Article category: Original Research

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

Robert L Coleman, MD,[1]* Amit M Oza, MD,[2] Domenica Lorusso, MD,[3] Carol Aghajanian, MD,[4] Ana Oaknin, MD,[5] Andrew Dean, MD,[6] Nicoletta Colombo, PhD,[7] Johanne I Weberpals, MD,[8] Andrew Clamp, PhD,[9] Giovanni Scambia, MD,[10] Alexandra Leary, MD,[11] Robert W Holloway, MD,[12] Margarita Amenedo Gancedo, MD,[13] Peter C Fong, FRACP,[14] Jeffrey Goh, FRACP,[15] David M O'Malley, MD,[16] Deborah K Armstrong, MD,[17] Jesus Garcia-Donas, MD,[18] Elizabeth M Swisher, MD,[19] Anne Floquet, MD,[20] Gottfried E Konecny, MD,[21] Iain A McNeish, FCRP,[22] Clare L Scott, PhD,[23] Terri Cameron, MSc,[24] Lara Maloney, BA,[24] Jeff Isaacson, PhD,[24] Sandra Goble, MS,[24] Caroline Grace, BSc,[24] Thomas C Harding, PhD,[24] Mitch Raponi, PhD,[24] James Sun, PhD,[25] Kevin K Lin, PhD,[24] Heidi Giordano, MA,[24] Jonathan A Ledermann, MD,[26]* the ARIEL3 investigators[†]

[1]*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*

[2]*Department of Medicine, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto M5G 2M9, Canada*

[3]*MITO and Gynecologic Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Giacomo Venezian, 1, 20133 Milan, Italy*

[4]*Department of Medical Oncology, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY, USA*

[5]*Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), 119-129, 08035, Barcelona, Spain*

[6]*Department of Oncology, Saint John of God Subiaco Hospital, 314/25 McCourt St., Subiaco, Western Australia 6008, Australia*

[7]*Gynecologic Cancer Program, European Institute of Oncology and University of Milan-Bicocca, Via Ripamonti 435, Milan, Italy*

[8]*Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, Canada K1H 8L6*

[9]*Department of Medical Oncology, The Christie NHS Foundation Trust and University of Manchester, 550 Wilmslow Road, Manchester, M20 4BX UK*

[10]*Gynecologic Oncology, Università Cattolica Roma, Largo Francesco Vito, 1, 00168 Roma, Italy*

[11]*GINECO and Gynecological Unit, Department of Medicine, Gustave Roussy Cancer Center and INSERM U981, 114 Rue Edouard-Vaillant, 94805, Villejuif, France*

[12]*Department of Gynecologic Oncology, Florida Hospital Cancer Institute, 2501 North Orange Avenue, Suite 683, Orlando, FL, USA*

[13]*Medical Oncology Department, Oncology Center of Galicia, Doctor Camilo Veiras, 1, 15009 La Coruña, Spain*

[14]*Medical Oncology Department, Auckland City Hospital, 2 Park Rd, Grafton, Auckland 1023, New Zealand*

[15]*Department of Oncology, Cancer Care Services, Royal Brisbane and Women's Hospital, Level 5 Joyce Tweddell Building, Butterfield Street, Herston, Queensland 4029 Australia*

[16]*Gynecologic Oncology, The Ohio State University, James Cancer Center, M210 Starling Loving, 320 W 10th Ave, Columbus, OH 43210, USA*

[17]*The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Room 190, 1650 Orleans Street, Baltimore, MD 21287, USA*

[18]*HM Hospitales – Centro Integral Oncológico HM Clara Campal, Calle Oña, 10, Planta -1, 28050 Madrid, Spain*

[19]*University of Washington, 1959 Northeast Pacific Street, Seattle, WA 98195, USA*

[20]*GINECO and Institut Bergonié, 229, cours de l'Argonne, 33076 Bordeaux, France*

[21]*Department of Medicine, University of California Los Angeles, 100 Medical Plaza, Los Angeles, CA 90095, USA*

[22]*Institute of Cancer Sciences, University of Glasgow, 1053 Great Western Road, Glasgow, G12 0YN UK*

