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Title: Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a phase 3, international, randomised, double-blind trial

Article Type: Fast Track (Randomised Controlled Trial)

Corresponding Author: Dr. Robert L. Coleman, MD

Corresponding Author's Institution: University of Texas, M.D. Anderson Cancer Center

First Author: Robert L. Coleman, MD

Order of Authors: Robert L. Coleman, MD; Amit M Oza; Domenica Lorusso; Carol Aghajanian; Ana Oaknin; Andrew Dean; Nicoletta Colombo; Johanne I Weberpals; Andrew Clamp; Giovanni Scambia; Alexandra Leary; Robert W Holloway; Margarita Amenedo Gancedo; Peter C Fong; Jeffrey C Goh; David M O'Malley; Deborah K Armstrong; Jesus Garcia-Donas; Elizabeth M Swisher; Anne Floquet; Gottfried E Konecny; Iain A McNeish; Clare L Scott; Terri Cameron; Lara Maloney; Jeff Isaacson; Sandra Goble; Caroline Grace; Thomas C Harding; Mitch Raponi; James Sun; Kevin K Lin; Heidi Giordano; Jonathan A Ledermann

Abstract: Background: Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has anticancer activity in recurrent ovarian carcinoma harbouring a BRCA mutation or a high percentage of genome-wide loss of heterozygosity (LOH). ARIEL3 evaluated rucaparib versus placebo following response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma.
Methods: ARIEL3 is an international, randomised, double-blind, phase 3 study performed at 87 hospitals and cancer centres. Patients were randomised 2:1 to receive oral rucaparib 600 mg twice daily or placebo using a computer-generated sequence (block size of six). Patients, investigators, site staff, and study sponsor were blinded to assignments. The primary endpoint (investigator-assessed progression-free survival) was evaluated using an ordered step-down procedure for three nested cohorts: (1) BRCA mutant (carcinoma associated with deleterious germline or somatic BRCA mutation); (2) homologous recombination deficient (HRD) (BRCA mutant or BRCA wild type/LOH high); and (3) intent-to-treat population. ARIEL3 is registered with ClinicalTrials.gov, NCT01968213; enrolment is complete.
Findings: Between April 7, 2014, and July 19, 2016, 564 patients were randomised, 375 to rucaparib and 189 to placebo. Median progression-free survival in patients with a BRCA-mutant carcinoma (n=130, rucaparib; n=66, placebo) was 16·6 months versus 5·4 months (p<0·0001), respectively (hazard ratio [HR] 0·23; 95% confidence interval [CI] 0·16-0·34); in patients with an HRD carcinoma (n=236, rucaparib; n=118, placebo) it was 13·6 months versus 5·4 months (p<0·0001), respectively (HR 0·32; 95% CI 0·24-0·42); and in the intent-to-treat population it was 10·8 months and 5·4 months (p<0·0001), respectively (HR 0·36; 95% CI 0·30-0·45). The most common grade 3 or higher adverse events in the safety population (n=372, rucaparib; n=189, placebo) were anaemia/decreased haemoglobin (70 [19%],

rucaparib; one [1%], placebo) and increased alanine or aspartate aminotransferase (39 [10%], rucaparib; none, placebo). Interpretation: Across all primary analysis groups, rucaparib significantly improved progression-free survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy.

August 24, 2017

Robert L. Coleman, M.D.
Professor
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
1155 Herman Pressler Dr.
CPB6.3590
Houston, TX 77030
Phone: +1 713 745 3357
Fax: +1 713 792 7586
rcoleman@mdanderson.org

Dr. Stuart Spencer
Editor
The Lancet
125 London Wall
London, EC2Y 5AS, UK

Dear Dr. Spencer:

On behalf of my coauthors, I thank you and the reviewers for providing insightful comments on our manuscript entitled “Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a phase 3, international, randomised, double-blind trial” (THELANCET-D-17-05358). We are grateful to receive an opportunity to resubmit our manuscript to *The Lancet*.

Enclosed please find our point-by-point responses to the reviewers’ comments. Line numbers referenced below refer to the tracked version of the manuscript.

Thank you for your consideration. We look forward to receiving your response.

Sincerely,

Robert L. Coleman, MD

Reviewer #2 Comment 1: Page 10 '...at regular intervals' bit more detail please.

> **Author Response 2.1:** We have updated the manuscript to clarify that the independent data monitoring committee reviewed the safety and efficacy data from ARIEL3 approximately every 6 months (lines 204-207):
>
> > **“**Per the protocol, an independent data monitoring committee monitored enrolment and reviewed the safety and efficacy of the trial approximately every 6 months, including maturity of progression-free survival events.”

Reviewer #2 Comment 2: How was the proportionality of hazards verified? Show the results for this.

> **Author Response 2.2:** We thank the reviewer for their inquiry. The Cox proportional hazard assumption (ie, constant relative hazard) was verified graphically using log-log plots generated using SAS version 9.3 (Cary, NC, USA).

Reviewer #2 Comment 3: Figure 2 (and S2) are presented well. My preference is to show an initial Kaplan-Meier curve over all patients (no treatment) with a 95% confidence interval (CI).

> **Author Response 2.3:** We thank the reviewer for their thoughtful review of the figures and their suggestion. We have provided Kaplan-Meier curves of investigator-assessed and blinded independent central radiology review–assessed progression-free survival in all patients (intent-to-treat population) in the supplementary appendix (figure S6). Furthermore, these Kaplan-Meier curves are not stratified by treatment.

Reviewer #2 Comment 4: Figure 3 (and elsewhere) short on details (e.g., include events). X-axis should be redrawn on a log scale (95% CIs symmetric under this transformation).

> **Author Response 2.4:** We thank the reviewer for their suggestion. We have revised Figure 3 to use a $\log_2$ scale on the X axis and also provided additional details about the cumulative number of events in each arm for all subgroups. This information was added in two new columns on the forest plot (figure 3).

Reviewer #2 Comment 5: Discrepancy in numbers between protocol (Section 6.1) and study. Protocol states 'approximately 540' (Section 6.1) with no more than 360 to be stratified into subgroups. Whereas 564 were recruited (375 into subgroups). Section 10.8 makes reference to an independent DMC's monitoring of study size which may explain it.

> **Author Response 2.5:** We thank the reviewer for this thoughtful comment. Per the protocol (Section 6.1), approximately 540 patients were to be enrolled in ARIEL3. A minimum of 180 and a maximum of 200 patients with a deleterious *BRCA* mutation were to be enrolled. Additionally, no more than 360 patients without a *BRCA* mutation (referred to as “nbHRD and biomarker negative” in Section 6.1 of the protocol) were to be enrolled in ARIEL3.
>
> The independent data monitoring committee surveyed enrolment of the patients with a *BRCA* mutation and informed the study sponsor (Clovis Oncology, Inc.) when the target enrolment number for the *BRCA*-mutant cohort was anticipated to be reached. Once notified, patients who were in the screening process were allowed to complete screening and enrol into the study if they met all eligibility criteria. Thus, 196 patients with a *BRCA* mutation were enrolled in ARIEL3, which is within the maximum limit of 200 prespecified patients in the protocol. We have clarified this point in the Statistical analysis section (lines 288-296):
>
> > “ARIEL3 was designed to enrol approximately 540 patients, including between 180 and 200 patients with a *BRCA* mutation in their carcinoma (with no more than 150 patients with a known deleterious germline *BRCA* mutation) and no more than 360 patients without a *BRCA* mutation in their carcinoma. The independent data monitoring committee surveyed enrolment of patients with a *BRCA* mutation and informed the study sponsor (Clovis Oncology, Inc.) when the target enrolment number for the *BRCA*-mutant cohort was anticipated to be reached. Once notified, patients who were in the screening process were allowed to complete screening and enrol into the study if they met all eligibility criteria.”

Reviewer #2 Comment 6: I haven't seen your CONSORT Statement (apologies if I've missed it).

Author Response 2.6: We thank the reviewer for their careful review of our manuscript. Per *The Lancet*'s guidelines, we have ensured that our manuscript conforms to CONSORT guidelines and provided our completed check-list with resubmission.

Reviewer #3 Comment 1: Page 23, middle of page: "No cases of Hy's law were observed". Not sure what this means

Author Response 3.1: We thank the reviewer for the comment. As outlined in a Guidance for Industry document from the US Department of Health and Human Services, Food and Drug Administration, "Hy's law" is a translation of Dr. Hyman Zimmerman's observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an indicator of the potential for a drug to cause serious liver injury (Department of Health and Human Services. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/Guidances/UCM174090.pdf). "Hy's law" was coined by Dr. Robert Temple (Deputy Center Director for Clinical Science, Center for the Evaluation of Drug Research and Acting Deputy Director of the Office of Drug Evaluation I [ODE-I] at the US Food and Drug Administration) in the 1980s.

According to Hy's law, patients are at risk for hepatocellular injury if they have alanine aminotransferase or aspartate aminotransferase levels greater than 3 times the upper limit of normal (ULN) at the same time as having bilirubin levels greater than 2 times ULN and alkaline phosphatase levels less than 2 times ULN. As noted by Dr. Temple, "…Hy's Law is not a benefit-risk judgment, an automatic trip into oblivion for any drug that meets its test. It is a safety biomarker, an indicator of a risk that must be weighed against the benefits of a treatment." (Temple. *Pharmacoepidemiology and drug safety.* 2006;15:241-3.)

In ARIEL3, no patients met the criteria for Hy's law. Given the context above, we have revised the manuscript to clarify our statement (lines 495-499):

> "No cases were considered to meet Hy's law criteria for drug-induced liver injury (ie, alanine aminotransferase or aspartate aminotransferase greater than 3 times the upper limit of normal with concomitant bilirubin greater than 2 times the upper limit of normal without alkaline phosphatase elevations or another clear reason for the elevations)."

Reviewer #3 Comment 2: Page 23: One should not misinterpret hazard ratios as relative risks. For example, the HR 0.44 does not translate in to a 56% reduction in the risk of disease progression or death. The HR only refers to risk during a specific timeframe, so broad inference should probably be avoided.

Author Response 3.2: We thank the reviewer for this thoughtful comment. We have revised the language in the discussion accordingly (lines 464-471 and 538-545):

> "The prolonged progression-free survival among patients receiving rucaparib in the intent-to-treat population (HR 0·36) demonstrates that patients with platinum-sensitive ovarian carcinoma can derive robust clinical benefit from rucaparib maintenance treatment. A similar improvement over placebo (HR 0·35) was seen in the secondary endpoint of assessment by BICR review, supporting the validity of the benefit observed with rucaparib maintenance treatment."

> "Preplanned analysis of progression-free survival in patients with a *BRCA* wild-type/LOH-high carcinoma, wherein patients treated with rucaparib had an increase in median progression-free survival (HR 0·44) compared with placebo, shows that the improvement observed in the HRD cohort was not driven solely by patients with a *BRCA*-mutant carcinoma. The benefit in progression-free survival seen in patients with a *BRCA* wild-type/LOH-high carcinoma (HR 0·44) compared with patients with a *BRCA* wild-type/LOH-low carcinoma (HR 0·58) demonstrates the utility of HRD…"

Reviewer #3 Comment 3: The authors clearly discuss PARP inhibitor clinical trials of relevance, including NOVA and SOLO2. They also appropriately conclude that the results of this trial are consistent with what has been published. While they are also correct in the statement that direct comparisons cannot be performed, it does little to help the readers make PRACTICAL sense of this data. For example, given the availability of niraparib, with positive impact on PFS regardless of mBRCA status, what would make rucaparib different?? I would suggest that the finding of an objective response rate in this trial population is quite interesting and potentially differentiating, including a reported 18% CR rate among those who entered with measurable disease.

Author Response 3.3: We thank the reviewer for sharing this insightful comment and agree that the proportion of patients with measurable disease at baseline who achieved a complete response is unique to ARIEL3 in the maintenance setting and may be of particular interest to clinicians. We have elaborated on this point further in the Discussion (lines 532-535):

> "A number of patients with measurable residual disease at study entry showed further reduction in carcinoma burden with rucaparib maintenance treatment, including conversion to a complete response per RECIST in several patients in the nested *BRCA*-mutant and HRD cohorts and the overall intent-to-treat population."

In addition, at the time the ARIEL3 study was designed, we did not know whether the treatment effect of a PARP inhibitor would be maintained across all cohorts in the setting of a randomised, controlled phase 3 study, including the *BRCA* wild-type population or the intent-to-treat population (at that time, data from NOVA were not available, and SOLO2 only evaluated olaparib in patients with tumours with germline *BRCA* mutations). As stated in the manuscript, our findings extend those from the NOVA study and demonstrate that rucaparib can provide benefit to patients with tumours associated with or without a *BRCA* mutation *vs* placebo in the maintenance treatment setting.

Reviewer #4 Comment 1: For Figure 3, under the rucaparib and placebo columns the number of patients with the binary yes/no for measurable does not equal the n=375 and n=189. Why are there so many missing values?

Author Response 4.1: We thank the reviewer for the inquiry. We have updated figure 3 to accurately reflect the number of patients who did not have measurable disease at baseline (234, rucaparib; 123, placebo). The corresponding hazard ratio and 95% confidence interval data have been updated to reflect this correction.

Reviewer #4 Comment 2: For the analysis of the rucaparib vs placebo in figure 3, should there not be under bulky lesions actually 3 columns: bulky lesion >2cm, measurable disease (n=141 as in table 1), and no measurable disease if the authors want to emphasize how rucaparib can benefit patients with partial response and bulky disease as they conclude?

Author Response 4.2: We thank the reviewer for this suggestion.

A total of 207 patients (141, rucaparib; 66, placebo) were assessed by the investigator to have measurable disease (ie, target lesion of any size) at baseline. Data for measurable disease (yes/no) is presented under the "Measurable disease at baseline (per investigator)" heading in figure 3 (see also, response to **Reviewer #4 Comment 1**).

As part of a separate assessment, the presence of bulky disease was determined by independent radiological review (see Study design and patients, lines 221-224). Bulky disease was defined as any target or nontarget lesion greater than 2 cm. Data for bulky disease (yes/no) is therefore presented as a separate, distinct subgroup because some patients had nontarget lesions that could not be included in the category "Measurable disease at baseline." We have amended the figure to clarify this subtle but important point.

Notably, the hazard ratios and 95% confidence intervals for all of these subgroups (ie, patients with bulky disease; patients without bulky disease, inclusive of patients with tumours <2 cm; and those with no measurable disease) do not cross unity, showing that the benefit of rucaparib vs placebo is maintained in all of these subgroups.

Reviewer #4 Comment 3: Is there a reason that they did not analyze the time to subsequent chemotherapy treatment in their subsequent cohorts?

Author Response 4.3: Time to subsequent anticancer treatment was an exploratory endpoint. As part of long-term follow-up, those data are continuing to be collected.

At the visit cutoff date (April 15, 2017), median time to first subsequent anticancer treatment in the intent-to-treat population was 12·5 months in the rucaparib arm (censoring rate, 39%) and 7·4 months (censoring rate, 13%) in the placebo arm. Median time to second subsequent anticancer treatment was 22·2 months (censoring rate, 58%) and 18·6 months (censoring rate, 48%), respectively.

Given the amount of censoring in the rucaparib arm, we consider those data to be immature. We intend to report those data at a future medical congress once they are fully mature.

Reviewer #4 Comment 4: The paper never mentions the additional cost/benefit ratio by adding two testing panels of Foundation Medicine T5 NGS assay and BRCAnalysis CDx test in order to stratify patients for rucaparib therapy. Since financial costs are being more important considerations in cancer care, it would be beneficial for the authors to acknowledge this issue as part of the discussion.

Author Response 4.4: We agree with the reviewer that the use of two testing panels may be burdensome and costly to patients and practitioners. As such, Foundation Medicine will be integrating *BRCA1/BRCA2* mutational analysis with LOH determination into a single test with a cost that will be comparable to the original FoundationFocus CDx_{BRCA} companion diagnostic (CoDx). This integrated, all-in-one CoDx will be submitted to regulatory agencies in parallel with the ARIEL3 clinical data and will be marketed following regulatory review/approval under the name FoundationFocus $CDx_{BRCA\ HRD}$, with "HRD" reflecting the integration of LOH into the test. We are optimistic that this approach will help patients avoid the need to undergo additional, duplicative testing that may yield similar/overlapping information. A cost-effectiveness analysis will be the subject of a future report.

Reviewer #4 Comment 5: Minor issue: enrollment is misspelled throughout the text.

Author Response 4.5: We thank the reviewer for their comment. Given that *The Lancet* is a British journal, we have used the British spelling "enrolment." We have also checked our spellings of the other forms of the word, and although it may seem inconsistent, they are correctly spelled "enrol" and "enrolled" per British convention.

Editorial Point 1: Please indicate after each of the reviewers' points the text changes which have been made (if any) and the line number on the revised manuscript at which your change can be found. [Line numbers can be added to your word document using the 'page layout' tab. Please select continuous numbers.]

Author Response: We have inserted line numbers to the updated manuscript and referenced these in our response to the editorial and reviewer comments.

Editorial Point 2: When interpreting editorial points made by reviewers, please remember we will further edit the final manuscript if accepted]

Author Response: We have responded to reviewer comments regarding editorial points (eg**, Reviewer #4 Comment 5**) understanding that *The Lancet's* editors will assist with final editing of the text.

Editorial Point 3: Please indicate any authors who are full professors

Author Response: We have provided this information in the updated manuscript (lines 12-55).

Editorial Point 4: For randomised trials please follow the CONSORT reporting guidelines http://www.consort-statement.org and include a CONSORT checklist.

Editorial Point 5: Please follow CONSORT for abstracts (eg method of randomisation)

Author Response: We have ensured that our manuscript, including the Summary, conforms to CONSORT guidelines. We have provided the method of randomisation and information about blinding to the Summary (lines 75-78):

> "Patients were randomised 2:1 to receive oral rucaparib 600 mg twice daily or placebo; using a computer-generated sequence (block size of six). Patients, investigators, site staff, and the study sponsor were blinded to assignments."

Our completed checklists have been provided with resubmission.

Editorial Point 6: At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit. Please also state which author(s) had access to all the data, and which author(s) were responsible for the decision to submit the manuscript etc.

Author Response: The role of the funding source is provided (lines 339-342). We also indicate that all authors had access to the data and were responsible for the final decision to submit the manuscript (lines 342-343).

Editorial Point 7: Please give 95% confidence intervals for hazard ratios/ odds ratios

Author Response: We have ensured that 95% confidence intervals are provided for all hazard ratios presented in the results.

Editorial Point 8: Please limit the summary to pre-defined primary endpoints and safety endpoints.

Author Response: In the Summary, we have provided the results for the prespecified, primary endpoint of investigator-assessed progression-free survival and relevant safety data.

Editorial Point 9: Please report all outcomes specified in the protocol

Author Response: We have ensured that all outcomes specified in the protocol have been addressed in the manuscript.

Editorial Point 10: Please explain any deviations from the protocol

Author Response: Major protocol deviations as of the visit cutoff date (April 15, 2017) have been provided as part of the supplemental appendix (p 5). These protocol deviations did not result in the exclusion of patients from the final analysis or affect the assessment of primary or secondary endpoints in the study.

