125 measurements by the central laboratory
- PFS2 (PFS on the subsequent line of treatment) defined as the time from randomization to the second event of disease progression or death, as assessed by the investigator
- ORR per RECIST v1.1, as assessed by both the investigator and IRR, in patients with measureable disease at study entry
- DOR per RECIST Version 1.1, as assessed by both the investigator and IRR
- PRO as measured by the EQ-5D total score
- Rucaparib PK, invPFS, irrPFS, CA-125, AEs, clinical laboratory abnormalities, and dose modifications

11.2.7.1 Change from Baseline in CA-125

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the CA-125 measurements from the central laboratory. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

The association between the change from baseline in CA-125 measurements and invPFS will be evaluated using a Cox proportional hazards model. A measure of CA-125 kinetics such as the rate of change from baseline in CA-125 may also be associated with invPFS using a Cox model.

11.2.7.2 Progression Free Survival 2 (PFS2)

The second event of PFS, PFS2, is defined as the time from randomization to the second event of disease progression as assessed by the investigator, or death due to any cause. The first event of disease progression will be captured as the primary endpoint in this study and thus the second event will be the next event of disease progression as assessed by the investigator. This second event of PFS may be a documented event per RECIST guidelines or may be an event of symptomatic progression.

11.2.7.3 Overall Response Rate

ORR is defined as a best response of CR or PR using the RECIST v1.1 criteria (Appendix B), as assessed by both investigator and IRR, in patients with measurable disease at study entry. ORR will be summarized with frequencies and percentages in the safety population.

11.2.7.4 Duration of Response

The DOR is measured from the time measurement criteria are met for CR/PR per RECIST v1.1 criteria (Appendix B), as assessed by both the investigator and IRR, until the first date that recurrent or PD is objectively documented. The DOR will be summarized with descriptive statistics. Only patients with a response will be included in the summary.

11.2.7.5 Patient Reported Outcome EQ-5D

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the EQ-5D instrument. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an ANCOVA using the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

11.2.7.6 Relationship between Rucaparib Exposure and Efficacy and Safety

The primary endpoint of invPFS will be presented for subgroups of patients defined by levels of rucaparib exposure. These analyses are exploratory in nature so the definition of relevant subgroups may be data-driven.

11.3 Interim Analysis

No formal interim efficacy analyses will be performed.

11.4 Sample Size Considerations

The total enrollment planned is 540 patients. A minimum of 180 and a maximum of 200 patients with a deleterious *tBRCA* mutation will be enrolled. Enrollment of patients with a known deleterious *gBRCA* mutation documented in their medical record will not exceed 150. There is no minimum number of patients required for each of the nbHRD and biomarker negative subgroups; however, no more than 360 total patients will be randomized for stratification into these subgroups combined. Prior to final efficacy analysis, HRD classification will be determined by the FCTA, which will evaluate homologous recombination gene mutations and/or extent of genomic scarring in tumor tissue.

Table 4 below provides estimated sample sizes and power calculations.

Table 4. Estimated Sample Sizes and Power Calculations

Group	Hazard Ratio	Cumulative N	Minimum Number of Events (70%)	Median PFS Placebo vs Rucaparib (months)	Power	One-sided Alpha
BRCA HRD	0.50	180	126	6 vs 12	90%	0.025
All HRD (BRCA + nbHRD)	0.60	300	210	6 vs 10	90%	0.025
ITT Population (BRCA + nbHRD + Biomarker Negative)	0.70	540	378	6 vs 8.5	90%	0.025

The study will end after 70% of the patients in the tBRCA subgroup have an observed event of investigator-determined disease progression or death. If the minimum number of tBRCA patients are enrolled, then the study will end following the 126th event of investigator-determined disease progression or death. Similarly, if the maximum number of tBRCA patients are enrolled, then the study will end following the 140th event of investigator-determined disease progression or death.

The IDMC will inform the Sponsor when the required number of PFS events have been observed in order to ensure the Sponsor remains blinded to which patients are in the tBRCA subgroup. If the nbHRD and/or biomarker negative subgroups have observed events of invPFS in fewer than 60% of the patients, the IDMC may recommend that the study continue for up to 6 more months if it is likely that the nbHRD and biomarker negative subgroups will observe enough additional events of PFS to reach 60%.