[23] *Royal Melbourne Hospital, 300 Grattan Street, Parkville, Victoria, 3052, Australia*

[24]*Clovis Oncology, Inc., 5500 Flatiron Parkway, Boulder, CO 80301, USA*

[25]*Foundation Medicine, Inc., 150 Second St, Cambridge, MA, 02141, USA*

[26]*UCL Cancer Institute and UCL Hospitals, 90 Tottenham Court Road, London W1T 4TJ, UK*

*Joint lead clinical investigators
†Members listed in the appendix

Correspondence: Dr. R. 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; Email: rcoleman@mdanderson.org

Target Journal: *Lancet*

Abstract word count (300 max) = 299

Manuscript word count (4500 max) = 4213

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

References (30 max) = 30

Summary

Background: Rucaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has shown anticancer activity in patients with recurrent ovarian carcinoma which harbours 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 randomised patients receive oral rucaparib 600 mg twice daily or placebo. 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) 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 was 10.8 months and 5.4 months (p<0.0001), respectively (HR, 0.37; 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 [18.8%], rucaparib; one [0.5%], placebo) and increased alanine aminotransferase or aspartate aminotransferase (39 [10.5%], 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). The first of these, 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 its results 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 residual disease less 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 the study.

Added value of this study

ARIEL3 enrolled patients with or without a germline or somatic *BRCA* mutation, and 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 used in the phase 2

ARIEL2 study, which combines mutation analysis of *BRCA1* and *BRCA2* genes with measurement of the percentage of genome-wide loss of heterozygosity (LOH) in the carcinoma 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 for maintenance treatment, such as PARP inhibitors, alone and 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, tools to identify patients who may benefit most from these therapies, and 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 (53.8%, n=106) 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 that was optimized based on results of ARIEL2 Part 1 as a predictive biomarker for sensitivity to rucaparib treatment.

METHODS

Study design and patients

ARIEL3 (NCT1968213) 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, including maturity of progression-free survival events.

Eligible patients were aged 18 years or older and 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 following 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 an amendment was added to the protocol restricting the most recent platinum-based regimen to a chemotherapy doublet administered for a minimum of four cycles (ie, bevacizumab or other biologics were not allowed as part of the most recent therapy). 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 that had persistent lesions greater than 2 cm 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 an active second malignancy or symptomatic/untreated central nervous system metastases, had received anticancer therapy less than 14 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 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 next-generation sequencing 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.[11] Germline mutations were identified by BRCAnalysis CDx test (Myriad Genetics). 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 (Craigavon, United Kingdom) using a block size of six. Randomisation stratification factors included: HRD 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 adverse event (additional details in the appendix p 3). Treatment was discontinued for a toxicity-related dose interruption lasting more than 14 consecutive days (unless otherwise agreed upon between the investigator, the study's joint lead clinical investigators, and the study sponsor).

Disease assessments were performed at screening, every 12 weeks, 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 (NCCN-FACT) 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 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. 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] 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 DSR-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, disease burden at baseline). The proportion of patients achieving an objective response was an exploratory endpoint of ARIEL3, and was determined by the proportion of patients with measurable disease at study entry who achieved a best response of complete or partial response per RECIST as assessed by investigator.

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. 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 (24.0%) and 9 (4.8%) 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, 0.37; 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 between-arm difference 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. Additional details on health-related quality of life will be reported separately.

At the visit cutoff date (April 15, 2017), overall survival data were not mature. Overall, during the study follow-up 123 (21.8%) patients had died. A follow-up analysis will be performed when approximately 70% of the patients have died.

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). In patients with carcinomas that were *BRCA* wild type, a progression-free survival benefit 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 the progression-free survival assessed by BICR (appendix p 13).