Editorial Point 11: If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses are post-hoc

Author Response: All analyses presented in the manuscript were prespecified except for a retrospective analysis of investigator-assessed progression-free survival in patients with or without prior bevacizumab as part of their penultimate or earlier treatment. We have indicated that this analysis was exploratory in the Supplemental Methods, Efficacy analysis of subgroups section (appendix, pp 3-4).

In response to **Reviewer #2 Comment 3,** we have included a post hoc analysis of investigator-assessed and blinded independent central radiology review–assessed progression-free survival in all enrolled patients, not stratified by treatment (appendix, p 4; figure S6). This analysis was not prespecified and has been indicated as post hoc in the text and figure title.

Editorial Point 12: p-values should be exact to 4 decimal places (eg p<0.0001). Two decimals are acceptable in tables for non-significant p-values.

Editorial Point 13: Please provide absolute numbers to accompany all percentages

Author Response: We have reviewed the manuscript and ensured that all P values are provided to 4 decimal places and that all percentages are accompanied by absolute numbers.

Editorial Point 14: Please provide numbers at risk for Kaplan-Meier plots

Author Response: Data for patients at risk are provided for all Kaplan-Meier plots.

Editorial Point 15: Please provide the text, tables and figures in an editable format.

Editorial Point 16: For figures please consult http://download.thelancet.com/flatcontentassets/authors/artwork-guidelines.pdf

Editorial Point 17: If accepted, only 5-6 non-text items (figures or tables) can be accommodated in the print edition; additional material can be provided for a web appendix.

Author Response: Figures have been developed in accordance with *The Lancet's* artwork guidelines and have been provided in an editable format. Our manuscript currently contains four figures and two tables.

Editorial Point 18: Please provide a research in context panel with 3 parts: Systematic review (which includes a description of how you searched for evidence and how you

assessed the quality of that evidence); the added value of the study; and Interpretation of the totality of evidence when added to previous work.

> **Author Response:** A research in context panel with the three requested sections has been provided (lines 101-163).

Editorial Point 19: If you have not yet done so, please return all signed authorship statements and conflict of interest forms. A paragraph summarizing authors' disclosures must be made in the manuscript, please.

Editorial Point 20: For any personal communication, please provide a letter showing that the person agrees to their name being used. We also require signed statements from any named person in the acknowledgements saying that they agree to be acknowledged

> **Author Response:** All signed authorship statements (TL Author forms), conflict of interest forms (ICMJE), and signed acknowledgement letters have been provided with resubmission; we have provided combined pdfs containing all authors' forms for each of these categories.

Editorial Point 21: Please ensure there is a statement of contributions explaining what each author contributed at the end of the text

> **Author Response:** A contributions section is provided at the end of the main text (lines 561-568).

Editorial Point 22: Please ensure that there is a section in the Methods section confirming ethics approval and consent from all patients has been obtained.

> **Author Response:** Confirmation of ethics approval and written consent of patients is outlined in the Methods (lines 201-204).

Editorial Point 23: As corresponding author, please confirm that all authors have seen and approved of the final text

> **Author Response:** I confirm that authors have seen and approved the final text.

Editorial Point 24: Our production system is not compatible with Endnotes. Please convert to normal text.

> **Author Response:** Endnote references have been converted to normal text.

Editorial Point 25: Please note our guideline length for research articles is 3000 words. Allowing for additional material requested by reviewers and editors we can allow a little leeway but we hope for final manuscript below 3500 words (4500 words for RCTs).

> **Author Response:** In accordance with the word limit for manuscripts reporting randomised controlled trials, our manuscript is currently within the limit of 4500 words (final word count: 4440 words).

Editorial Point 26: Please provide a revised manuscript, a tracked changes version showing the changes made, and a point-by-point response to ALL EDITORS' and reviewers' comments - typed immediately following each specific point.

Editorial Point 27: PLEASE do not use boxes for replies. This slows checking and can result in a delayed decision.

> **Author Response:** As requested, we have provided our point-by-point responses to all editor and reviewer comments, using tracked changes in the manuscript.

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a phase 3, international, randomised, double-blind trial

Robert L Coleman, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann,* on behalf of the ARIEL3 investigators*[†]

Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler Dr., CPB6.3590 Houston, TX 77030, USA (Prof R L Coleman MD); Department of Medicine, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto M5G 2M9, Canada (Prof A M Oza MD); MITO and Gynecologic Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian, 1, 20133 Milan, Italy (D Lorusso MD); Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY, USA (C Aghajanian MD); Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), 119-129, 08035, Barcelona, Spain (A Oaknin MD); Department of Oncology, St. John of God Subiaco Hospital, 12 Salvado Rd., Subiaco, Western Australia 6008, Australia (A Dean MD); Gynecologic Cancer

Program, European Institute of Oncology and University of Milan-Bicocca, Via Ripamonti 435, Milan, Italy (Prof N Colombo PhD); Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, Canada K1H 8L6 (J I Weberpals MD); Department of Medical Oncology, The Christie NHS Foundation Trust and University of Manchester, 550 Wilmslow Road, Manchester, M20 4BX UK (A Clamp PhD); Gynecologic Oncology, Università Cattolica Roma, Largo Francesco Vito, 1, 00168 Roma, Italy (Prof G Scambia MD); GINECO and Gynecological Unit, Department of Medicine, Gustave Roussy Cancer Center and INSERM U981, 114 Rue Edouard-Vaillant, 94805, Villejuif, France (A Leary MD); Department of Gynecologic Oncology, Florida Hospital Cancer Institute, 2501 North Orange Avenue, Suite 683, Orlando, FL, USA (R W Holloway MD); Medical Oncology Department, Oncology Center of Galicia, Doctor Camilo Veiras, 1, 15009 La Coruña, Spain (M Amenedo Gancedo MD); Medical Oncology Department, Auckland City Hospital, 2 Park Rd, Grafton, Auckland 1023, New Zealand (P C Fong FRACP); Department of Oncology, Cancer Care Services, Royal Brisbane and Women's Hospital, Level 5 Joyce Tweddell Building, Butterfield Street, Herston, Queensland 4029, Australia (J C Goh FRACP); Gynecologic Oncology, The Ohio State University, James Cancer Center, M210 Starling Loving, 320 W 10th Ave, Columbus, OH 43210, USA (D M O'Malley MD); The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Room 190, 1650 Orleans Street, Baltimore, MD 21287, USA (Prof D K Armstrong MD); HM Hospitales – Centro Integral Oncológico HM Clara Campal, Calle Oña, 10, Planta -1, 28050 Madrid, Spain (J Garcia-Donas MD); University of Washington, 1959 Northeast Pacific Street, Seattle, WA 98195, USA (Prof E M Swisher MD); GINECO and Institut Bergonié, 229, cours de l'Argonne, 33076

Bordeaux, France (A Floquet MD); Department of Medicine, University of California Los Angeles, 100 Medical Plaza, Los Angeles, CA 90095, USA (Prof G E Konecny MD); Institute of Cancer Sciences, University of Glasgow, 1053 Great Western Road, Glasgow, G12 0YN UK (Prof I A McNeish FCRP); Royal Melbourne Hospital, 300 Grattan Street, Parkville, Victoria, 3052, Australia (C L Scott PhD); Clovis Oncology, Inc., 5500 Flatiron Parkway, Boulder, CO 80301, USA (T Cameron MSc, L Maloney BA, J Isaacson PhD, S Goble MS, C Grace BSc, T C Harding PhD, M Raponi PhD, K K Lin PhD, H Giordano MA); Foundation Medicine, Inc., 150 Second St, Cambridge, MA, 02141, USA (J Sun PhD); UCL Cancer Institute and UCL Hospitals, 90 Tottenham Court Road, London W1T 4TJ, UK (Prof J A Ledermann MD)

*Joint lead clinical investigators.

†Members listed in the appendix.

Correspondence to: Dr Robert L Coleman, The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler Dr., CPB6.3590 Houston, TX 77030, USA; Phone: 713 745 3357; Fax: 713 792 7586; rcoleman@mdanderson.org

Abstract word count (300 max): 310

Manuscript word count (4500 max): 4440

Table/Figure number: 2 tables + 4 figures = 6

References (30 max): 30

Summary

Background: Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has anticancer activity in recurrent ovarian carcinoma harbouring a *BRCA* mutation or a high percentage of genome-wide loss of heterozygosity (LOH). ARIEL3 evaluated rucaparib versus placebo following response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma.

Methods: ARIEL3 is an international, randomised, double-blind, phase 3 study performed at 87 hospitals and cancer centres. Patients were randomised 2:1 to receive oral rucaparib 600 mg twice daily or placebo using a computer-generated sequence (block size of six). Patients, investigators, site staff, and study sponsor were blinded to assignments. The primary endpoint (investigator-assessed progression-free survival) was evaluated using an ordered step-down procedure for three nested cohorts: (1) *BRCA* mutant (carcinoma associated with deleterious germline or somatic *BRCA* mutation); (2) homologous recombination deficient (HRD) (*BRCA* mutant or *BRCA* wild type/LOH high); and (3) intent-to-treat population. ARIEL3 is registered with ClinicalTrials.gov, NCT01968213; enrolment is complete.

Findings: Between April 7, 2014, and July 19, 2016, 564 patients were randomised, 375 to rucaparib and 189 to placebo. Median progression-free survival in patients with a *BRCA*-mutant carcinoma (n=130, rucaparib; n=66, placebo) was 16·6 months versus 5·4 months (p<0·0001), respectively (hazard ratio [HR] 0·23; 95% confidence interval [CI] 0·16–0·34); in patients with an HRD carcinoma (n=236, rucaparib; n=118, placebo) it was 13·6 months versus 5·4 months (p<0·0001), respectively (HR 0·32; 95% CI 0·24–0·42); and in the intent-to-treat population it was 10·8 months and 5·4 months

(p<0·0001), respectively (HR 0·36; 95% CI 0·30–0·45). The most common grade 3 or higher adverse events in the safety population (n=372, rucaparib; n=189, placebo) were anaemia/decreased haemoglobin (70 [19%], rucaparib; one [1%], placebo) and increased alanine or aspartate aminotransferase (39 [10%], rucaparib; none, placebo).

Interpretation: Across all primary analysis groups, rucaparib significantly improved progression-free survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy.

Funding: Clovis Oncology, Inc.

Research in context

Evidence before this study

Evidence of the clinical effectiveness of poly(ADP-ribose) polymerase (PARP) inhibitors as maintenance treatment for platinum-sensitive ovarian carcinoma is limited. In a search of PubMed (conducted July 31, 2017; search term: (“PARP inhibitor” OR rucaparib OR olaparib OR niraparib OR veliparib OR talazoparib) AND (ovarian AND (cancer OR carcinoma)) AND "maintenance"), we found that data have been published in a PubMed-indexed journal for only three clinical trials, Study 19 (NCT00753545), NOVA (NCT01847274), and SOLO2 (NCT01874353). Study 19, a randomised, placebo-controlled, phase 2 study, enrolled patients with platinum-sensitive ovarian carcinoma who had received at least two prior platinum-based chemotherapies. Progression-free survival was significantly improved with olaparib maintenance treatment in the overall population, as well as in patients with a germline or somatic *BRCA* mutation. Study 19 data were published prior to the commencement of ARIEL3 and supported the investigation of rucaparib as a maintenance treatment for patients with recurrent platinum-sensitive ovarian carcinoma in ARIEL3. In late 2016, results from the NOVA trial provided additional support for the role of a PARP inhibitor as maintenance treatment. In that randomised, placebo-controlled, phase 3 study, niraparib demonstrated a significant improvement in progression-free survival when used as a maintenance treatment in patients with ovarian carcinoma with or without a germline *BRCA* mutation who had received at least two prior platinum-based chemotherapies and had no measurable disease greater than 2 cm. Results from one other phase 3 study with olaparib maintenance treatment, SOLO2, were published in

July 2017. That randomised, placebo-controlled study enrolled patients with platinum-sensitive ovarian carcinoma who had received at least two prior platinum-based chemotherapies and carried a germline mutation in *BRCA*. Similar to the results seen in Study 19, progression-free survival was significantly improved with olaparib maintenance treatment in patients enrolled in SOLO2.

Added value of this study

ARIEL3 enrolled patients with or without a germline or somatic *BRCA* mutation, and the size of residual disease was not restricted. Our results show that rucaparib maintenance treatment significantly improved progression-free survival for patients across all primary analysis groups for patients with recurrent, platinum-sensitive ovarian carcinoma who achieved a response to platinum-based therapy, including in the intent-to-treat population. We demonstrate that rucaparib maintenance treatment can provide clinical benefit not only to patients with ovarian carcinoma associated with a *BRCA* mutation, but also to those with *BRCA* wild-type ovarian carcinoma. A novel aspect of the ARIEL3 trial was the prospective validation of the tumour-based, next-generation sequencing (NGS) homologous recombination deficiency (HRD) assay that was initially utilised in the phase 2 ARIEL2 study. This NGS assay combines mutation analysis of *BRCA1* and *BRCA2* genes with measurement of the percentage of genome-wide loss of heterozygosity (LOH) in the cancer tissue as a biomarker for sensitivity to rucaparib treatment. ARIEL2 enrolled patients with measurable, recurrent ovarian carcinoma, and provided initial evidence that patients with carcinomas with high LOH benefited from rucaparib treatment. The current study (ARIEL3) validated the utility of the HRD assay overall and LOH assessment in particular in the maintenance treatment setting, where

rucaparib-treated patients with carcinomas that were *BRCA* wild type/LOH high also had improvements in progression-free survival, with a lower hazard ratio than in patients with carcinomas that were *BRCA* wild type/LOH low.

Implications of all the available evidence

Combined with the evidence from prior studies, our study supports the use of PARP inhibitors, such as rucaparib, as maintenance treatment for patients with platinum-sensitive ovarian cancer who achieved a response to platinum-based chemotherapy. ARIEL3 is the first phase 3 study to prospectively assess progression-free survival in patients with recurrent ovarian carcinoma associated with HRD as a primary endpoint, and our results demonstrate that HRD as a predictive biomarker can be an informative tool for clinicians when making treatment decisions for this patient population. In addition to PARP inhibitors, the targeted agents bevacizumab and cediranib have proven useful in extending progression-free survival for patients in this setting. Our findings strengthen the rationale for continued investigation of targeted therapies, such as PARP inhibitors, for maintenance treatment as either monotherapy or in combination with other agents, in an effort to provide the best care for patients with advanced ovarian cancer.

Introduction

Ovarian cancer is the eighth leading cause of death from cancer in women worldwide.[1] Most patients with advanced stage ovarian carcinoma initially receive platinum-based chemotherapy and achieve a clinical response; however, the majority of these patients will ultimately relapse.[2] The treatment for initial recurrent disease depends on many factors, including duration of initial treatment response, antecedent and persistent adverse events, performance status, histology, location and burden of disease, and, increasingly, tumour genomics such as *BRCA* mutation status.[3] For patients with platinum-sensitive recurrent ovarian carcinoma, maintenance treatment with targeted agents has resulted in greater prolongation of progression-free survival.[4-9] However, clinical benefit is typically transient, hence there is an ongoing pursuit for new therapies and tools to identify patients who may benefit most from these therapies, as well as to identify the optimal therapeutic strategy for patients.

The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved in the United States for the treatment of patients with deleterious *BRCA* mutation (germline or somatic) associated advanced ovarian carcinoma who have been treated with two or more chemotherapy regimens. Approval of rucaparib was based on the objective response rate (57 of 106 patients [54%]) observed in a pooled population of patients with *BRCA*-mutant high-grade ovarian carcinoma from the Study 10 (CO-338-10; NCT01482715) and ARIEL2 (CO-338-017; NCT01891344) clinical trials.[10,11]

In Part 1 of the ARIEL2 trial, rucaparib treatment was found to be efficacious not only in patients with relapsed, platinum-sensitive, high-grade ovarian carcinoma with a *BRCA*

mutation, but also in patients with *BRCA* wild-type carcinomas with high genomic loss of heterozygosity (LOH),[11] a potential marker for homologous recombination deficiency (HRD) and thus PARP inhibitor activity.[12-15] In the current phase 3, randomised, placebo-controlled study (ARIEL3), our objective was to evaluate the efficacy and safety of rucaparib versus placebo following response to second-line or later platinum-based chemotherapy in patients with high-grade, platinum-sensitive ovarian carcinoma (including fallopian tube and primary peritoneal carcinomas) and to prospectively test the genomic LOH cutoff discriminator that was optimised based on results of ARIEL2 Part 1 as a predictive biomarker for sensitivity to rucaparib treatment.

Methods

Study design and patients

ARIEL3 (NCT01968213) was a phase 3, international, randomised, placebo-controlled study conducted at 87 hospitals and cancer centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, United Kingdom, and the United States. The trial 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. Per the protocol, an independent data monitoring committee monitored enrolment and reviewed the safety and efficacy of the trial approximately every 6 months, including maturity of progression-free survival events.

Eligible patients were aged 18 years or older, had platinum-sensitive (ie, documented radiologic disease progression more than 6 months following the last dose of the penultimate platinum administered), high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma and had received at least two prior platinum-based chemotherapy regimens. Prior treatment with bevacizumab was permitted, with the exception of bevacizumab maintenance treatment following the most recent platinum-based regimen. On November 4, 2014, after 91 patients had been randomised, an amendment was made 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. Patients must have achieved either a complete response by Response Evaluation Criteria In Solid Tumors version 1·1 (RECIST)[16] or a partial response, defined as either a RECIST partial response or a serologic response per Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 (CA-125)[17] response criteria, to their last platinum-based regimen. For patients who achieved a partial response, no restriction was placed on residual carcinoma size at study entry; those who had persistent lesions greater than 2 cm as defined by independent radiological review were defined as having “bulky” residual disease. Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry into ARIEL3. Additionally, CA-125 was required to be less than the upper limit of normal. Patients had Eastern Cooperative Oncology Group Performance Status of 0 to 1 and adequate organ function. Patients were ineligible if they had symptomatic/untreated central nervous system metastases, had received anticancer therapy 14 or fewer days before starting the study, or had

received prior treatment with a PARP inhibitor. A complete list of inclusion and exclusion criteria is provided in the appendix (p 6), and the full study protocol is available in the appendix.

Central testing of DNA derived from patient archival tumour tissue samples was performed to detect mutations in homologous recombination pathway genes (appendix p 8) and assess genomic LOH using Foundation Medicine's T5 NGS assay (Cambridge, MA). Based on retrospective analysis of data from ARIEL2 Part 1, a cutoff of 16% or greater was prespecified for ARIEL3 as a discriminator for high genomic LOH.[11] Germline mutations were identified by BRCAnalysis CDx test (Myriad Genetics, Salt Lake City, UT). Further details of the tumour tissue testing are provided in the appendix (p 2).

Randomisation and masking

Within 8 weeks of their last dose of platinum, eligible patients were randomised 2:1 to receive oral rucaparib (600 mg twice daily) or matched placebo. Randomisation was computer-generated by Almac Clinical Technologies (Souderton, PA) using a block size of six. Randomisation stratification factors included: homologous recombination repair gene mutation status (based on gene mutation only); progression-free interval following penultimate platinum-based regimen; and best response to most recent platinum-based regimen (additional details in the appendix p 3). Patients were assigned to the rucaparib arm or placebo arm in a blinded manner using Almac Clinical Technologies' interactive web and voice response system (IXRS®); patients, investigators, site staff, and the study sponsor were blinded to assignments. To ensure blinding was maintained, rucaparib and placebo tablets were manufactured to have identical appearances.