Following the collection of the required number of PFS events, the outstanding queries for all visits and events prior to the data cutoff date will be resolved and the database will be locked before the blind break and subsequent primary analysis.

12 PATIENT DISPOSITION

12.1 Removal of patients from therapy or assessment

A patient must be discontinued from treatment with study drug if any of the following apply:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative
- Progression of patient's underlying disease by RECIST v1.1 as assessed by the investigator
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy
- A positive pregnancy test at any time during the study.

The sponsor may discontinue the trial early for any of the reasons noted in Section 13.6.

12.2 Procedures for discontinuation

The sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of study drug must be documented in the eCRF and source documents. To the extent possible, end-of-study procedures should be performed on all patients who receive study drug. The Treatment Discontinuation visit should occur 28 (±3) days following the last dose of study drug. Patients will be followed for 28 days after the last dose of study drug for safety; those with ongoing SAEs/ AESIs will be followed until either resolution or stabilization has been determined.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonization (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; Food and Drug Administration (FDA) regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki.

13.1.1 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to concerned regulatory agencies for approval prior to the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 (or equivalent) and provide the completed form according to written instructions to the sponsor (or designee). Each investigator must submit to the sponsor (or designee) financial disclosure information according to national law and/or local regulations.

U.S.-generated data will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The trial will be registered at www.clinicaltrials.gov, EudraCT, and other applicable trial registry systems as appropriate.

13.1.2 Independent Ethics Committee/Institutional Review Board

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, drug dosing diaries, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IEC/IRB. This also applies to protocol amendments.

Clovis Oncology will supply relevant data for the investigator to submit the study protocol and additional study documents to the IEC/IRB. The principal investigator will submit the study protocol for review and approval by an IEC/IRB, according to national law and/or local regulations, and will provide the IEC/IRB with all appropriate materials.

Verification of the IEC's/IRB's unconditional approval of the study protocol and the written informed consent form will be transmitted to Clovis Oncology. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IEC/IRB approval of the study protocol has been received, the investigator has obtained the signed and dated informed consent form, and the sponsor is notified.

The principal investigator will submit appropriate reports on the progress of the study to the IEC/IRB at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IEC/IRB and sponsor.

The IEC/IRB must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

13.2 Confidentiality of Information

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient initials and an identification code (i.e. not names) should be recorded on any form submitted to the sponsor and the IRB. The investigator must record all screened and enrolled patients in the eCRF. The investigator must have a list where the identity of all treated patients can be found.

The investigator agrees that all information received from Clovis Oncology, including, but not limited to, the Investigator's Brochure, this protocol, eCRFs, the protocol-specified treatment, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

13.3 Patient Informed Consent

All information about the clinical study, including the patient information and the informed consent form, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed informed consent forms from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures.

The informed consent form, prepared by the investigator with the assistance of the sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the sponsor.

The patient must be provided with the patient information and informed consent form consistent with the study protocol version used and approved by the relevant IEC/IRB. The informed consent form must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the informed consent form. A copy of the signed informed consent form will be retained by the patient and the original will be filed in the investigator file unless otherwise agreed.

13.4 Study Monitoring

On behalf of Clovis Oncology, a CRO monitor will contact and visit the investigator at the study center prior to the entry of the first patient (unless Clovis or the CRO has worked with the center recently in which case this initial visit maybe waived) and at predetermined appropriate intervals during the study until after the last patient is completed. The monitor will also perform a study closure visit. Visits may also be conducted by Clovis Oncology personnel.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (i.e. the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (i.e. source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the investigator file. Representatives from Clovis Oncology may also contact and visit the investigators and monitor data during the study.

13.5 Case Report Form

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Prior to study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

For each patient enrolled, an eCRF should be completed and reviewed by the principal investigator or co-investigator within a reasonable time period (<2 weeks) after data collection. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

Full information regarding electronic data capture and completing eCRFs is included in the investigator files. All questions or comments related to electronic capture should be directed to the assigned monitor.

13.6 Study Termination and Site Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, Clovis Oncology and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Clovis Oncology reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30 day written notification will be given.