The majority of patients (374 [66.3%]) in ARIEL3 had achieved a partial response to the platinum-based therapy received prior to randomisation. A prespecified exploratory analysis of objective response was conducted in 207 of these 374 patients (55.3%) who had investigator-assessed, RECIST-measurable disease at baseline. In evaluable patients with a *BRCA*-mutant carcinoma, 15 of 40 (37.5%) in the rucaparib arm and two of 23 (8.7%) 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 of 85 [27.1%] patients) than the placebo arm (3 of 41 [7.3%] patients). A similar result was observed in the intent-to-treat population among patients with measurable disease at baseline (26 of 141 [18.4%] patients in the rucaparib arm; 5 of 66 [7.6%] patients in the placebo arm). Complete responses were observed in the rucaparib arm in seven (17.5%), 10 (11.8%), and 10 (7.1%) patients with measurable disease at baseline in the nested *BRCA*-mutant and HRD cohorts, and the overall intent-to-treat population, respectively. Only one (1.5%) complete response was observed in the placebo arm, and this occurred in the intent-to-treat population.

In the safety population (372, rucaparib; 189, placebo), the median (interquartile range [IQR]) 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 (100.0%) patients in the rucaparib arm and 182 (96.3%) patients 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 [75.3%] patients in the rucaparib arm and 69 [36.5%] patients in the placebo arm), asthenia or fatigue (258 [69.4%] patients and 83 [43.9%] patients), dysgeusia (146 [39.2%] patients and 13 [6.9%] patients), anaemia/decreased haemoglobin (139 [37.4%] patients and 11 [5.8%] patients), constipation (136 [36.6%] patients and 45 [23.8%] patients), and vomiting (136 [36.6%] patients and 28 [14.8%] patients). Treatment-emergent adverse events of grade 3 or greater were reported in 209 (56.2%) patients in the rucaparib arm and 28 (14.8%) patients in the placebo arm, the most common of which were anaemia/decreased haemoglobin (70 [18.8%] patients in the rucaparib arm and one [0.5%] patient in the placebo arm) and increase in alanine aminotransferase or aspartate aminotransferase (39 [10.5%] patients 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 (21.0%) patients in the rucaparib arm and 20 (10.6%) patients in the placebo arm. The most common serious adverse events (reported in at least 1.5% of patients in either arm) included anaemia

(16 [4.3%] patients in the rucaparib arm and one [0.5%] patient in the placebo arm), pyrexia (six [1.6%] patients and no patients), vomiting (six [1.6%] patients and two [1.1%] patients), and small intestinal obstruction (three [0.8%] patients and three [1.6%] patients).

Myelodysplastic syndrome and acute myeloid leukaemia were reported in three (0.8%) patients 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.

Dose reduction due to a treatment-emergent adverse event occurred in 203 (54.6%) and 8 (4.2%) patients in the rucaparib and placebo arms, respectively (appendix p 9). Treatment interruption due to a treatment-emergent adverse event occurred in 237 (63.7%) and 19 (10.1%) patients in the rucaparib and placebo arms, respectively (appendix p 9). In the rucaparib and placebo arms, 117 (31.5%) and 6 (3.2%) patients, respectively, had both a dose reduction due to a treatment-emergent adverse event and a treatment interruption due to a treatment-emergent adverse event during the study. Of patients who received rucaparib, 50 (13.4%) discontinued due to a treatment-emergent adverse event (excluding disease progression) compared with three (1.6%) of patients in the placebo arm (appendix p 10). As of the visit cutoff date, there were six deaths due to adverse events in the rucaparib arm: two patients due to progressive disease, one due to acute myeloid leukaemia, one due to cardiac arrest, one due to haematophagic histiocytosis, and one due to myelodysplastic syndrome. In the placebo arm, two

patients died due to adverse events: 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 progression or death observed for patients receiving rucaparib in the intent-to-treat population 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 was seen in the secondary endpoint of assessment by blinded, independent central radiology review, supporting the validity of the benefit observed with rucaparib maintenance treatment. Furthermore, the lower risk of disease progression or death associated with rucaparib 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 health-related quality of life data gathered in ARIEL3 are planned and will be reported separately.