Procedures

Patients received study drug in continuous 28-day cycles until disease progression, death, or other reason for discontinuation. Dose reductions (in decrements of 120 mg) were permitted if a patient had a grade 3 or greater or persistent grade 2 adverse event (additional details in the appendix p 3). Treatment was discontinued for a toxicity-related treatment interruption lasting more than 14 consecutive days (unless otherwise agreed upon between the investigator and the study sponsor).

Disease assessments were performed at screening, every 12 weeks during treatment (and post-treatment for patients who discontinued for any reason other than disease progression), at discontinuation of treatment, and as clinically indicated. Disease progression was determined by RECIST. Patients with a complete response at study entry were only considered to have disease progression if an unequivocal new lesion was identified. Increased CA-125 levels alone were not considered to indicate disease progression unless confirmed by RECIST. All computed tomography scans and other imaging were provided to a blinded, independent central radiology review (BICR).

The National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy Ovarian Symptom Index 18 (FOSI-18)[18] questionnaire was used to assess patient-reported outcomes at screening and throughout treatment. Safety was assessed by monitoring for adverse events, laboratory testing, assessing vital signs and conducting physical examinations. Adverse events were classified in accordance with the Medical Dictionary for Drug Regulatory Activities classification system version 18·1[19] and graded for severity in accordance with the National Cancer Institute Common

Terminology Criteria for Adverse Events version 4·03.[20] Serious adverse events were classified as defined in the protocol (see appendix).

Outcomes

The primary endpoint was investigator-assessed progression-free survival, defined as time from randomisation to investigator-assessed disease progression per RECIST or death. Secondary endpoints included progression-free survival by BICR, patient-reported outcomes as evaluated by time to worsening in the FOSI-18 disease-related symptoms–physical (DRS-P) subscale (defined as ≥4-point decrease) and total score (defined as ≥8-point decrease), overall survival, safety, and population pharmacokinetic modelling. Additional details are available in the appendix (p 3). The secondary endpoint of population pharmacokinetic modelling will be reported separately.

Statistical analysis

ARIEL3 was designed to enrol approximately 540 patients, including between 180 and 200 patients with a *BRCA* mutation in their carcinoma (with no more than 150 patients with a known deleterious germline *BRCA* mutation) and no more than 360 patients without a *BRCA* mutation in their carcinoma. The independent data monitoring committee surveyed enrolment of patients with a *BRCA* mutation and informed the study sponsor (Clovis Oncology, Inc.) when the target enrolment number for the *BRCA*-mutant cohort was anticipated to be reached. Once notified, patients who were in the screening process were allowed to complete screening and enrol into the study if they met all eligibility criteria. These subgroup sizes were designed to result in 90% power to determine statistical significance between rucaparib and placebo at a one-sided alpha

level of 0·025 given the following assumptions for median investigator-assessed progression-free survival for the efficacy analysis cohorts: *BRCA* mutant (carcinoma associated with a deleterious germline or somatic *BRCA* mutation), 12·0 months in the rucaparib arm versus 6·0 months in the placebo arm (hazard ratio [HR] 0·5); HRD (includes patients with a *BRCA*-mutated carcinoma and patients with *BRCA* wild-type/LOH-high carcinomas), 10·0 versus 6·0 months (HR 0·6); and intent-to-treat population (all randomised patients), 8·5 versus 6·0 months (HR 0·7).

Classification of HRD status in the carcinoma (based on *BRCA* mutation and/or LOH) for the efficacy analysis was determined before database lock and the final efficacy analysis. Per protocol, the primary analysis was to be performed after the independent data monitoring committee determined that investigator-assessed disease progression or death had occurred in at least 70% of expected patients in the *BRCA*-mutant cohort.

All efficacy analyses were performed for the intent-to-treat population. The efficacy analyses are presented separately for the nested cohorts: *BRCA* mutant, HRD, and intent-to-treat population. The primary endpoint was tested using an ordered step-down multiple comparisons procedure[21] for the three nested cohorts: *BRCA* mutant, HRD, and the intent-to-treat population. Investigator-assessed progression-free survival in patients with a *BRCA*-mutant carcinoma was tested first at a one-sided 0·025 significance level. Analysis of investigator-assessed progression-free survival in patients with an HRD carcinoma followed by analysis in the intent-to-treat population was contingent upon a statistically significant result in the analysis of patients with a *BRCA*-mutant carcinoma. Analysis of the key secondary endpoints of patient-reported outcomes and overall survival were to follow in a similar ordered step-down procedure.

Once statistical significance was not achieved for one test, the statistical significance was not declared for all subsequent analyses in the ordered step-down procedure. Progression-free survival by BICR was evaluated as a key stand-alone secondary endpoint, separate from the step-down procedure described above. Time to progression-free survival (by investigator and by BICR) and time to worsening in the FOSI-18 DRS-P subscale were analysed using stratified Kaplan-Meier methodology where distributions between rucaparib and placebo arms were compared using a stratified log-rank test. A stratified Cox proportional hazards model was used to estimate the HR between the arms. Exploratory analyses of progression-free survival were performed in subgroups based on patient characteristics (eg, randomisation stratification factors, demographics, disease burden at baseline). For patients with measurable disease at study entry, the proportion of patients achieving a confirmed complete or partial response per RECIST as assessed by the investigator was a prespecified exploratory endpoint of ARIEL3.

Safety, including adverse events and clinical laboratory investigations, was evaluated in all patients who received at least one dose of protocol-specified treatment.

Statistical analyses were performed using SAS version 9·4 (SAS Institute, Cary, NC). Additional details are available in the appendix (p 4).

Role of the funding source

The study was designed by the sponsor, Clovis Oncology, Inc., and the coordinating investigators (RLC and JAL). Data presented herein were collected by the investigators, analysed by Clovis Oncology, and interpreted by all authors. All authors had access to

the data and had final responsibility for the decision to submit for publication. Writing and editorial assistance were supported by the sponsor.

Results

Between April 7, 2014, and July 19, 2016, 564 patients (intent-to-treat population) were randomised, 375 to rucaparib and 189 to placebo (figure 1; appendix p 11). At the visit cutoff date (April 15, 2017), 90 (24%) and 9 (5%) patients in the rucaparib and placebo arms, respectively, were still receiving treatment. Baseline demographic and clinical characteristics were generally well balanced between the treatment arms (table 1).

Following the ordered step-down multiple comparisons procedure, the analysis of investigator-assessed progression-free survival was evaluated first in patients with a *BRCA*-mutant carcinoma (130, rucaparib; 66, placebo; appendix p 11). Median time to progression or death was 16·6 months versus 5·4 months (stratified log-rank p<0·0001) in the rucaparib and placebo arms, respectively (HR 0·23; 95% confidence interval [CI] 0·16–0·34; p<0·0001) (figure 2). In patients with an HRD carcinoma (236, rucaparib; 118, placebo), median progression-free survival was 13·6 months and 5·4 months (stratified log-rank p<0·0001), respectively (HR 0·32; 95% CI 0·24–0·42; p<0·0001). Median progression-free survival in the intent-to-treat population was 10·8 months and 5·4 months (stratified log-rank p<0·0001), respectively (HR 0·36; 95% CI 0·30–0·45; p<0·0001).

In a prespecified analysis of the key stand-alone, secondary endpoint of progression-free survival assessed by BICR, results were similar to those of investigator-assessed progression-free survival for the patients with a *BRCA*-mutant carcinoma (median 26·8 months *vs* 5·4 months; HR 0·20; 95% CI 0·13–0·32; p<0·0001), the patients with an HRD carcinoma (median 22·9 months *vs* 5·5 months; HR 0·34; 95% CI 0·24–0·47; p<0·0001), and the intent-to-treat population (median 13·7 months *vs* 5·4 months; HR 0·35; 95% CI 0·28–0·45; p<0·0001) (figure 2).

Analysis of the secondary endpoint of time to worsening in the FOSI-18 DRS-P subscale score was assessed in the step-down procedure for the three nested subgroups. In patients with a *BRCA*-mutant carcinoma, there was no significant difference between arms in the time to worsening in the FOSI-18 DRS-P subscale (stratified log-rank p=0·29) (HR 1·24; 95% CI 0·82–1·86; p=0·30). As statistical significance was not reached in patients with a *BRCA*-mutant carcinoma, in accordance with the prespecified step-down procedure, statistical significance could not be determined for the remaining secondary analyses.

At the visit cutoff date (April 15, 2017), overall survival data were not mature (123 [22%] patients had died). A follow-up analysis will be performed when approximately 70% of the patients have died (≈395 overall survival events).

Preplanned subgroup analyses of investigator-assessed progression-free survival demonstrated that the progression-free survival benefit for rucaparib versus placebo was observed across all clinical subgroups, irrespective of presence or absence of measurable disease or bulky disease (defined as any lesion >2 cm) at baseline,

response to last platinum-based regimen (complete or partial response), LOH (high, low, or indeterminate), or *BRCA* mutation (germline or somatic; *BRCA1* or *BRCA2*) (figure 3; appendix p 12). Further supporting the efficacy observed in the intent-to-treat population, in the non-nested subgroups of patients with carcinomas that were *BRCA* wild type, a progression-free survival benefit as assessed by the investigator was observed with rucaparib in patients with LOH-high carcinomas (median 9·7 months *vs* 5·4 months; HR 0·44; 95% CI 0·29–0·66; p<0·0001) and patients with LOH-low carcinomas (median 6·7 months *vs* 5·4 months; HR 0·58; 95% CI 0·40–0·85; p=0·0049) (figure 4); similar results were also observed in progression-free survival assessed by BICR (appendix p 13).

The majority of patients (374 [66%]) in ARIEL3 had achieved a partial response to the platinum-based therapy prior to randomisation. For 207 (37%) of 564 patients with measurable disease per investigator at study entry, a prespecified exploratory analysis of confirmed response was conducted. In the subgroup of patients with measurable disease at study entry with a *BRCA*-mutant carcinoma, 15 (38%) of 40 in the rucaparib arm and two (9%) of 23 in the placebo arm achieved a confirmed RECIST response (appendix p 8). In patients with an HRD carcinoma with measurable disease at baseline, the objective response was also higher in the rucaparib arm (23 [27%] of 85 patients) than the placebo arm (3 [7%] of 41 patients). A similar result was observed in the intent-to-treat population among patients with measurable disease at baseline (26 [18%] of 141 patients in the rucaparib arm; 5 [8%] of 66 patients in the placebo arm). Complete responses were observed in the rucaparib arm in seven (18%), 10 (12%), and 10 (7%) patients with measurable disease at baseline in the nested *BRCA*-mutant and

HRD cohorts, and the overall intent-to-treat population, respectively. Only one (2%) complete response was observed in the placebo arm; this occurred in the intent-to-treat population.

The safety population included 372 patients who received rucaparib (three patients were withdrawn prior to receiving rucaparib) and 189 patients who received placebo. For the safety population, the median (interquartile range) treatment duration was 8·3 (3·4–16·1) months in the rucaparib arm and 5·5 (2·8–8·3) months in the placebo arm. A treatment-emergent adverse event of any grade occurred in 372 patients (100%) in the rucaparib arm and 182 patients (96%) in the placebo arm (table 2). The most common treatment-emergent adverse events (reported in at least 35% of patients in either arm) included nausea (280 patients [75%] in the rucaparib arm and 69 patients [37%] in the placebo arm), asthenia or fatigue (258 patients [69%] and 83 patients [44%]), dysgeusia (146 patients [39%] and 13 patients [7%]), anaemia/decreased haemoglobin (139 patients [37%] and 11 patients [6%]), constipation (136 patients [37%] and 45 patients [24%]), and vomiting (136 patients [37%] and 28 patients [15%]). Treatment-emergent adverse events of grade 3 or greater were reported in 209 patients (56%) in the rucaparib arm and 28 patients (15%) in the placebo arm, the most common of which were anaemia/decreased haemoglobin (70 patients [19%] and one patient [1%]) and increase in alanine aminotransferase or aspartate aminotransferase (39 patients [10%] and no patients). For patients in the rucaparib arm, a decline in haemoglobin level from baseline generally occurred in the first few cycles (appendix p 14). Elevations in alanine aminotransferase or aspartate aminotransferase were generally transient, self-limiting,

and not associated with other signs of liver toxicity (appendix p 15). The frequency of treatment-emergent adverse events was comparable across the three nested cohorts.

One or more serious adverse events were reported in 78 patients (21%) in the rucaparib arm and 20 patients (11%) in the placebo arm. The most common serious adverse events (reported in at least 2% of patients in either arm) included anaemia (16 patients [4%] in the rucaparib arm and one patient [1%] in the placebo arm), pyrexia (six patients [2%] and no patients), vomiting (six patients [2%] and two patients [1%]), and small intestinal obstruction (three patients [1%] and three patients [2%]).

Myelodysplastic syndrome and acute myeloid leukaemia were reported in three patients (1%) in the rucaparib arm (two had a germline *BRCA*-mutant carcinoma, and one had a *BRCA* wild-type/LOH-low carcinoma). One patient died due to myelodysplastic syndrome and one due to acute myeloid leukaemia. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia in the placebo arm.

Treatment interruption due to a treatment-emergent adverse event occurred in 237 (64%) and 19 (10%) patients in the rucaparib and placebo arms, respectively (appendix p 9). Dose reduction due to a treatment-emergent adverse event occurred in 203 (55%) and eight (4%) patients in the rucaparib and placebo arms, respectively (appendix p 9). In the rucaparib and placebo arms, 117 (31%) and six (3%) patients, respectively, had both a treatment interruption due to a treatment-emergent adverse event and a dose reduction due to a treatment-emergent adverse event. Of patients who received rucaparib, 50 (13%) discontinued due to a treatment-emergent adverse event (excluding disease progression) compared with three (2%) patients in the placebo arm

(appendix p 10). As of the visit cutoff date, in the rucaparib arm there were four deaths due to adverse events considered unrelated to treatment by the investigator (two patients due to progressive disease, one due to cardiac arrest, and one due to haematophagic histiocytosis) and two deaths considered treatment related by the investigator (one due to acute myeloid leukaemia and one due to myelodysplastic syndrome). In the placebo arm, two patients died due to adverse events considered unrelated to treatment by the investigator (one due to progressive disease and one due to pulmonary embolism).

Discussion

In ARIEL3, rucaparib maintenance treatment versus placebo significantly improved progression-free survival in all primary analysis groups of patients with recurrent ovarian carcinoma following a complete or partial response to platinum-based therapy. The prolonged progression-free survival among patients receiving rucaparib in the intent-to-treat population (HR 0·36) demonstrates that patients with platinum-sensitive ovarian carcinoma can derive robust clinical benefit from rucaparib maintenance treatment. A similar improvement over placebo (HR 0·35) was seen in the secondary endpoint of assessment by BICR review, supporting the validity of the benefit observed with rucaparib maintenance treatment. Furthermore, the lower hazard of disease progression or death associated with rucaparib in the study was observed across all prespecified subgroups that were analysed. Analysis of non-nested, non-overlapping patient subpopulations (ie, *BRCA* wild-type/LOH-high and *BRCA* wild-type/LOH-low

patients) indicate that the statistically significant improvement in progression-free survival observed in the intent-to-treat population was not driven only by the results in the nested HRD or *BRCA*-mutant cohorts.

Patient-reported outcomes were evaluated as a secondary endpoint of ARIEL3 as part of the step-down procedure, with no significant difference in time to worsening in the FOSI-18 DRS-P subscale observed between the rucaparib and placebo arms. Further analyses of the patient-reported health outcome data gathered in ARIEL3 are planned and will be reported separately.

Overall survival data were not mature at the time of the visit cutoff, with less than 25% of the events needed for final analysis. Patient follow-up is continuing in a blinded manner and overall survival will be assessed after about 70% maturity is reached.

As reported in prior studies of rucaparib and other PARP inhibitors,[5,6,9-11] gastrointestinal side effects, asthenia or fatigue, and myelosuppression were common treatment-emergent adverse events in the rucaparib arm. Management of adverse events included supportive care and dose modifications (including treatment interruption and/or dose reduction). Common laboratory abnormalities observed in the rucaparib arm included elevations in alanine aminotransferase, aspartate aminotransferase, and blood creatinine. Alanine aminotransferase and aspartate aminotransferase were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity, and generally resolved over time. No cases were considered to meet Hy's law criteria for drug-induced liver injury (ie, alanine aminotransferase or aspartate aminotransferase greater than 3 times the upper limit of normal with concomitant bilirubin greater than 2 times the upper limit of normal without alkaline phosphatase

elevations or another clear reason for the elevations).[22,23] Similarly, elevations in creatinine, which have also been observed with olaparib,[24] were self-limiting and stabilised over time. Creatinine is secreted into urine via renal transporters (eg, MATE1, MATE2-K, OCT-1, and OCT-2), which have been shown to be inhibited in vitro by multiple PARP inhibitors, including rucaparib, olaparib, and veliparib.[25-27] Patterns of elevation and stabilisation of these laboratory abnormalities similar to those reported here were observed in the treatment setting with rucaparib.[28,29]

The results of ARIEL3 are consistent with those of other placebo-controlled studies of PARP inhibitors in the maintenance treatment setting, including NOVA (NCT01847274) with niraparib and Study 19 (NCT00753545) and SOLO2 (NCT01874353) with olaparib.[5,6,9] However, direct comparisons with these other trials cannot be made due to differences in patient groups analysed (eg, SOLO2 only enrolled patients with a germline *BRCA* mutation), definition of HRD (eg, in NOVA, HRD included patients with somatic mutations in *BRCA*, as well as those with non-*BRCA*–related HRD), the method of primary endpoint assessment (eg, investigator *vs* BICR), and study design (eg, residual disease was restricted to <2 cm in NOVA).[5,6,9,30]

Although having a CA-125 below the upper limit of normal is not a requirement of response per GCIG CA-125 criteria or a RECIST partial response, ARIEL3 required that patients have CA-125 below the upper limit of normal prior to study entry; this eligibility requirement was intended to ensure that patients had controlled disease at study entry. Similar restrictions on CA-125 levels were included in the enrolment criteria of other studies investigating PARP inhibitors in the maintenance treatment setting, although it is unknown how many patients in these studies had CA-125 levels greater than the upper

limit of normal at study entry.[5,6,9] Furthermore, it is not known whether inclusion of patients with CA-125 levels exceeding the upper limit of normal affects the efficacy of PARP inhibitors in the maintenance treatment setting.

Although ARIEL3 extends the findings of previous studies of PARP inhibitors in this setting, there are some important differences between ARIEL3 and other studies in the maintenance treatment setting. Notably, patients in ARIEL3 with carcinomas associated with a germline or somatic *BRCA* mutation were both included in the three nested cohorts (*BRCA* mutant, HRD, and intent-to-treat population), a feature that is unique to ARIEL3 among clinical trials in this setting. In addition, ARIEL3 did not restrict enrolment based on target lesion size for patients with residual disease (partial response to prior platinum). A number of patients with measurable residual disease at study entry showed further reduction in carcinoma burden with rucaparib maintenance treatment, including conversion to a complete response per RECIST in several patients in the nested *BRCA*-mutant and HRD cohorts and the overall intent-to-treat population.