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical
- The stated objectives of the study are achieved
- The sponsor discontinues the development of oral rucaparib

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

13.7 Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of Clovis Oncology. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval prior to their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

13.8 Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, drug accountability records, correspondence with the IEC/IRB and Clovis Oncology, and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated informed consent forms, copies of all eCRFs,

query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and Clovis Oncology or its designees.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by Clovis Oncology. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of Clovis Oncology. Should the investigator wish to assign the study records to another party or move them to another location, Clovis Oncology must be notified in writing of the new responsible person and/or the new location. Clovis Oncology will inform the investigator, in writing, when the trial-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

13.9 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of Clovis Oncology and signed by the sponsor's chief medical officer, thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

13.10 Study Publication

The results of this study will be published and/or presented at scientific meetings in a timely manner. Any formal publication of study results will be a collaborative effort between the sponsor and the investigator(s). All data generated from this study are the property of Clovis Oncology and shall be held in strict confidence along with all information furnished by Clovis Oncology. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of Clovis Oncology. Written permission to the investigator will be contingent on the review by Clovis Oncology of the statistical analysis and manuscript, and will provide for nondisclosure of Clovis Oncology confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days prior to submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties. The sponsor may request a delay in publication if there are important intellectual property concerns relating to publication, but does not have the right to suppress publication of the study results indefinitely.

Result of this pivotal study will also be posted to www.clinicaltrials.gov within 30 days of marketing approval for rucaparib in the US and to EudraCT within one year of the end of the trial.

13.11 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by Clovis Oncology. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, standard operating procedures (SOPs), ICH GCPs, and the applicable regulatory requirements. The investigator and the sponsor may also be subject to an inspection by FDA, European Regulatory authorities, or other applicable regulatory authorities at any time. The auditor and regulatory authorities will require authorization from the investigator to have direct access to the patients' medical records. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

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15 APPENDICES

Appendix A. List of Homologous Recombination Genes for HRD Stratification by the ICTA

Appendix B. Response Evaluation Criteria in Solid Tumors Criteria

Appendix C. Gynecological Cancer Intergroup (GCIG) Guidelines

Appendix D. Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Appendix E. Quality of Life Questionnaires

Appendix F. Inhibitors and Inducers of CYP1A2 and CYP3A

15.1 Appendix A

List of Homologous Recombination Genes for HRD Stratification by the ICTA

tBRCA	nbHRD		Biomarker-negative
BRCA1	*ATM*	*FANCI*	Genes not included in the tBRCA or nbHRD groups
BRCA2	*ATR*	*FANCL*	
	ATRX	*FANCM*	
	BARD1	*MRE11A*	
	BLM	*NBN*	
	BRIP1	*PALB2*	
	CHEK1	*RAD50*	
	CHEK2	*RAD51*	
	FANCA	*RAD51B*	
	FANCC	*RAD51C*	
	FANCD2	*RAD51D*	
	FANCE	*RAD52*	
	FANCF	*RAD54L*	
	FANCG	*RPA1*	

15.2 Appendix B

Response Evaluation Criteria in Solid Tumors Criteria

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[31] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded n millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non target Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE = Not evaluable.			

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation

CT scans are required at screening and at the end of every 3rd cycle of treatment.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

15.3 Appendix C

Modified Gynecological Cancer Intergroup (GCIG) Guidelines

GCIG Guidelines for Response Using CA-125[32] (adapted for use in this trial)

GCIG CA-125 definitions are available at http://gcig.igcs.org/CA-125.html.

To be evaluable for response by CA-125 requires at least one pre-treatment sample >2 x ULN and two post-treatment samples confirming a response

A response to CA-125 has occurred if there is at least a 50% decrease as the result of the treatment. The pre / post treatment samples must satisfy the following criteria:

1. There must be at least one sample that is >2 x ULN prior to initiation of treatment
2. The second sample (post-treatment) must be ≤ 50% of the pre-treatment sample;
3. The confirmatory third sample must be ≥21 days after the second sample and ≤ 110% of the second sample;
4. Any intervening samples between samples 2 and 3 must be ≤ 110% of the previous sample unless considered to be increasing because of tumor lysis.

Per inclusion criteria #5, CA-125 must =be <ULN prior to study entry. This requirement applies to all patients, including those who achieved a best response of PR by serologic CA-125 response criteria. Thus, patients must have achieved a >50% reduction in CA-125 level and also have CA-125 <ULN.