Additionally, ARIEL3 is the first phase 3 study to prospectively assess the primary endpoint of progression-free survival in patients with recurrent ovarian carcinoma associated with HRD. Preplanned analysis of progression-free survival in patients with a *BRCA* wild-type/LOH-high carcinoma, wherein patients treated with rucaparib had an increase in median progression-free survival (HR 0·44) compared with placebo, shows that the improvement observed in the HRD cohort was not driven solely by patients with a *BRCA*-mutant carcinoma. The benefit in progression-free survival seen in patients with a *BRCA* wild-type/LOH-high carcinoma (HR 0·44) compared with patients with a *BRCA* wild-type/LOH-low carcinoma (HR 0·58) demonstrates the utility of HRD, in

particular high genomic LOH as defined by Foundation Medicine's T5 assay, as a predictive biomarker for sensitivity to rucaparib treatment. Based on our findings, HRD assessment may be an informative tool for clinicians making treatment decisions for patients with *BRCA* wild-type associated platinum-sensitive ovarian carcinoma. However, response to rucaparib was also clearly observed in the cohort of patients with carcinomas that were *BRCA* wild type/LOH low, with more than 30% of patients in the rucaparib arm achieving benefit of more than a year's duration compared with less than 10% in the placebo arm. Therefore, the biomarker does not appear to be sufficiently precise to predict lack of benefit on an individual basis.

In summary, rucaparib improved progression-free survival in women with platinum-sensitive ovarian carcinoma following a complete or partial response to second-line or later platinum-based chemotherapy. Treatment-emergent adverse events in the rucaparib arm were generally managed with dose modifications and were not associated with increased mortality or morbidity compared with the placebo arm.

Contributors

RLC, JI, KKL, HG, and JAL were responsible for the study design. RLC, AMO, DL, CA, AO, AD, NC, JIW, AC, GS, AL, RWH, MAG, PCF, JCG, DMO, DKA, JGD, EMS, AF, GEK, IAM, CLS, and JAL treated patients. RLC, AMO, DL, CA, AO, AD, NC, JIW, AC, GS, CA, AL, RWH, MAG, PCF, JCG, DMO, DKA, JGD, EMS, AF, GEK, IAM, CLS, KKL, and JAL acquired the data. RLC, TC, LM, JI, SG, CG, TCH, MR, JS, KKL, HG, and JAL interpreted the data. All authors were responsible for writing the manuscript, and reviewed draft and final versions of the manuscript.

Declaration of interests

RLC reports grants from AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, Merck, Clovis Oncology, Esperance, and AbbVie, and reports serving as an advisor to AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, Merck, Clovis Oncology, Esperance, Tesaro, GamaMabs, Pfizer, Genmab, Gradalis, Bayer, and AbbVie. AMO has served on advisory boards for Amgen, Verastem, Clovis Oncology, and Immunovaccine; has received support for travel and/or accommodation from AstraZeneca; and has received honoraria from WebRx. DL has served in a consulting or advisory role for AstraZeneca, Clovis Oncology, Roche, Tesaro, and PharmaMar; and has received support for travel and/or accommodation from Roche and PharmaMar. CA served on a steering committee for Mateon Therapeutics; and has served on advisory boards for Clovis Oncology, Cerulean Pharma, Bayer, VentiRx, and AstraZeneca. AO has served on advisory boards for Roche, AstraZeneca, PharmaMar, Clovis Oncology, and Tesaro; and has received support for travel and/or accommodation from Roche, AstraZeneca, and PharmaMar. NC has served in a consulting or advisory role for Roche, AstraZeneca, Tesaro, PharmaMar, Clovis Oncology, and Advaxis. JIW has received research support from Abbvie and AstraZeneca; and has served on advisory boards for AstraZeneca. AC has served on advisory boards for AstraZeneca and Roche; and has received research support from AstraZeneca. AL has served on an advisory board for Clovis Oncology, Pfizer, and PharmaMar; reports institutional research grant support from GamaMabs and Merus; and reports boarding and travel expenses for congress activities from AstraZeneca.

RWH has served on a speakers bureau for AstraZeneca, Clovis Oncology, and Tesaro. PCF has served on advisory boards for Clovis Oncology and AstraZeneca; and has received honoraria from AstraZeneca. JCG has served on advisory boards for Roche, AstraZeneca, Janssen, Merck, and Bristol-Myers Squibb; and has received support for travel and/or accommodation from Roche, Bristol-Myers Squibb, and Astellas. DMO received research funding from Clovis Oncology; received institutional research support from AMGEN, VentiRx, Regeneron, Immunogen, Array Biopharma, Janssen R&D, Clovis Oncology, EMD Serono, Ergomed, Ajinomoto, and Genentech/Roche; and served on a steering committee, advisory boards and/or consulting for Amgen, AstraZeneca, Janssen, Clovis Oncology, Tesaro, Novocure, Genentech/Roche, and Eisai. JGD has received research funding from AstraZeneca; and has served on advisory boards for Janssen, Clovis Oncology, and Genentech/Roche. AF has served on advisory boards for AstraZeneca, Roche, and Tesaro. IAM has served on advisory boards for Clovis Oncology, Tesaro, and AstraZeneca. CLS has served in a consulting or advisory role for AstraZeneca, Clovis Oncology, Roche, and Eisai Australia; has received support for travel and/or accommodation from AstraZeneca, Clovis Oncology, and Roche; has received drug for research from Eisai Australia; and CLS' institution received in kind research support for parallel laboratory work using rucaparib. TC, LM, JI, SG, CG, TCH, KKL, and HG are employees of Clovis Oncology; MR was employed at Clovis Oncology at the time of the study and owns stock in the company. JS is an employee of Foundation Medicine, the developer of the homologous recombination deficiency assay used in ARIEL3. JAL has served in advisory role for Clovis Oncology

and AstraZeneca; served on a speakers bureau for AstraZeneca; and received research grants from AstraZeneca. All other authors have nothing to disclose.

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727

Figure legends

Figure 1: **CONSORT diagram**

*A full description of protocol deviations is provided in the appendix (p 5); these protocol deviations are reported as of the visit cutoff date (April 15, 2017) and did not result in the exclusion of patients or data from any efficacy or safety analyses in the study.

Figure 2: **Investigator-assessed and blinded independent central radiology review–assessed progression-free survival**

Kaplan-Meier estimates of progression-free survival as assessed by the investigator (A–C) and by BICR (D–F) in the rucaparib (blue) and placebo (red) arms for patients with a *BRCA*-mutant carcinoma (A, D), patients with an HRD carcinoma (B, E), and the intent-to-treat population (C, F). BICR=blinded independent central radiology review. CI=confidence interval. HR=hazard ratio. HRD=homologous recombination deficient. NR=not reached.

Figure 3: **Investigator-assessed progression-free survival in subgroups of the intent-to-treat population**

CA-125=cancer antigen 125. CI=confidence interval. CR=complete response. GCIG=Gynecologic Cancer InterGroup. HR=hazard ratio. LOH=loss of heterozygosity. PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors version 1·1. *By local germline test, central germline test, or tumour testing. †Tumour sample was not evaluable for percent of genomic LOH due to low tumour content or low

aneuploidy. ‡Prior treatment with bevacizumab was permitted as part of penultimate or earlier treatment.

Figure 4: **Investigator-assessed progression-free survival in patients with a *BRCA* wild-type carcinoma**

Kaplan-Meier estimates of progression-free survival as assessed by the investigator in the rucaparib (blue) and placebo (red) arms for patients with a *BRCA* wild-type carcinoma with LOH high (A) and LOH low (B). CI=confidence interval. HR=hazard ratio. LOH=loss of heterozygosity.

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a phase 3, international, randomised, double-blind trial

Robert L Coleman, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann,* on behalf of the ARIEL3 investigators†*

Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler Dr., CPB6.3590 Houston, TX 77030, USA (Prof R L Coleman MD); Department of Medicine, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto M5G 2M9, Canada (Prof A M Oza MD); MITO and Gynecologic Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian, 1, 20133 Milan, Italy (D Lorusso MD); Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY, USA (C Aghajanian MD); Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), 119-129, 08035, Barcelona, Spain (A Oaknin MD); Department of Oncology, St. John of God Subiaco Hospital, 12 Salvado Rd., Subiaco, Western Australia 6008, Australia (A Dean MD); Gynecologic Cancer

Program, European Institute of Oncology and University of Milan-Bicocca, Via Ripamonti 435, Milan, Italy (Prof N Colombo PhD); Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, Canada K1H 8L6 (J I Weberpals MD); Department of Medical Oncology, The Christie NHS Foundation Trust and University of Manchester, 550 Wilmslow Road, Manchester, M20 4BX UK (A Clamp PhD); Gynecologic Oncology, Università Cattolica Roma, Largo Francesco Vito, 1, 00168 Roma, Italy (Prof G Scambia MD); GINECO and Gynecological Unit, Department of Medicine, Gustave Roussy Cancer Center and INSERM U981, 114 Rue Edouard-Vaillant, 94805, Villejuif, France (A Leary MD); Department of Gynecologic Oncology, Florida Hospital Cancer Institute, 2501 North Orange Avenue, Suite 683, Orlando, FL, USA (R W Holloway MD); Medical Oncology Department, Oncology Center of Galicia, Doctor Camilo Veiras, 1, 15009 La Coruña, Spain (M Amenedo Gancedo MD); Medical Oncology Department, Auckland City Hospital, 2 Park Rd, Grafton, Auckland 1023, New Zealand (P C Fong FRACP); Department of Oncology, Cancer Care Services, Royal Brisbane and Women's Hospital, Level 5 Joyce Tweddell Building, Butterfield Street, Herston, Queensland 4029, Australia (J C Goh FRACP); Gynecologic Oncology, The Ohio State University, James Cancer Center, M210 Starling Loving, 320 W 10th Ave, Columbus, OH 43210, USA (D M O'Malley MD); The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Room 190, 1650 Orleans Street, Baltimore, MD 21287, USA (Prof D K Armstrong MD); HM Hospitales – Centro Integral Oncológico HM Clara Campal, Calle Oña, 10, Planta -1, 28050 Madrid, Spain (J Garcia-Donas MD); University of Washington, 1959 Northeast Pacific Street, Seattle, WA 98195, USA (Prof E M Swisher MD); GINECO and Institut Bergonié, 229, cours de l'Argonne, 33076

Bordeaux, France (A Floquet MD); Department of Medicine, University of California Los Angeles, 100 Medical Plaza, Los Angeles, CA 90095, USA (Prof G E Konecny MD); Institute of Cancer Sciences, University of Glasgow, 1053 Great Western Road, Glasgow, G12 0YN UK (Prof I A McNeish FCRP); Royal Melbourne Hospital, 300 Grattan Street, Parkville, Victoria, 3052, Australia (C L Scott PhD); Clovis Oncology, Inc., 5500 Flatiron Parkway, Boulder, CO 80301, USA (T Cameron MSc, L Maloney BA, J Isaacson PhD, S Goble MS, C Grace BSc, T C Harding PhD, M Raponi PhD, K K Lin PhD, H Giordano MA); Foundation Medicine, Inc., 150 Second St, Cambridge, MA, 02141, USA (J Sun PhD); UCL Cancer Institute and UCL Hospitals, 90 Tottenham Court Road, London W1T 4TJ, UK (Prof J A Ledermann MD)

*Joint lead clinical investigators.

†Members listed in the appendix.

Correspondence to: Dr Robert L Coleman, The University of Texas MD Anderson Cancer Center, 1155 Herman Pressler Dr., CPB6.3590 Houston, TX 77030, USA; Phone: 713 745 3357; Fax: 713 792 7586; rcoleman@mdanderson.org

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Summary

Background: Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has ~~demonstrated~~ anticancer activity in ~~patients with~~ recurrent ovarian carcinoma ~~that harbours~~harbouring a *BRCA* mutation or ~~has~~ a high percentage of genome-wide loss of heterozygosity (LOH). ARIEL3 evaluated rucaparib versus placebo following response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma.

Methods: ARIEL3 is an international, randomised, double-blind, phase 3 study performed at 87 hospitals and cancer centres ~~in which~~. Patients were randomised ~~patients~~2:1 to receive oral rucaparib 600 mg twice daily or placebo using a computer-generated sequence (block size of six). Patients, investigators, site staff, and study sponsor were blinded to assignments. The primary endpoint (investigator-assessed progression-free survival) was evaluated using an ordered step-down procedure for three nested cohorts: (1) *BRCA* mutant (carcinoma associated with deleterious germline or somatic *BRCA* mutation); (2) homologous recombination deficient (HRD) (*BRCA* mutant or *BRCA* wild type/LOH high); and (3) intent-to-treat population. ARIEL3 is registered with ClinicalTrials.gov, NCT01968213; enrolment is complete.

Findings: Between April 7, 2014, and July 19, 2016, 564 patients ~~(intent-to-treat population)~~ were randomised, 375 to rucaparib and 189 to placebo. Median progression-free survival in patients with a *BRCA*-mutant carcinoma (n=130, rucaparib; n=66, placebo) was 16·6 months versus 5·4 months (p<0·0001), respectively (hazard ratio [HR] 0·23; 95% confidence interval [CI] 0·16–0·34); in patients with an HRD carcinoma (n=236, rucaparib; n=118, placebo) it was 13·6 months versus 5·4 months

(p<0·0001), respectively (HR 0·32; 95% CI 0·24–0·42); and in the intent-to-treat population it was 10·8 months and 5·4 months (p<0·0001), respectively (HR 0·36; 95% CI 0·30–0·45). The most common grade 3 or higher ~~treatment-emergent~~ adverse events in the safety population (n=372, rucaparib; n=189, placebo) were anaemia/decreased haemoglobin (70 [19%], rucaparib; one [1%], placebo) and increased alanine ~~aminotransferase~~ or aspartate aminotransferase (39 [10%], rucaparib; none, placebo).

Interpretation: Across all primary analysis groups, rucaparib significantly improved progression-free survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy.

Funding: Clovis Oncology, Inc.

Research in context

Evidence before this study

Evidence of the clinical effectiveness of poly(ADP-ribose) polymerase (PARP) inhibitors as maintenance treatment for platinum-sensitive ovarian carcinoma is limited. In a search of PubMed (conducted July 31, 2017; search term: (“PARP inhibitor” OR rucaparib OR olaparib OR niraparib OR veliparib OR talazoparib) AND (ovarian AND (cancer OR carcinoma)) AND "maintenance"), we found that data have been published in a PubMed-indexed journal for only three clinical trials, Study 19 (NCT00753545), NOVA (NCT01847274), and SOLO2 (NCT01874353). Study 19, a randomised, placebo-controlled, phase 2 study, enrolled patients with platinum-sensitive ovarian carcinoma who had received at least two prior platinum-based chemotherapies. Progression-free survival was significantly improved with olaparib maintenance treatment in the overall population, as well as in patients with a germline or somatic *BRCA* mutation. Study 19 data were published prior to the commencement of ARIEL3 and supported the investigation of rucaparib as a maintenance treatment for patients with recurrent platinum-sensitive ovarian carcinoma in ARIEL3. In late 2016, results from the NOVA trial provided additional support for the role of a PARP inhibitor as maintenance treatment. In that randomised, placebo-controlled, phase 3 study, niraparib demonstrated a significant improvement in progression-free survival when used as a maintenance treatment in patients with ovarian carcinoma with or without a germline *BRCA* mutation who had received at least two prior platinum-based chemotherapies and had no measurable disease greater than 2 cm. Results from one other phase 3 study with olaparib maintenance treatment, SOLO2, were published in

July 2017. That randomised, placebo-controlled study enrolled patients with platinum-sensitive ovarian carcinoma who had received at least two prior platinum-based chemotherapies and carried a germline mutation in *BRCA*. Similar to the results seen in Study 19, progression-free survival was significantly improved with olaparib maintenance treatment in patients enrolled in SOLO2.

Added value of this study

ARIEL3 enrolled patients with or without a germline or somatic *BRCA* mutation, and the size of residual disease was not restricted. Our results show that rucaparib maintenance treatment significantly improved progression-free survival for patients across all primary analysis groups for patients with recurrent, platinum-sensitive ovarian carcinoma who achieved a response to platinum-based therapy, including in the intent-to-treat population. We demonstrate that rucaparib maintenance treatment can provide clinical benefit not only to patients with ovarian carcinoma associated with a *BRCA* mutation, but also to those with *BRCA* wild-type ovarian carcinoma. A novel aspect of the ARIEL3 trial was the prospective validation of the tumour-based, next-generation sequencing (NGS) homologous recombination deficiency (HRD) assay that was initially utilised in the phase 2 ARIEL2 study. This NGS assay combines mutation analysis of *BRCA1* and *BRCA2* genes with measurement of the percentage of genome-wide loss of heterozygosity (LOH) in the ~~carcinoma~~cancer tissue as a biomarker for sensitivity to rucaparib treatment. ARIEL2 enrolled patients with measurable, recurrent ovarian carcinoma, and provided initial evidence that patients with carcinomas with high LOH benefited from rucaparib treatment. The current study (ARIEL3) validated the utility of the HRD assay overall and LOH assessment in particular in the maintenance treatment

setting, where rucaparib-treated patients with carcinomas that were *BRCA* wild type/LOH high also had improvements in progression-free survival, with a lower hazard ratio than in patients with carcinomas that were *BRCA* wild type/LOH low.

Implications of all the available evidence

Combined with the evidence from prior studies, our study supports the use of PARP inhibitors, such as rucaparib, as maintenance treatment for patients with platinum-sensitive ovarian cancer who achieved a response to platinum-based chemotherapy~~, including patients who have bulky residual disease.~~. ARIEL3 is the first phase 3 study to prospectively assess progression-free survival in patients with recurrent ovarian carcinoma associated with HRD as a primary endpoint, and our results demonstrate that HRD as a predictive biomarker can be an informative tool for clinicians when making treatment decisions for this patient population. In addition to PARP inhibitors, the targeted agents bevacizumab and cediranib have proven useful in extending progression-free survival for patients in this setting. Our findings strengthen the rationale for continued investigation of targeted therapies, such as PARP inhibitors, for maintenance treatment as either monotherapy or in combination with other agents, in an effort to provide the best care for patients with advanced ovarian cancer.

Introduction

Ovarian cancer is the eighth leading cause of death from cancer in women worldwide.[1] Most patients with advanced stage ovarian carcinoma initially receive platinum-based chemotherapy and achieve a clinical response; however, the majority of these patients will ultimately relapse.[2] The treatment for initial recurrent disease depends on many factors, including duration of initial treatment response, antecedent and persistent adverse events, performance status, histology, location and burden of disease, and, increasingly, tumour genomics such as *BRCA* mutation status.[3] For patients with platinum-sensitive recurrent ovarian carcinoma, maintenance treatment with targeted agents has resulted in greater prolongation of progression-free survival.[4-9] However, clinical benefit is typically transient, hence there is an ongoing pursuit for new therapies and tools to identify patients who may benefit most from these therapies, as well as to identify the optimal therapeutic strategy for patients.