Patients are not evaluable by CA-125 if they have received mouse antibodies or if there has been medical or surgical interference with their peritoneum or pleura during the previous 28 days.

15.4 Appendix D

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

ECOG Performance Status	
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work or office work).
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.
5	Dead.

In the event performance status is assessed by the Karnofsky Performance Status scale, the following conversion chart applies.

Karnofsky Performance Status			**ECOG Performance Status**
General Description	**Score**	**Specific Description**	**Score**
Able to carry on normal activity and to work; no special care needed	100	Normal; no complaints; no evidence of disease	0
	90	Able to carry on normal activity; minor signs or symptoms of disease	1
	80	Normal activity with effort; some signs or symptoms of disease	
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do active work	2
	60	Requires occasional assistance, but is able to care for most of personal needs	
	50	Requires considerable assistance and frequent medical care	3

Karnofsky Performance Status			**ECOG Performance Status**
General Description	**Score**	**Specific Description**	**Score**
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance	
	30	Severely disabled; hospital admission is indicated although death not imminent	4
	20	Very sick; hospital admission necessary; active supportive treatment necessary	
	10	Moribund; fatal processes progressing rapidly	
	0	Dead	5

15.5 Appendix E

National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy (NCCN-FACT) FACT - Ovarian Symptom Index (FOSI-18) instrument (NCCN-FACT FOSI-18) – English Version

Sample form and background available at: http://www.facit.org/FACITOrg/Questionnaires.

Patients will complete the instrument on an electronic device. This device is a Class 1 listed (i.e. approved) device.

Below is a list of statements that other people with your illness have said are important.

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	O3	I have cramps in my stomach area	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	Cx6	I am bothered by constipation	0	1	2	3	4
	O1	I have swelling in my stomach area	0	1	2	3	4
	C3	I have control of my bowels	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
TSE	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	O2	I have been vomiting	0	1	2	3	4
	BMT15	I am bothered by skin problems	0	1	2	3	4
FWB	BMT5	I am able to get around by myself	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4

GF7	I am content with the quality of my life right now	0	1	2	3	4

Euro-QoL5D (EQ-5D) – English Version for the US

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

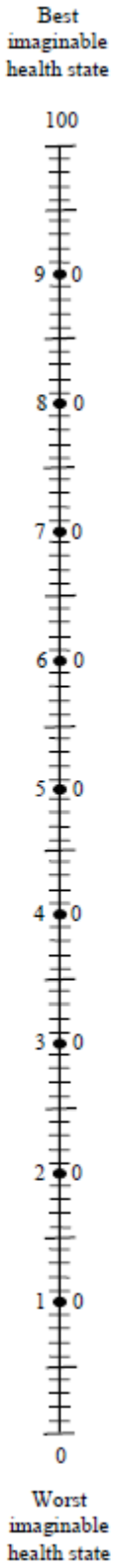
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



15.6 Appendix F

Examples of CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	Substrates with Narrow Therapeutic Range[a]
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

The table is based on the Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012 (http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf).[48]

[a] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

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November 27, 2019

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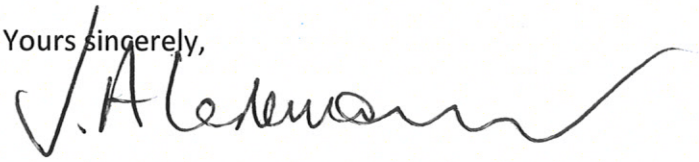
Dear Editor,

On behalf of my fellow authors, I hereby state that I have obtained permission to acknowledge the contributions of Nathan Yardley and Shannon Davis of Ashfield Healthcare Communications to our manuscript, "Postprogression outcomes and updated safety data for patients with platinum-sensitive recurrent ovarian carcinoma treated with rucaparib in the phase 3 ARIEL3 study."

Each contribution is detailed in the Acknowledgment section of the manuscript.

Yours sincerely,



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Each contribution is detailed in the Acknowledgment section of the manuscript.

Sincerely,

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Dear Editor,

I hereby grant permission to be acknowledged for my contribution to the manuscript, "Postprogression outcomes and updated safety data for patients with platinum-sensitive recurrent ovarian carcinoma treated with rucaparib in the phase 3 ARIEL3 study" by Dr Jonathan Ledermann and colleagues. I provided copywriting support under the authors' guidance in preparation for the article's submission.