The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved in the United States for the treatment of patients with deleterious *BRCA* mutation (germline or somatic) associated advanced ovarian carcinoma who have been treated with two or more chemotherapy regimens. Approval of rucaparib was based on the objective response rate (~~54%, n=~~57 of 106~~)~~ patients [54%]) observed in a pooled population of patients with *BRCA*-mutant high-grade ovarian carcinoma from the Study 10 (CO-338-10; NCT01482715) and ARIEL2 (CO-338-017; NCT01891344) clinical trials.[10,11]

In Part 1 of the ARIEL2 trial, rucaparib treatment was found to be efficacious not only in patients with relapsed, platinum-sensitive, high-grade ovarian carcinoma with a *BRCA*

mutation, but also in patients with *BRCA* wild-type carcinomas with high genomic loss of heterozygosity (LOH),[11] a potential marker for homologous recombination deficiency (HRD) and thus PARP inhibitor activity.[12-15] In the current phase 3, randomised, placebo-controlled study (ARIEL3), our objective was to evaluate the efficacy and safety of rucaparib versus placebo following response to second-line or later platinum-based chemotherapy in patients with high-grade, platinum-sensitive ovarian carcinoma (including fallopian tube and primary peritoneal carcinomas) and to prospectively test the genomic LOH cutoff discriminator that was optimised based on results of ARIEL2 Part 1 as a predictive biomarker for sensitivity to rucaparib treatment.

Methods

Study design and patients

ARIEL3 (NCT01968213) was a phase 3, international, randomised, placebo-controlled study conducted at 87 hospitals and cancer centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, United Kingdom, and the United States. The trial 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. Per the protocol, an independent data monitoring committee monitored enrolment and reviewed the safety and efficacy of the trial ~~at regular intervals~~approximately every 6 months, including maturity of progression-free survival events.

Eligible patients were aged 18 years or older, had platinum-sensitive (ie, documented radiologic disease progression more than 6 months following the last dose of the penultimate platinum administered), high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma ~~,~~ and had received at least two prior platinum-based chemotherapy regimens. Prior treatment with bevacizumab was permitted, with the exception of bevacizumab maintenance treatment following the most recent platinum-based regimen. On November 4, 2014, after 91 patients had been randomised, an amendment was ~~added~~made 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. Patients must have achieved either a complete response by Response Evaluation Criteria In Solid Tumors version 1·1 (RECIST)[~~16~~16] or a partial response, defined as either a RECIST partial response or a serologic response per Gynecologic Cancer InterGroup (GCIG) cancer antigen 125 (CA-125)[17] response criteria, to their last platinum-based regimen. For patients who achieved a partial response, no restriction was placed on residual carcinoma size at study entry; those who had persistent lesions greater than 2 cm as defined by independent radiological review were defined as having "bulky" residual disease. Responses must have been maintained through the completion of chemotherapy and during the interval period between completion of chemotherapy and entry into ARIEL3. Additionally, CA-125 was required to be less than the upper limit of normal. Patients had Eastern Cooperative Oncology Group Performance Status of 0 to 1 and adequate organ function. Patients were ineligible if they had symptomatic/untreated central nervous system metastases, had received anticancer therapy 14 or fewer days before starting the study, or had

received prior treatment with a PARP inhibitor. A complete list of inclusion and exclusion criteria is provided in the appendix (p 6), and the full study protocol is available in the appendix.

Central testing of DNA derived from patient archival tumour tissue samples was performed to detect mutations in homologous recombination pathway genes (appendix p 8) and assess genomic LOH using Foundation Medicine's T5 NGS assay (Cambridge, MA). Based on retrospective analysis of data from ARIEL2 Part 1, a cutoff of 16% or greater ~~for high genomic LOH~~ was prespecified for ARIEL3 as a discriminator for high genomic LOH.[11] Germline mutations were identified by BRCAnalysis CDx test (Myriad Genetics, Salt Lake City, UT). Further details of the tumour tissue testing are provided in the appendix (p 2).

Randomisation and masking

Within 8 weeks of their last dose of platinum, eligible patients were randomised 2:1 to receive oral rucaparib (600 mg twice daily) or matched placebo. Randomisation was computer-generated by Almac Clinical Technologies (Souderton, PA) using a block size of six. Randomisation stratification factors included: homologous recombination repair gene mutation status (based on gene mutation only); progression-free interval following penultimate platinum-based regimen; and best response to most recent platinum-based regimen (additional details in the appendix p 3). Patients were assigned to the rucaparib arm or placebo arm in a blinded manner using Almac Clinical Technologies' interactive web and voice response system (IXRS®); patients, investigators, site staff, and the study sponsor were blinded to assignments. To ensure blinding was maintained, rucaparib and placebo tablets were manufactured to have identical appearances.

Procedures

Patients received study drug in continuous 28-day cycles until disease progression, death, or other reason for discontinuation. Dose reductions (in decrements of 120 mg) were permitted if a patient had a grade 3 or greater or persistent grade 2 adverse event (additional details in the appendix p 3). Treatment was discontinued for a toxicity-related treatment interruption lasting more than 14 consecutive days (unless otherwise agreed upon between the investigator and the study sponsor).

Disease assessments were performed at screening, every 12 weeks during treatment (and post-treatment for patients who discontinued for any reason other than disease progression), at discontinuation of treatment, and as clinically indicated. Disease progression was determined by RECIST. Patients with a complete response at study entry were only considered to have disease progression if an unequivocal new lesion was identified. Increased CA-125 levels alone were not considered to indicate disease progression unless confirmed by RECIST. All computed tomography scans and other imaging were provided to a blinded, independent central radiology review (BICR).

The National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy Ovarian Symptom Index 18 (FOSI-18)[18] questionnaire was used to assess patient-reported outcomes at screening and throughout treatment. Safety was assessed by monitoring for adverse events, laboratory testing, assessing vital signs and conducting physical examinations. Adverse events were classified in accordance with the Medical Dictionary for Drug Regulatory Activities classification system version 18·1[19] and graded for severity in accordance with the National Cancer Institute Common

Terminology Criteria for Adverse Events version 4·03.[2020] Serious adverse events were classified as defined in the protocol (see appendix).

Outcomes

The primary endpoint was investigator-assessed progression-free survival, defined as time from randomisation to investigator-assessed disease progression per RECIST or death. Secondary endpoints included progression-free survival by BICR, patient-reported outcomes as evaluated by time to worsening in the FOSI-18 disease-related symptoms–physical (DRS-P) subscale (defined as ≥4-point decrease) and total score (defined as ≥8-point decrease), overall survival, safety, and population pharmacokinetic modelling. Additional details are available in the appendix (p 3). The secondary endpoint of population pharmacokinetic modelling will be reported separately.

Statistical analysis

ARIEL3 was designed to enrol approximately 540 patients, including between 180 and 200 patients with a *BRCA* mutation in their carcinoma (with no more than 150 patients with a known deleterious germline *BRCA* mutation) and no more than 360 patients without a *BRCA* mutation in their carcinoma. The independent data monitoring committee surveyed enrolment of patients with a *BRCA* mutation and informed the study sponsor (Clovis Oncology, Inc.) when the target enrolment number for the *BRCA*-mutant cohort was anticipated to be reached. Once notified, patients who were in the screening process were allowed to complete screening and enrol into the study if they met all eligibility criteria. These subgroup sizes were designed to result in 90% power to determine statistical significance between rucaparib and placebo at a one-sided alpha

level of 0·025 given the following assumptions for median investigator-assessed progression-free survival for the efficacy analysis cohorts: *BRCA* mutant (carcinoma associated with a deleterious germline or somatic *BRCA* mutation), 12·0 months in the rucaparib arm versus 6·0 months in the placebo arm (hazard ratio [HR] 0·5); HRD (includes patients with a *BRCA*-mutated carcinoma and patients with *BRCA* wild-type/LOH-high carcinomas), 10·0 versus 6·0 months (HR 0·6); and intent-to-treat population (all randomised patients), 8·5 versus 6·0 months (HR 0·7).

Classification of HRD status in the carcinoma (based on *BRCA* mutation and/or LOH) for the efficacy analysis was determined before database lock and the final efficacy analysis. Per protocol, the primary analysis was to be performed after the independent data monitoring committee determined that investigator-assessed disease progression or death had occurred in at least 70% of expected patients in the *BRCA*-mutant cohort.

All efficacy analyses were performed for the intent-to-treat population. The efficacy analyses are presented separately for the nested cohorts: *BRCA* mutant, HRD, and intent-to-treat population. The primary endpoint was tested using an ordered step-down multiple comparisons procedure[~~21,22~~21] for the three nested cohorts: *BRCA* mutant, HRD, and the intent-to-treat population. Investigator-assessed progression-free survival in patients with a *BRCA*-mutant carcinoma was tested first at a one-sided 0·025 significance level. Analysis of investigator-assessed progression-free survival in patients with an HRD carcinoma followed by analysis in the intent-to-treat population was contingent upon a statistically significant result in the analysis of patients with a *BRCA*-mutant carcinoma. Analysis of the key secondary endpoints of patient-reported outcomes and overall survival were to follow in a similar ordered step-down procedure.

Once statistical significance was not achieved for one test, the statistical significance was not declared for all subsequent analyses in the ordered step-down procedure. Progression-free survival by BICR was evaluated as a key stand-alone secondary endpoint, separate from the step-down procedure described above. Time to progression-free survival (by investigator and by BICR) and time to worsening in the FOSI-18 DRS-P subscale were analysed using stratified Kaplan-Meier methodology where distributions between rucaparib and placebo arms were compared using a stratified log-rank test. A stratified Cox proportional hazards model was used to estimate the HR between the arms. Exploratory analyses of progression-free survival were performed in subgroups based on patient characteristics (eg, randomisation stratification factors, demographics, disease burden at baseline). For patients with measurable disease at study entry, the proportion of patients achieving a confirmed complete or partial response per RECIST as assessed by the investigator was ~~an~~a prespecified exploratory endpoint of ARIEL3.

Safety, including adverse events and clinical laboratory investigations, was evaluated in all patients who received at least one dose of protocol-specified treatment.

Statistical analyses were performed using SAS version 9·4 (SAS Institute, Cary, NC). Additional details are available in the appendix (p 4).

Role of the funding source

The study was designed by the sponsor, Clovis Oncology, Inc., and the coordinating investigators (RLC and JAL). Data presented herein were collected by the investigators, analysed by Clovis Oncology, and interpreted by all authors. All authors had access to

the data and had final responsibility for the decision to submit for publication. Writing and editorial assistance were supported by the sponsor.

Results

Between April 7, 2014, and July 19, 2016, 564 patients (intent-to-treat population) were randomised, 375 to rucaparib and 189 to placebo (figure 1; appendix p 11). At the visit cutoff date (April 15, 2017), 90 (24%) and 9 (5%) patients in the rucaparib and placebo arms, respectively, were still receiving treatment. Baseline demographic and clinical characteristics were generally well balanced between the treatment arms (table 1).

Following the ordered step-down multiple comparisons procedure, the analysis of investigator-assessed progression-free survival was evaluated first in patients with a *BRCA*-mutant carcinoma (130, rucaparib; 66, placebo; appendix p 11). Median time to progression or death was 16·6 months versus 5·4 months (stratified log-rank p<0·0001) in the rucaparib and placebo arms, respectively (HR 0·23; 95% confidence interval [CI] 0·16–0·34; p<0·0001) (figure 2). In patients with an HRD carcinoma (236, rucaparib; 118, placebo), median progression-free survival was 13·6 months and 5·4 months (stratified log-rank p<0·0001), respectively (HR 0·32; 95% CI 0·24–0·42; p<0·0001). Median progression-free survival in the intent-to-treat population was 10·8 months and 5·4 months (stratified log-rank p<0·0001), respectively (HR 0·36; 95% CI 0·30–0·45; p<0·0001).

In a prespecified analysis of the key stand-alone, secondary endpoint of progression-free survival assessed by BICR, results were similar to those of investigator-assessed progression-free survival for the patients with a *BRCA*-mutant carcinoma (median 26·8 months *vs* 5·4 months; HR 0·20; 95% CI 0·13–0·32; p<0·0001), the patients with an HRD carcinoma (median 22·9 months *vs* 5·5 months; HR 0·34; 95% CI 0·24–0·47; p<0·0001), and the intent-to-treat population (median 13·7 months *vs* 5·4 months; HR 0·35; 95% CI 0·28–0·45; p<0·0001) (figure 2).

Analysis of the secondary endpoint of time to worsening in the FOSI-18 DRS-P subscale score was assessed in the step-down procedure for the three nested subgroups. In patients with a *BRCA*-mutant carcinoma, there was no significant difference between arms in the time to worsening in the FOSI-18 DRS-P subscale (stratified log-rank p=0·29) (HR 1·24; 95% CI 0·82–1·86; p=0·30). As statistical significance was not reached in patients with a *BRCA*-mutant carcinoma, in accordance with the prespecified step-down procedure, statistical significance could not be determined for the remaining secondary analyses.

At the visit cutoff date (April 15, 2017), overall survival data were not mature (123 [~~21·8~~22%] patients had died). A follow-up analysis will be performed when approximately 70% of the patients have died~~.~~ (≈395 overall survival events).

Preplanned subgroup analyses of investigator-assessed progression-free survival demonstrated that the progression-free survival benefit for rucaparib versus placebo was observed across all clinical subgroups, irrespective of presence or absence of measurable disease or bulky disease (defined as any lesion >2 cm) at baseline,

response to last platinum-based regimen (complete or partial response), LOH (high, low, or indeterminate), or *BRCA* mutation (germline or somatic; *BRCA1* or *BRCA2*) (figure 3; appendix p 12). Further supporting the efficacy observed in the intent-to-treat population, in the non-nested subgroups of patients with carcinomas that were *BRCA* wild type, a progression-free survival benefit as assessed by the investigator was observed with rucaparib in patients with LOH-high carcinomas (median 9·7 months *vs* 5·4 months; HR 0·44; 95% CI 0·29–0·66; p<0·0001) and patients with LOH-low carcinomas (median 6·7 months *vs* 5·4 months; HR 0·58; 95% CI 0·40–0·85; p=0·0049) (figure 4); similar results were also observed in progression-free survival assessed by BICR (appendix p 13).

The majority of patients (374 [66%]) in ARIEL3 had achieved a partial response to the platinum-based therapy prior to randomisation. For 207 (37%) of 564 patients with measurable disease per investigator at study entry, a prespecified exploratory analysis of confirmed response was conducted. In the subgroup of patients with measurable disease at study entry with a *BRCA*-mutant carcinoma, 15 (38%) of 40 in the rucaparib arm and two (9%) of 23 in the placebo arm achieved a confirmed RECIST response (appendix p 8). In patients with an HRD carcinoma with measurable disease at baseline, the objective response was also higher in the rucaparib arm (23 [27%] of 85 patients) than the placebo arm (3 [7%] of 41 patients). A similar result was observed in the intent-to-treat population among patients with measurable disease at baseline (26 [18%] of 141 patients in the rucaparib arm; 5 [8%] of 66 patients in the placebo arm). Complete responses were observed in the rucaparib arm in seven (18%), 10 (12%), and 10 (7%) patients with measurable disease at baseline in the nested *BRCA*-mutant and

HRD cohorts, and the overall intent-to-treat population, respectively. Only one (2%) complete response was observed in the placebo arm; this occurred in the intent-to-treat population.

The safety population included 372 patients who received rucaparib (three patients were withdrawn prior to receiving rucaparib) and 189 patients who received placebo. For the safety population, the median (interquartile range) treatment duration was 8·3 (3·4–16·1) months in the rucaparib arm and 5·5 (2·8–8·3) months in the placebo arm. A treatment-emergent adverse event of any grade occurred in 372 patients (100%) in the rucaparib arm and 182 patients (96%) in the placebo arm (table 2). The most common treatment-emergent adverse events (reported in at least 35% of patients in either arm) included nausea (280 patients [75%] in the rucaparib arm and 69 patients [37%] in the placebo arm), asthenia or fatigue (258 patients [69%] and 83 patients [44%]), dysgeusia (146 patients [39%] and 13 patients [7%]), anaemia/decreased haemoglobin (139 patients [37%] and 11 patients [6%]), constipation (136 patients [37%] and 45 patients [24%]), and vomiting (136 patients [37%] and 28 patients [15%]). Treatment-emergent adverse events of grade 3 or greater were reported in 209 patients (56%) in the rucaparib arm and 28 patients (15%) in the placebo arm, the most common of which were anaemia/decreased haemoglobin (70 patients [19%] and one patient [1%]) and increase in alanine aminotransferase or aspartate aminotransferase (39 patients [10%] and no patients). For patients in the rucaparib arm, a decline in haemoglobin level from baseline generally occurred in the first few cycles (appendix p 14). Elevations in alanine aminotransferase or aspartate aminotransferase were generally transient, self-limiting,

and not associated with other signs of liver toxicity (appendix p 15). The frequency of treatment-emergent adverse events was comparable across the three nested cohorts.

One or more serious adverse events were reported in 78 patients (21%) in the rucaparib arm and 20 patients (11%) in the placebo arm. The most common serious adverse events (reported in at least 2% of patients in either arm) included anaemia (16 patients [4%] in the rucaparib arm and one patient [1%] in the placebo arm), pyrexia (six patients [2%] and no patients), vomiting (six patients [2%] and two patients [1%]), and small intestinal obstruction (three patients [1%] and three patients [2%]).

Myelodysplastic syndrome and acute myeloid leukaemia were reported in three patients (1%) in the rucaparib arm (two had a germline *BRCA*-mutant carcinoma, and one had a *BRCA* wild-type/LOH-low carcinoma). One patient died due to myelodysplastic syndrome and one due to acute myeloid leukaemia. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia in the placebo arm.

Treatment interruption due to a treatment-emergent adverse event occurred in 237 (64%) and 19 (10%) patients in the rucaparib and placebo arms, respectively (appendix p 9). Dose reduction due to a treatment-emergent adverse event occurred in 203 (55%) and eight (4%) patients in the rucaparib and placebo arms, respectively (appendix p 9). In the rucaparib and placebo arms, 117 (31%) and six (3%) patients, respectively, had both a treatment interruption due to a treatment-emergent adverse event and a dose reduction due to a treatment-emergent adverse event. Of patients who received rucaparib, 50 (13%) discontinued due to a treatment-emergent adverse event (excluding disease progression) compared with three (2%) ~~of~~ patients in the placebo

arm (appendix p 10). As of the visit cutoff date, in the rucaparib arm there were four deaths due to adverse events considered unrelated to treatment by the investigator (two patients due to progressive disease, one due to cardiac arrest, and one due to haematophagic histiocytosis) and two deaths considered treatment related by the investigator (one due to acute myeloid leukaemia and one due to myelodysplastic syndrome). In the placebo arm, two patients died due to adverse events considered unrelated to treatment by the investigator (one due to progressive disease and one due to pulmonary embolism).