Sincerely,

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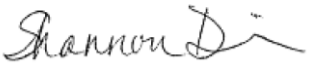
Sincerely,



Shannon Davis

Reviewer comment	Author response and changes made	Page number(s) in clean version
1. Summary – findings: Data for CFI and TSST have not been provided. For transparency, please consider providing the summary data (rucaparib vs placebo) for each of the four outcomes, rather than outcomes for the nested cohorts.	The Summary – Findings section was revised to provide summary datafor CFI and TSST for the intention-to-treat population (rucaparib vs placebo): "In the intention-to-treat population (n=375 rucaparib *vs* n=189 placebo), **median (95% CI) CFI was 14·3 (13·0–17·4) versus 8·8 (8·0–10·3) months (hazard ratio 0·43 [95% CI 0·35–0·53]; p<0·0001),** median (95% CI) TFST was 12·4 (11·1–15·2) versus 7·2 (6·4–8·6) months (0·43 [0·35–0·52]; p<0·0001), median (95% CI) PFS2 was 21·0 (18·9–23·6) versus 16·5 (15·2–18·4) months (0·66 [0·53–0·82]; p=0·0002), **and median TSST was 22·4 (19·1–24·5) versus 17·3 (14·9–19·4) months (0·68 [0·54–0·85]; p=0·0007). CFI, TFST, PFS2, and TSST were also significantly longer with rucaparib than placebo in the *BRCA*-mutant and homologous recombination-deficient cohorts.**"	3
2. Summary – findings: Please provide adverse event results for each treatment group (rucaparib and placebo). 3. Summary – findings: Please add a brief sentence to summarise serious adverse events and events leading to death in the Summary-Findings section.	The most frequent TEAEs of any grade, and a summary of serious TEAEs and TEAEs leading to death were added to the Summary – Findings section: "**The most frequent treatment-emergent adverse events (TEAEs) of any grade were nausea (76% *vs* 37%) and asthenia or fatigue (71% *vs* 44%).** The most frequent grade 3 or greater TEAE was anaemia or decreased haemoglobin (22% *vs* 1%). **Serious TEAEs were reported in 22% and 11% of patients in the rucaparib and placebo groups. TEAEs leading to death were reported in 2% and 1% of patients, respectively.**	3
4. Main text – Results section: Please clearly state in the Results section if the PFS2-PFS1 analysis was done post-hoc.	The text was amended as suggested: "**In a post hoc analysis,** across all three cohorts there was no significant difference in PFS2–PFS1 between the rucaparib and placebo groups (appendix p 12)."	15

Reviewer comment	Author response and changes made	Page number(s) in clean version
5. Main text – Results section: thank you for providing at risk data on KM plots. Please also briefly summarise the numbers of patients who had an event (progression or died) in the main Results text.	The event data for each nested cohort were added in the main text for each endpoint.	14–16
6. Table 2: As we cannot have merged columns in tables, please move the top half of table 2 (summary of TEAEs, dose reductions/interruptions) to the appendix.	The table was updated as suggested.	32–33; appendix 4
7. Main text – Results and tables: Any percentages derived from N numbers of less than 1000 can be rounded to whole numbers (eg, in tables 1, 2, and main text). Please also add percentage symbols where appropriate in the tables.	Data were reviewed, and percentages in the main text and all tables and figures (main and supplemental) were rounded accordingly. Percentage symbols were added to tables as appropriate.	3, 13–20, 31–33, 37; appendix 4-7
8. Figure 2: Please delete the dashed horizontal lines in figure 2. 9. Figure 2: Please clarify if the y axis shows probability or percentage of patients having an event. If the latter, please could you reformat the axis as 0-100%?	Horizontal lines were deleted and the y-axis was revised to clarify that it represents the proportion of patients having an event for each endpoint.	35–36; appendix 11–15
10. Acknowledgments: Please state who funded the medical writing assistance in the Acknowledgments section.	This information is already included in the last sentence of the Acknowledgments: “Medical writing and editorial support **funded by Clovis Oncology** were provided by Nathan Yardley and Shannon Davis of Ashfield Healthcare Communications.”	26