Discussion

In ARIEL3, rucaparib maintenance treatment versus placebo significantly improved progression-free survival in all primary analysis groups of patients with recurrent ovarian carcinoma following a complete or partial response to platinum-based therapy. The ~~63% reduction in risk of disease~~prolonged progression~~ or death observed~~-free survival among patients receiving rucaparib in the intent-to-treat population (HR 0·36) demonstrates that patients with platinum-sensitive ovarian carcinoma can derive robust clinical benefit from rucaparib maintenance treatment. A similar ~~reduction (65%) in risk of disease progression or death~~improvement over placebo (HR 0·35) was seen in the secondary endpoint of assessment by BICR review, supporting the validity of the benefit observed with rucaparib maintenance treatment. Furthermore, the lower ~~risk~~hazard of disease progression or death associated with rucaparib in the study was observed across all prespecified subgroups that were analysed. Analysis of non-nested, non-

overlapping patient subpopulations (ie, *BRCA* wild-type/LOH-high and *BRCA* wild-type/LOH-low patients) indicate that the statistically significant improvement in progression-free survival observed in the intent-to-treat population was not driven only by the results in the nested HRD or *BRCA*-mutant cohorts.

Patient-reported outcomes were evaluated as a secondary endpoint of ARIEL3 as part of the step-down procedure, with no significant difference in time to worsening in the FOSI-18 DRS-P subscale observed between the rucaparib and placebo arms. Further analyses of the patient-reported health outcome data gathered in ARIEL3 are planned and will be reported separately.

Overall survival data were not mature at the time of the visit cutoff, with less than 25% of the events needed for final analysis. Patient follow-up is continuing in a blinded manner and overall survival will be assessed after about 70% maturity is reached.

As reported in prior studies of rucaparib and other PARP inhibitors,[5,6,9-11,~~23~~] gastrointestinal side effects, asthenia or fatigue, and myelosuppression were common treatment-emergent adverse events in the rucaparib arm. Management of adverse events included supportive care and dose modifications (including treatment interruption and/or dose reduction). Common laboratory abnormalities observed in the rucaparib arm included elevations in alanine aminotransferase, aspartate aminotransferase, and blood creatinine. Alanine aminotransferase and aspartate aminotransferase were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity, and generally resolved over time. ~~No cases of Hy's law were observed.~~No cases were considered to meet Hy's law criteria for drug-induced liver injury (ie, alanine aminotransferase or aspartate aminotransferase greater than 3 times

the upper limit of normal with concomitant bilirubin greater than 2 times the upper limit of normal without alkaline phosphatase elevations or another clear reason for the elevations).[22,23] Similarly, elevations in creatinine, which have also been observed with olaparib,[24] were self-limiting and stabilised over time. Creatinine is secreted into urine via renal transporters (eg, MATE1, MATE2-K, OCT-1, and OCT-2), which have been shown to be inhibited in vitro by multiple PARP inhibitors, including rucaparib, olaparib, and veliparib.[25-27] Patterns of elevation and stabilisation of these laboratory abnormalities similar to those reported here were observed in the treatment setting with rucaparib.[28,29]

The results of ARIEL3 are consistent with those of other placebo-controlled studies of PARP inhibitors in the maintenance treatment setting, including NOVA (NCT01847274) with niraparib and Study 19 (NCT00753545) and SOLO2 (NCT01874353) with olaparib.[5,6,9] However, direct comparisons with these other trials cannot be made due to differences in patient groups analysed (eg, SOLO2 only enrolled patients with a germline *BRCA* mutation), definition of HRD (eg, in NOVA, HRD included patients with somatic mutations in *BRCA*, as well as those with non-*BRCA*–related HRD), the method of primary endpoint assessment (eg, investigator *vs* BICR), and study design (eg, residual disease was restricted to <2 cm in NOVA).[5,6,9,30]

Although having a CA-125 below the upper limit of normal is not a requirement of response per GCIG CA-125 criteria or a RECIST partial response, ARIEL3 required that patients have CA-125 below the upper limit of normal prior to study entry; this eligibility requirement was intended to ensure that patients had controlled disease at study entry. Similar restrictions on CA-125 levels were included in the enrolment criteria of other

studies investigating PARP inhibitors in the maintenance treatment setting, although it is unknown how many patients in these studies had CA-125 levels greater than the upper limit of normal at study entry.[5,6,9] Furthermore, it is not known whether inclusion of patients with CA-125 levels exceeding the upper limit of normal affects the efficacy of PARP inhibitors in the maintenance treatment setting.

Although ARIEL3 extends the findings of previous studies of PARP inhibitors in this setting, there are some important differences between ARIEL3 and other studies in the maintenance treatment setting. Notably, patients in ARIEL3 with carcinomas associated with a germline or somatic *BRCA* mutation were both included in the three nested cohorts (*BRCA* mutant, HRD, and intent-to-treat population), a feature that is unique to ARIEL3 among clinical trials in this setting. In addition, ARIEL3 did not restrict enrolment based on target lesion size for patients with residual disease (partial response to prior platinum). A number of patients with measurable residual disease at study entry showed further reduction in carcinoma burden with rucaparib maintenance treatment, including conversion to a complete response per RECIST~~.~~ in several patients in the nested *BRCA*-mutant and HRD cohorts and the overall intent-to-treat population.

Additionally, ARIEL3 is the first phase 3 study to prospectively assess the primary endpoint of progression-free survival in patients with recurrent ovarian carcinoma associated with HRD. Preplanned analysis of progression-free survival in patients with a *BRCA* wild-type/LOH-high carcinoma, wherein patients treated with rucaparib had ~~a 56% decrease~~an increase in ~~risk of disease~~median progression ~~or death~~-free survival (HR 0·44) compared with placebo, shows that the improvement observed in the HRD cohort was not driven solely by patients with a *BRCA*-mutant carcinoma. The ~~lower risk~~

~~of disease~~benefit in progression ~~or death~~ free survival seen in patients with a *BRCA* wild-type/LOH-high carcinoma (HR 0·44) compared with patients with a *BRCA* wild-type/LOH-low carcinoma (HR 0·58) demonstrates the utility of HRD, in particular high genomic LOH as defined by Foundation Medicine's T5 assay, as a predictive biomarker for sensitivity to rucaparib treatment. Based on our findings, HRD assessment may be an informative tool for clinicians making treatment decisions for patients with *BRCA* wild-type associated platinum-sensitive ovarian carcinoma. However, response to rucaparib was also clearly observed in the cohort of patients with carcinomas that were *BRCA* wild type/LOH low, with more than 30% of patients in the rucaparib arm achieving benefit of more than a year's duration compared with less than 10% in the placebo arm. Therefore, the biomarker does not appear to be sufficiently precise to predict lack of benefit on an individual basis.

In summary, rucaparib improved progression-free survival in women with platinum-sensitive ovarian carcinoma following a complete or partial response to second-line or later platinum-based chemotherapy. Treatment-emergent adverse events in the rucaparib arm were generally managed with dose modifications and were not associated with increased mortality or morbidity compared with the placebo arm.

Contributors

RLC, JI, KKL, HG, and JAL were responsible for the study design. RLC, AMO, DL, CA, AO, AD, NC, JIW, AC, GS, AL, RWH, MAG, PCF, JCG, DMO, DKA, JGD, EMS, AF, GEK, IAM, CLS, and JAL treated patients. RLC, AMO, DL, CA, AO, AD, NC, JIW, AC, GS, CA, AL, RWH, MAG, PCF, JCG, DMO, DKA, JGD, EMS, AF, GEK, IAM, CLS, KKL,

and JAL acquired the data. RLC, TC, LM, JI, SG, CG, TCH, MR, JS, KKL, HG, and JAL interpreted the data. All authors were responsible for writing the manuscript, and reviewed draft and final versions of the manuscript.

Declaration of interests

RLC reports grants from AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, ~~Esperance, and AbbVie.~~Merck, Clovis Oncology, Esperance, and AbbVie, and reports serving as an advisor to AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, Merck, Clovis Oncology, Esperance, Tesaro, GamaMabs, Pfizer, Genmab, Gradalis, Bayer, and AbbVie. AMO has served on advisory boards for Amgen, Verastem, Clovis Oncology, and Immunovaccine; has received support for travel and/or accommodation from AstraZeneca; and has received honoraria from WebRx. DL has served in a consulting or advisory role for AstraZeneca, Clovis Oncology, Roche, Tesaro~~:~~, and PharmaMar; and has received support for travel and/or accommodation from Roche and PharmaMar. CA served on a steering committee for Mateon Therapeutics; and has served on advisory boards for Clovis Oncology, Cerulean Pharma, Bayer, VentiRx, and AstraZeneca. AO has served on advisory boards for Roche, AstraZeneca, PharmaMar, Clovis Oncology, and Tesaro; and has received support for travel and/or accommodation from Roche, AstraZeneca, and PharmaMar. NC has served in a consulting or advisory role for Roche, AstraZeneca, Tesaro, PharmaMar, Clovis Oncology, and Advaxis. JIW has received research support from Abbvie and AstraZeneca; and has served on advisory boards for AstraZeneca. AC has served on advisory boards for AstraZeneca and Roche; and has received research

support from AstraZeneca. AL has served on an advisory board for Clovis Oncology, Pfizer, and PharmaMar; ~~and~~ reports institutional research grant support from GamaMabs and Merus; and reports boarding and travel expenses for congress activities from AstraZeneca. RWH has served on a speakers bureau for AstraZeneca, Clovis Oncology, and Tesaro. PCF has served on advisory boards for Clovis Oncology and AstraZeneca; and has received honoraria from AstraZeneca. JCG has served on advisory boards for Roche, AstraZeneca, Janssen, Merck, and Bristol-Myers Squibb; and has received support for travel and/or accommodation from Roche, Bristol-Myers Squibb, and Astellas. DMO received research funding from Clovis Oncology; received institutional research support from AMGEN, VentiRx, Regeneron, Immunogen, Array Biopharma, Janssen R&D, Clovis Oncology, EMD Serono, Ergomed, Ajinomoto, and Genentech/Roche; and served on a steering committee, advisory boards and/or consulting for Amgen, AstraZeneca, Janssen, Clovis Oncology, Tesaro, Novocure, Genentech/Roche, and Eisai. JGD has received research funding from AstraZeneca; and has served on advisory boards for Janssen, Clovis Oncology, and Genentech/Roche. AF has served on advisory boards for AstraZeneca, Roche, and Tesaro. IAM has served on advisory boards for Clovis Oncology, Tesaro, and AstraZeneca. CLS has served in a consulting or advisory role for AstraZeneca, Clovis Oncology, Roche, and Eisai Australia; has received support for travel and/or accommodation from AstraZeneca, Clovis Oncology, and Roche; has received drug for research from Eisai Australia; and CLS' institution received in kind research support for parallel laboratory work using rucaparib. TC, LM, JI, SG, CG, TCH, KKL, and HG are employees of Clovis Oncology; MR was employed at Clovis Oncology at the time of the

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Figure legends

Figure 1: **CONSORT diagram**

*A full description of protocol deviations is provided in the appendix (p 5); these protocol deviations are reported as of the visit cutoff date (April 15, 2017) and did not result in the exclusion of patients or data from any efficacy or safety analyses in the study.

Figure 2: **Investigator-assessed and blinded independent central radiology review–assessed progression-free survival**

Kaplan-Meier estimates of progression-free survival as assessed by the investigator (A–C) and by BICR (D–F) in the rucaparib (blue) and placebo (red) arms for patients with a *BRCA*-mutant carcinoma (A, D), patients with an HRD carcinoma (B, E), and the intent-to-treat population (C, F). BICR=blinded independent central radiology review. CI=confidence interval. HR=hazard ratio. HRD=homologous recombination deficient. NR=not reached.

Figure 3: **Investigator-assessed progression-free survival in subgroups of the intent-to-treat population**

CA-125=cancer antigen 125. CI=confidence interval. CR=complete response. GCIG=Gynecologic Cancer InterGroup. HR=hazard ratio. LOH=loss of heterozygosity. PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors version 1·1. *By local germline test, central germline test, or tumour testing. †Tumour sample was not evaluable for percent of genomic LOH due to low tumour content or low

aneuploidy. ‡Prior treatment with bevacizumab was permitted as part of penultimate or earlier treatment.

Figure 4: **Investigator-assessed progression-free survival in patients with a *BRCA* wild-type carcinoma**

Kaplan-Meier estimates of progression-free survival as assessed by the investigator in the rucaparib (blue) and placebo (red) arms for patients with a *BRCA* wild-type carcinoma with LOH high (A) and LOH low (B). CI=confidence interval. HR=hazard ratio. LOH=loss of heterozygosity.

Figure 1

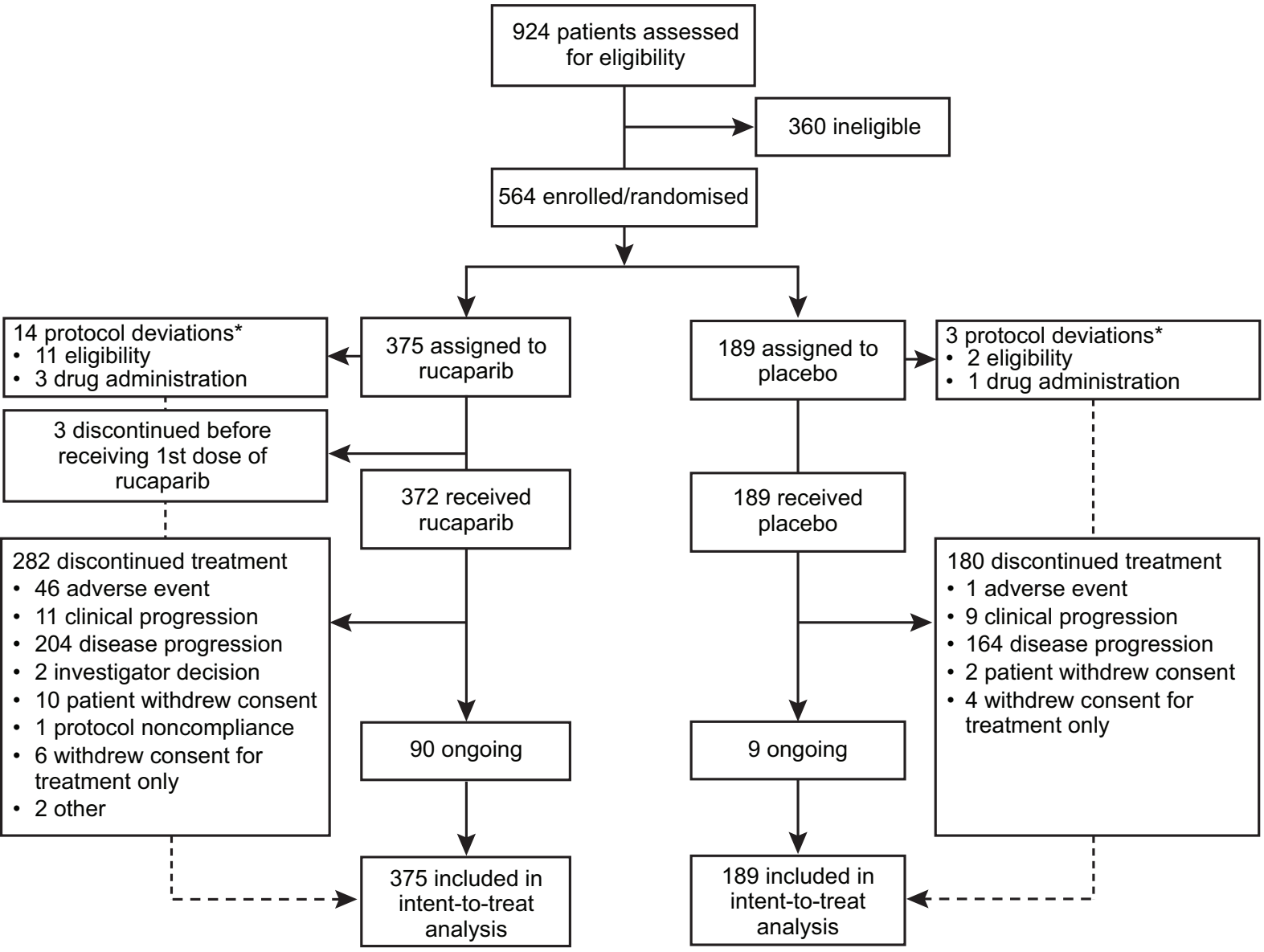
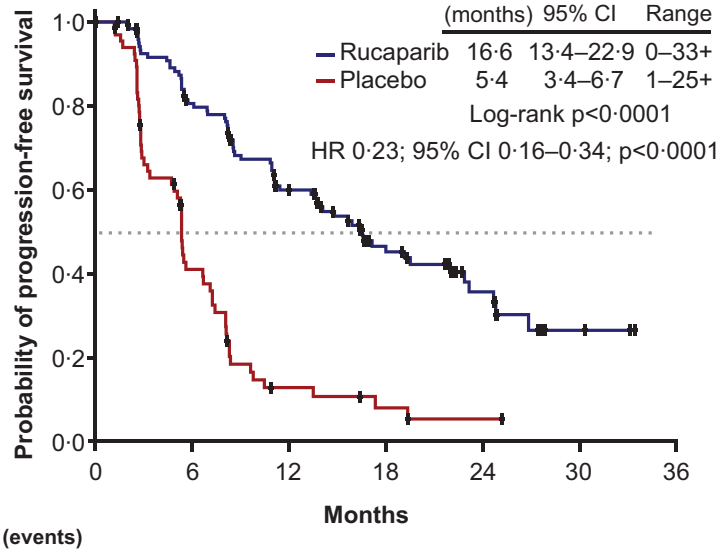

924 patients assessed for eligibility
360 ineligible
564 enrolled/randomised
14 protocol deviations*
• 11 eligibility
• 3 drug administration
375 assigned to rucaparib
189 assigned to placebo
3 protocol deviations*
• 2 eligibility
• 1 drug administration
3 discontinued before receiving 1st dose of rucaparib
372 received rucaparib
189 received placebo
282 discontinued treatment
• 46 adverse event
• 11 clinical progression
• 204 disease progression
• 2 investigator decision
• 10 patient withdrew consent
• 1 protocol noncompliance
• 6 withdrew consent for treatment only
• 2 other
180 discontinued treatment
• 1 adverse event
• 9 clinical progression
• 164 disease progression
• 2 patient withdrew consent
• 4 withdrew consent for treatment only
90 ongoing
9 ongoing
375 included in intent-to-treat analysis
189 included in intent-to-treat analysis

Figure 2

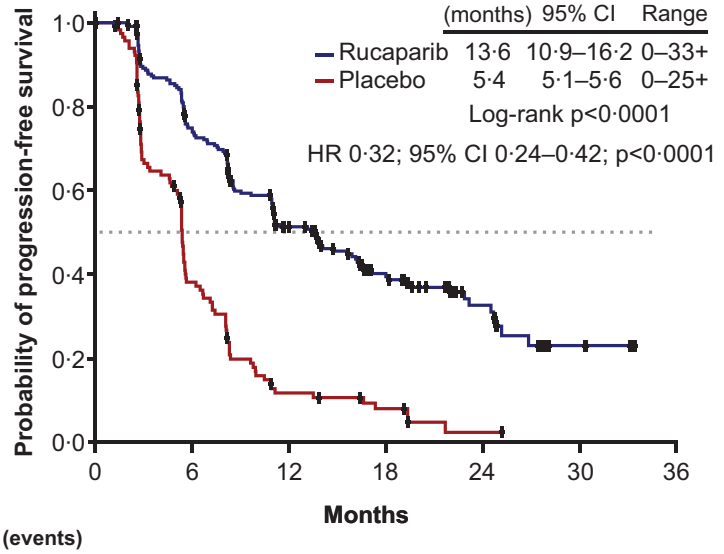
A



At risk (events)

Rucaparib	130 (0)	93 (23)	63 (46)	35 (58)	15 (64)	3 (67)	0 (67)
Placebo	66 (0)	24 (37)	6 (53)	3 (55)	1 (56)	0 (56)	

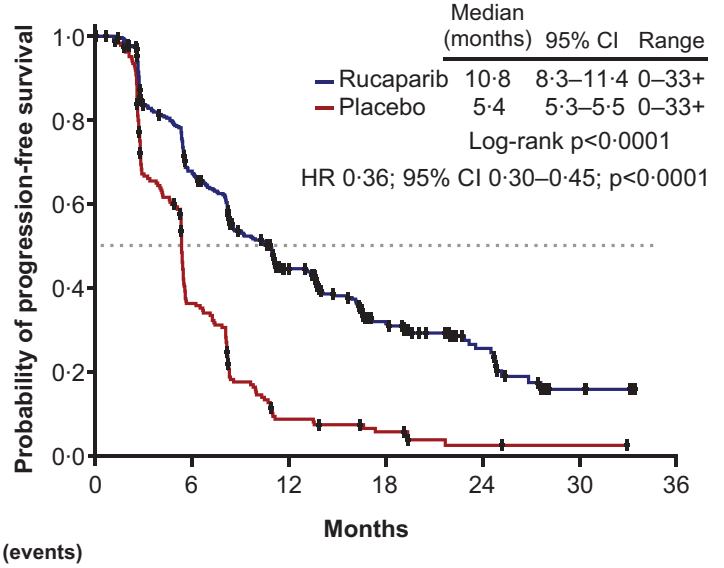
B



At risk (events)

Rucaparib	236 (0)	161 (55)	96 (104)	54 (122)	21 (129)	5 (134)	0 (134)
Placebo	118 (0)	40 (68)	11 (95)	6 (98)	1 (101)	0 (101)	

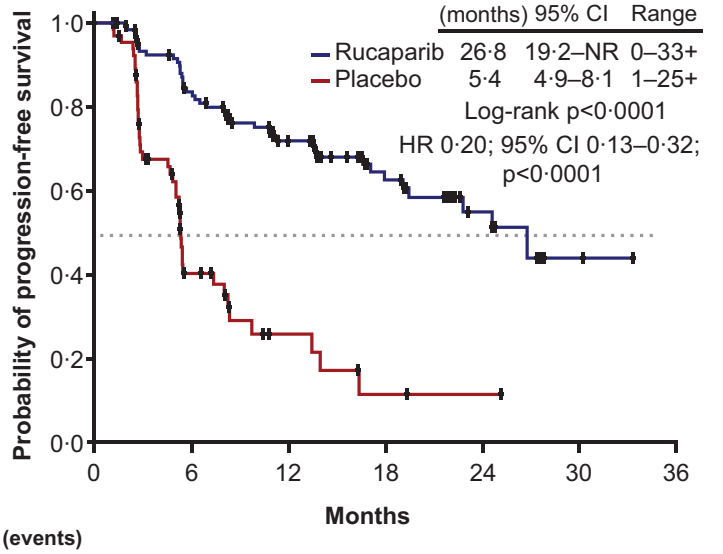
C



At risk (events)

Rucaparib	375 (0)	228 (111)	128 (186)	65 (217)	26 (226)	5 (234)	0 (234)
Placebo	189 (0)	63 (114)	13 (160)	7 (164)	2 (167)	1 (167)	0 (167)

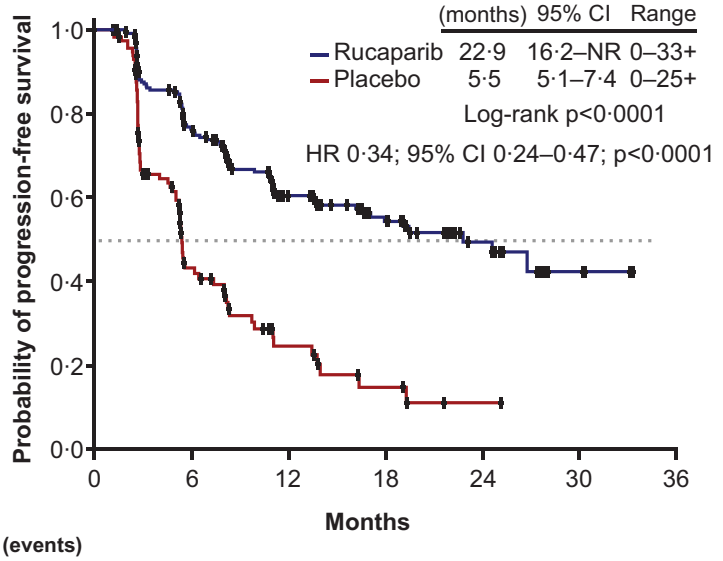
D



At risk (events)

Rucaparib	130 (0)	93 (19)	62 (31)	35 (36)	15 (40)	2 (42)	0 (42)
Placebo	66 (0)	18 (34)	6 (39)	2 (42)	1 (42)	0 (42)	

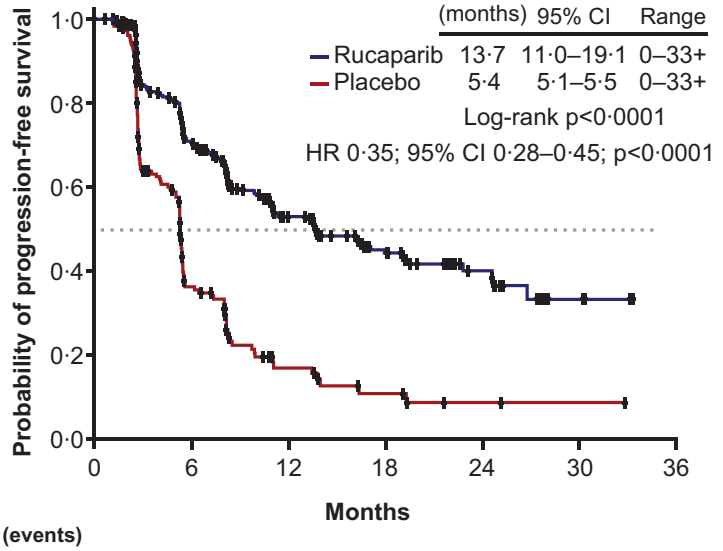
E



At risk (events)

Rucaparib	236 (0)	152 (49)	87 (78)	53 (84)	21 (88)	4 (90)	0 (90)
Placebo	118 (0)	34 (57)	12 (69)	5 (73)	1 (74)	0 (74)	

F



At risk (events)

Rucaparib	375 (0)	213 (95)	114 (143)	60 (157)	24 (162)	4 (165)	0 (165)
Placebo	189 (0)	50 (106)	13 (128)	6 (132)	2 (133)	1 (133)	0 (133)

Figure 3

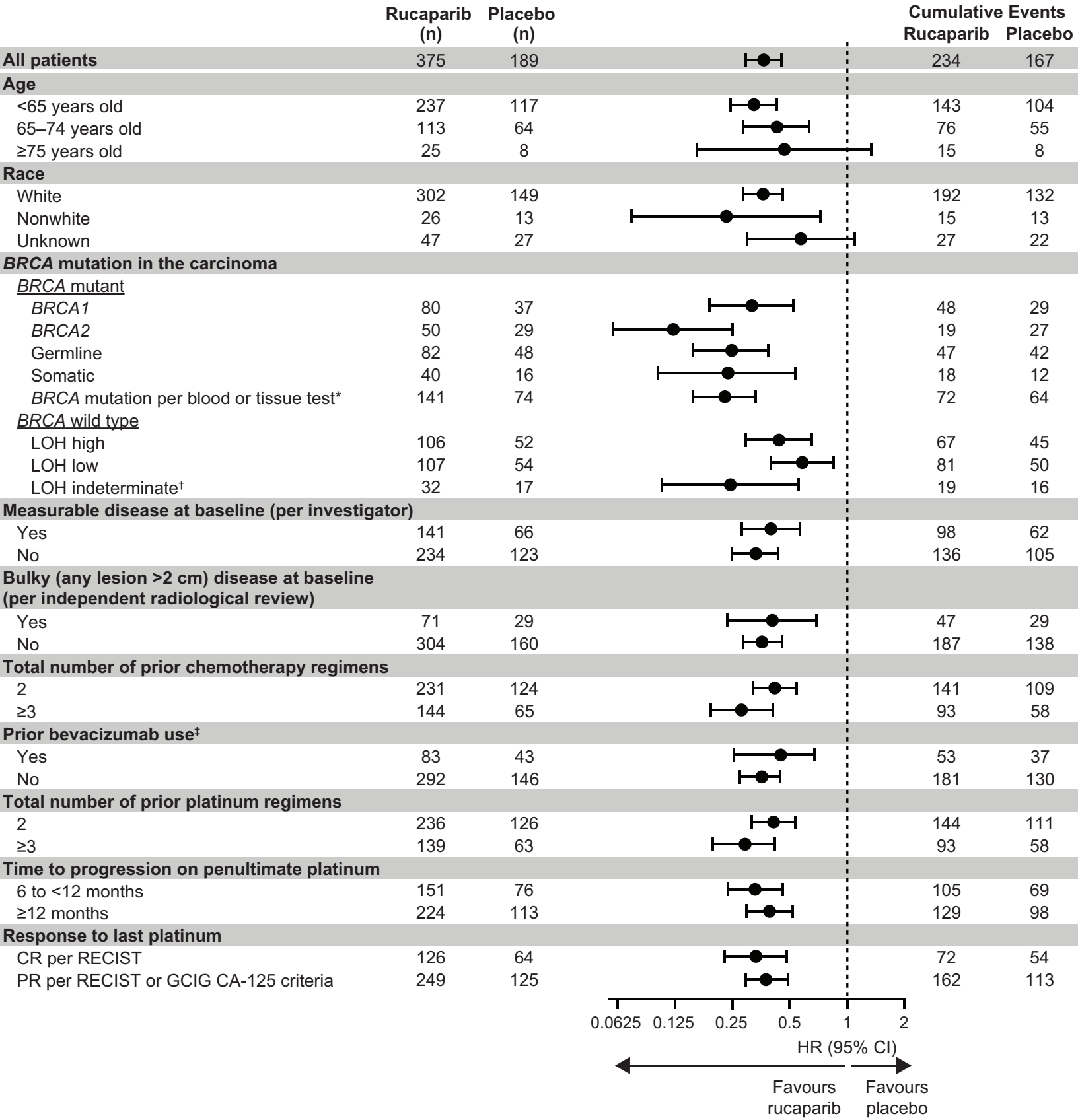
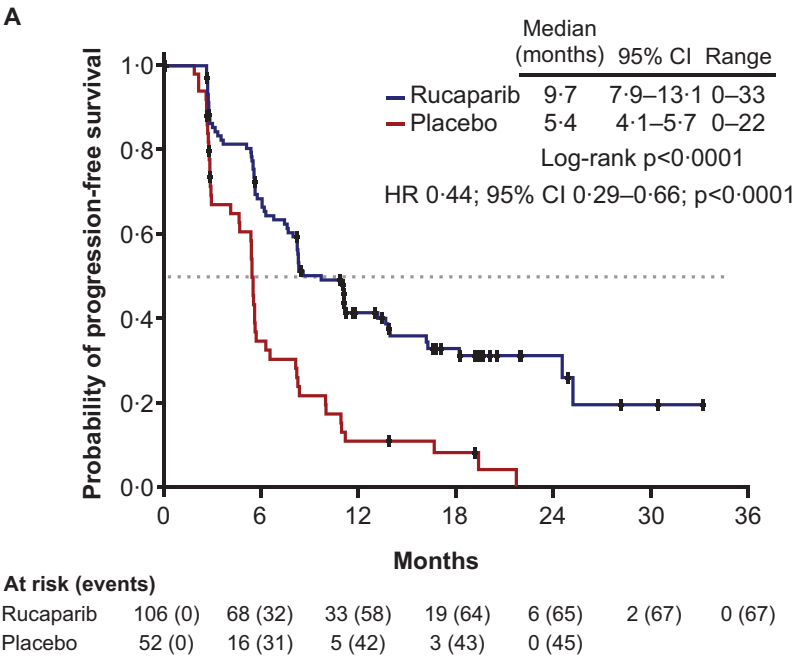

Rucaparib (n)
Placebo (n)
Cumulative Events
Rucaparib
Placebo
All patients 375 189 234 167
Age
<65 years old 237 117 143 104
65–74 years old 113 64 76 55
≥75 years old 25 8 15 8
Race
White 302 149 192 132
Nonwhite 26 13 15 13
Unknown 47 27 27 22
BRCA mutation in the carcinoma
BRCA mutant
BRCA1 80 37 48 29
BRCA2 50 29 19 27
Germline 82 48 47 42
Somatic 40 16 18 12
BRCA mutation per blood or tissue test* 141 74 72 64
BRCA wild type
LOH high 106 52 67 45
LOH low 107 54 81 50
LOH indeterminate† 32 17 19 16
Measurable disease at baseline (per investigator)
Yes 141 66 98 62
No 234 123 136 105
Bulky (any lesion >2 cm) disease at baseline (per independent radiological review)
Yes 71 29 47 29
No 304 160 187 138
Total number of prior chemotherapy regimens
2 231 124 141 109
≥3 144 65 93 58
Prior bevacizumab use‡
Yes 83 43 53 37
No 292 146 181 130
Total number of prior platinum regimens
2 236 126 144 111
≥3 139 63 93 58
Time to progression on penultimate platinum
6 to <12 months 151 76 105 69
≥12 months 224 113 129 98
Response to last platinum
CR per RECIST 126 64 72 54
PR per RECIST or GCIG CA-125 criteria 249 125 162 113
0.0625 0.125 0.25 0.5 1 2
HR (95% CI)
Favours rucaparib
Favours placebo

Figure 4


A
Median (months) 95% CI Range
Rucaparib 9·7 7·9–13·1 0–33
Placebo 5·4 4·1–5·7 0–22
Log-rank p<0·0001
HR 0·44; 95% CI 0·29–0·66; p<0·0001
Probability of progression-free survival
1·0
0·8
0·6
0·4
0·2
0·0
0 6 12 18 24 30 36
Months
At risk (events)
Rucaparib 106 (0) 68 (32) 33 (58) 19 (64) 6 (65) 2 (67) 0 (67)
Placebo 52 (0) 16 (31) 5 (42) 3 (43) 0 (45)

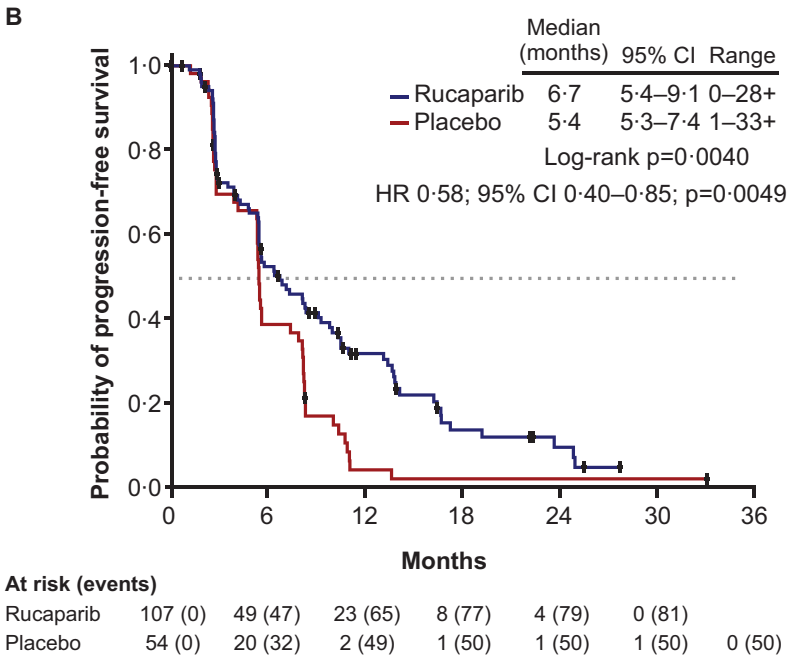

B
Median (months) 95% CI Range
Rucaparib 6·7 5·4–9·1 0–28+
Placebo 5·4 5·3–7·4 1–33+
Log-rank p=0·0040
HR 0·58; 95% CI 0·40–0·85; p=0·0049
Probability of progression-free survival
1·0
0·8
0·6
0·4
0·2
0·0
0 6 12 18 24 30 36
Months
At risk (events)
Rucaparib 107 (0) 49 (47) 23 (65) 8 (77) 4 (79) 0 (81)
Placebo 54 (0) 20 (32) 2 (49) 1 (50) 1 (50) 1 (50) 0 (50)

Table 1: Baseline patient and disease characteristics in the intent-to-treat population

Characteristic	Rucaparib (n=375)	Placebo (n=189)
Age (years)	61·0 (53·0–67·0)	62·0 (53·0–68·0)
Race		
White	302 (81%)	149 (79%)
Non-white	26 (7%)	13 (7%)
Unknown	47 (13%)	27 (14%)
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%)
Histology		
Serous	357 (95%)	179 (95%)
Endometrioid	16 (4%)	7 (4%)
Mixed	1 (<1%)	3 (2%)
Transitional	1 (<1%)	0
BRCA mutation in the 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 prior chemotherapy regimens	2 (2–3)	2 (2–3)
2	231 (62%)	124 (66%)
≥3	144 (38%)	65 (34%)
Prior bevacizumab use§	83 (22%)	43 (23%)
Number of platinum-based regimens	2 (2–3)	2 (2–3)
2	236 (63%)	126 (67%)
≥3	139 (37%)	63 (33%)
Measurable disease at baseline (per investigator)	141 (38%)	66 (35%)
Bulky disease (any lesion >2 cm) at baseline (per independent radiological review)	71 (19%)	29 (15%)
Randomisation stratification factors		

HRR gene mutation status		
BRCA mutant	130 (35%)	66 (35%)
Mutation in other, non-*BRCA* HRR gene	28 (7%)	15 (8%)
No mutation detected in *BRCA* or HRR gene	217 (58%)	108 (57%)
Time to progression with penultimate platinum (months)	13·8 (10·0–22·3)	14·6 (10·7–24·0)
6 to <12 months	151 (40%)	76 (40%)
≥12 months	224 (60%)	113 (60%)
Response to last platinum		
CR per RECIST	126 (34%)	64 (34%)
PR per RECIST or serologic response per GCIG CA-125 criteria	249 (66%)	125 (66%)

Data are median (interquartile range) or n (%). CA-125=cancer antigen 125. CR=complete response. ECOG=Eastern Cooperative Oncology Group. GCIG=Gynecologic Cancer InterGroup. HRR=homologous recombination repair. LOH=loss of heterozygosity. PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors version 1·1. *Per patient records, origin was fallopian tube and/or ovary. †Tumour sample was *BRCA* mutant by 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 percent of genomic LOH due to low tumour content or low aneuploidy. §Prior treatment with bevacizumab was permitted as part of penultimate or earlier treatment.

Table 2: Treatment emergent adverse events of any grade reported in ≥10% of patients in either arm in the safety population

	Rucaparib (n=372)				Placebo (n=189)			
	Any grade	**Grade 1–2**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 1–2**	**Grade 3**	**Grade 4**
At least one AE	372 (100%)*	163 (44%)	179 (48%)	24 (6%)	182 (96%)†	154 (81%)	24 (13%)	2 (1%)
Blood and lymphatic system disorders								
Anaemia; decreased haemoglobin	139 (37%)	69 (19%)	67 (18%)	3 (1%)	11 (6%)	10 (5%)	0	1 (1%)
Neutropenia; neutrophil count decreased	67 (18%)	42 (11%)	19 (5%)	6 (2%)	9 (5%)	7 (4%)	1 (1%)	1 (1%)
Thrombocytopenia; platelet count decreased	104 (28%)	85 (23%)	13 (3%)	6 (2%)	5 (3%)	5 (3%)	0	0
Gastrointestinal disorders								
Abdominal distension	41 (11%)	41 (11%)	0	0	22 (12%)	22 (12%)	0	0
Abdominal pain	111 (30%)	102 (27%)	9 (2%)	0	49 (26%)	48 (25%)	1 (1%)	0
Abdominal pain (upper)	52 (14%)	50 (13%)	2 (1%)	0	10 (5%)	10 (5%)	0	0
Constipation	136 (37%)	129 (35%)	7 (2%)	0	45 (24%)	43 (23%)	2 (1%)	0
Diarrhoea	118 (32%)	116 (31%)	2 (1%)	0	41 (22%)	39 (21%)	2 (1%)	0
Dyspepsia	54 (15%)	53 (14%)	1 (<1%)	0	9 (5%)	9 (5%)	0	0
Nausea	280 (75%)	266 (72%)	14 (4%)	0	69 (37%)	68 (36%)	1 (1%)	0
Vomiting	136 (37%)	121 (33%)	15 (4%)	0	28 (15%)	26 (14%)	2 (1%)	0
General disorders and administration site conditions								
Asthenia; fatigue	258 (69%)	233 (63%)	25 (7%)	0	83 (44%)	78 (41%)	5 (3%)	0
Oedema peripheral	39 (10%)	38 (10%)	1 (<1%)	0	14 (7%)	14 (7%)	0	0
Pyrexia	44 (12%)	44 (12%)	0	0	8 (4%)	8 (4%)	0	0
Infections and infestations								
Upper respiratory tract infection	41 (11%)	41 (11%)	0	0	6 (3%)	4 (2%)	2 (1%)	0
Investigations								
Increase in alanine aminotransferase or aspartate aminotransferase‡	126 (34%)	87 (23%)	39 (10%)	0	7 (4%)	7 (4%)	0	0
Increase in blood creatinine	57 (15%)	56 (15%)	1 (<1%)	0	3 (2%)	3 (2%)	0	0
Metabolism and nutrition disorders								
Decreased appetite	87 (23%)	85 (23%)	2 (1%)	0	26 (14%)	26 (14%)	0	0
Hypomagnesaemia	40 (11%)	39 (10%)	1 (<1%)	0	11 (6%)	11 (6%)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	57 (15%)	55 (15%)	2 (1%)	0	24 (13%)	24 (13%)	0	0
Back pain	45 (12%)	45 (12%)	0	0	28 (15%)	28 (15%)	0	0
Nervous system disorders								
Dizziness	54 (15%)	54 (15%)	0	0	15 (8%)	14 (7%)	1 (1%)	0
Dysgeusia	146 (39%)	146 (39%)	0	0	13 (7%)	13 (7%)	0	0
Headache	67 (18%)	66 (18%)	1 (<1%)	0	30 (16%)	29 (15%)	1 (1%)	0
Psychiatric disorders								
Insomnia	53 (14%)	53 (14%)	0	0	15 (8%)	15 (8%)	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	54 (15%)	54 (15%)	0	0	25 (13%)	25 (13%)	0	0
Dyspnoea	50 (13%)	50 (13%)	0	0	14 (7%)	14 (7%)	0	0
Skin and subcutaneous tissue disorders								
Photosensitivity reaction	64 (17%)	62 (17%)	2 (1%)	0	1 (1%)	1 (1%)	0	0
Pruritus	47 (13%)	47 (13%)	0	0	19 (10%)	19 (10%)	0	0
Rash	46 (12%)	45 (12%)	1 (<1%)	0	17 (9%)	17 (9%)	0	0

Data are n (%); the safety population includes all patients who received at least one dose of protocol-specified treatment.
AE=adverse event. *Includes six patients with a grade 5 treatment-emergent adverse event. †Includes two patients with a grade 5

treatment-emergent adverse event. ‡Elevations were transient, self-limiting, and not associated with other signs of liver toxicity.

Web Appendix

Click here to download Web Appendix: ARIEL3 Primary_OnlineAppendix_24Aug2017c.docx

Supplementary Material

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Supplementary Material

Click here to download Supplementary Material: CONSORT Extension for Abstracts Checklist_completed_082317.doc

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

Coordinating Investigators For the Study

Coordinating Investigator for North America:

Robert L. Coleman, M.D., FACOG, FACS
Professor, Department of Gynecologic Oncology and Reproductive Medicine
University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard, Unit 1362
Houston, TX 77030 – 4009
Telephone: +1 713 745 3357
Facsimile: +1 713 792 7586
E-mail: rcoleman@mdanderson.org

Coordinating Investigator for Europe, Middle East, and Asia Pacific:

Jonathan Ledermann, BSc, MD, FRCP
Professor, Medical Oncology
UCL Cancer Institute
University College London
90 Tottenham Court Road
London W1T 4TJ
United Kingdom
Telephone: +44 020 7679 9898
Facsimile: +44 020 7679 9899
E-mail: J.ledermann@ucl.ac.uk

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) _____

Table of Contents

Description **Page**

List of Tables

Description **Page**

List of Figures

Description **Page**

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

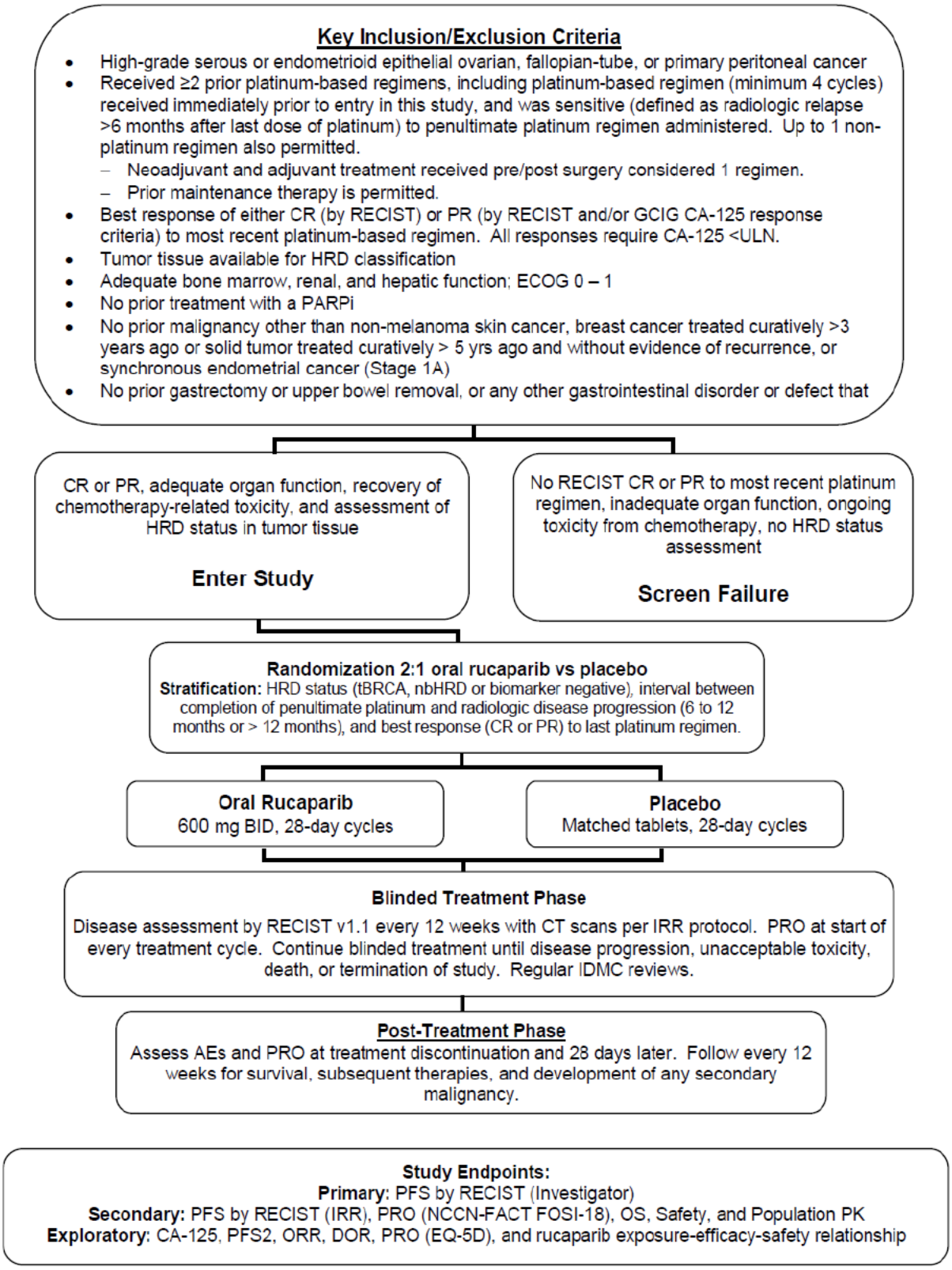
This is a multicenter, randomized, double-blind, placebo-controlled study.

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	❑

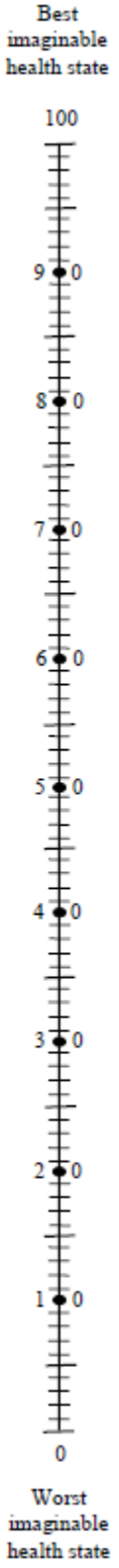
Anxiety/Depression

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

Coordinating Investigator for North America:

Robert L. Coleman, M.D., FACOG, FACS
Professor, Department of Gynecologic Oncology and Reproductive Medicine
University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard, Unit 1362
Houston, TX 77030 – 4009
Telephone: +1 713 745 3357
Facsimile: +1 713 792 7586
E-mail: rcoleman@mdanderson.org

Coordinating Investigator for Europe, Middle East, and Asia Pacific:

Jonathan Ledermann, BSc, MD, FRCP
Professor, Medical Oncology
UCL Cancer Institute
University College London
90 Tottenham Court Road
London W1T 4TJ
United Kingdom
Telephone: +44 020 7679 9898
Facsimile: +44 020 7679 9899
E-mail: J.ledermann@ucl.ac.uk

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) _____

Table of Contents

Description **Page**

List of Tables

Description **Page**

List of Figures

Description **Page**

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

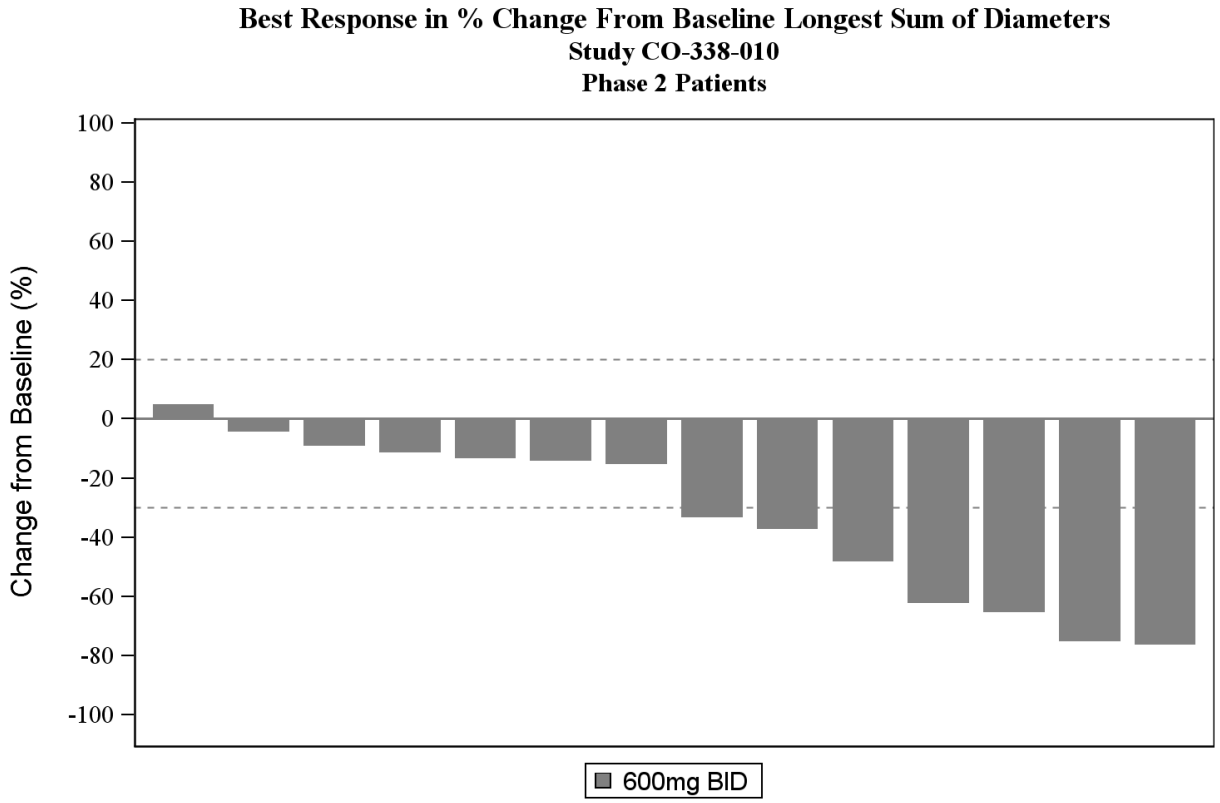
patients have died on study or within 30 days of last dose of rucaparib; all deaths were due to disease progression and were assessed as not related to rucaparib.

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

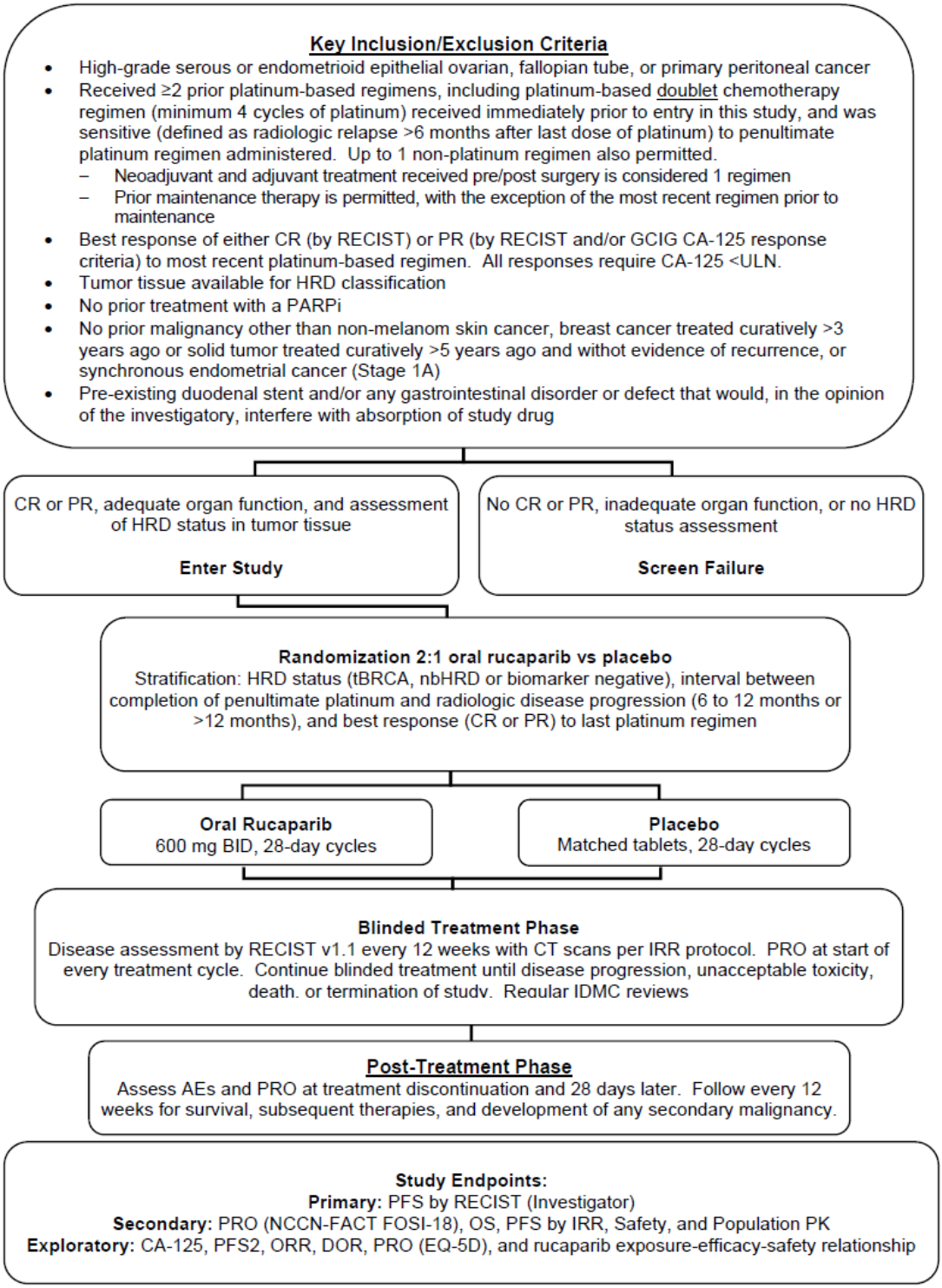
After the Treatment Discontinuation visit, all patients will be followed for AEs up to 28 days after last dose of study drug. Patients will also be followed for survival, subsequent treatments, and monitoring for secondary malignancy every 12 weeks (± 14 days) until death, loss to follow-up, withdrawal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

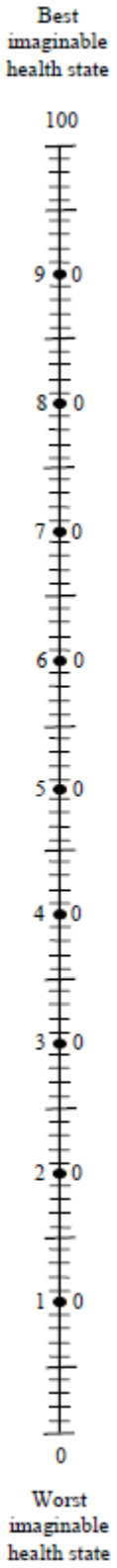
I am moderately anxious or depressed ❑

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).