Overall survival data were not mature at the time of the visit cut off, with less than 20% of the events needed for final analysis. Follow-up of patients 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 dose reductions). 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. Similarly, elevations in creatinine, which have also been observed with olaparib,[24] were self-limiting and stabilized 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 stabilization 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 study design (eg, residual disease was restricted to less than 2 cm in NOVA), 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), and the method of primary endpoint assessment (eg, investigator vs BICR).[5,6,9,30]

Similar to other studies of PARP inhibitors in the maintenance treatment setting,[5,6,9] patients were required to have CA-125 below the upper limit of normal prior to entry into ARIEL3. While not a requirement of response per GCIG CA-125 criteria or a RECIST partial response, this eligibility requirement supported that patients had controlled disease at study entry. It is possible that even greater benefit for rucaparib maintenance treatment may have been observed in a setting where CA-125 was not required to be below the upper limit of normal at baseline.

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 carcinoma 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 conversions to complete responses.

In addition, 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. 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 in risk of disease progression or death 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 progression or death 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 informing clinicians when making treatment decisions for patients with *BRCA* wild-type associated platinum-sensitive ovarian carcinoma. However, activity of rucaparib was also clearly observed in the cohort of patients with carcinomas that were not associated with HRD, with over 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 benefit or 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 interruptions or 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, JG, 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, JG, DMO, DKA, JGD, EMS, AF, GEK, IAM, CLS, KKL, and JAL acquired the data.

RLC, TC, LM, JI, SG, 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.

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, and PharmaMar; and has received support for travel and/or accommodation from Roche and PharmaMar.

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.

RWH has served on a speakers' bureau for AstraZeneca, Clovis Oncology, and Tesaro.

MAG

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

JG has served on advisory boards for Roche, AstraZeneca, Janssen, Merck and BMS; has received support for travel and/or accommodation from Roche 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.

DKA

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; and has received support for travel and/or accommodation from AstraZeneca, Clovis Oncology and Roche. CLS' institution received in kind research support for parallel laboratory work using rucaparib.

TC, LM, JI, SG, 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.

ACKNOWLEDGMENTS

The ARIEL3 study was funded by Clovis Oncology. Additional support was provided in part by the Ann Rife Cox Chair in Gynecology and the Judy Ries/Albert Pisani, MD Ovarian Cancer Research Fund (RLC), and the Experimental Cancer Medicine Centres at Glasgow (IAM) and University College London (JAL). Funding was also provided by the US Department of Defense Ovarian Cancer Research Program OC120506 (EMS), a V Foundation Translational Award (EMS), and a Stand Up To Cancer—Ovarian Cancer Research Fund Alliance—National Ovarian Cancer Coalition Dream Team Translational Research Grant (grant number SU2C-AACR-DT16-15 to EMS). Stand Up to Cancer is a programme of the Entertainment Industry Foundation; research grants are administered by the American Association for Cancer Research, a scientific partner of Stand Up To Cancer.

We thank all of the patients and their families and caregivers for their participation in ARIEL3, and we thank all of the ARIEL3 investigators (see appendix p 2) for their contributions to the administration and execution of the trial. We thank Jennifer Borrow, Amanda Cha, Azucena Lemus, Man-Wah Li, Tamsin Maclaren-Anderson, Elaina Mann, Olga Sirin, and Lan-Thanh Vo for clinical operations support and Simon Watkins, PhD for clinical scientific support of the ARIEL3 study. We thank Cheryl Chun, PhD and

549 Peter Morello, PhD for assistance in manuscript preparation. Medical writing and
550 editorial support was provided by Nathan Yardley, PhD, and Shannon Davis of Ashfield
551 Healthcare Communications and was funded by Clovis Oncology.

REFERENCES

1. Ferlay J, Soerjomataram I, Erik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. 2013. http://globocan.iarc.fr/Pages/summary_table_pop_sel.aspx (accessed August 1 2017).

2. McMeekin DS, Tillmanns T, Chaudry T, et al. Timing isn't everything: an analysis of when to start salvage chemotherapy in ovarian cancer. *Gynecol Oncol* 2004; **95**(1): 157-64.

3. Herzog TJ, Holloway RW, Stuart GCE. Workshop: options for therapy in ovarian cancer. *Gynecol Oncol* 2003; **90**(3): S45-S50.

4. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012; **30**(17): 2039-45.

5. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012; **366**(15): 1382-92.

6. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016; **375**(22): 2154-64.

7. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2017.

8. Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; **387**(10023): 1066-74.

9. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2017 [Epub ahead of print].

10. Kristeleit R, Shapiro GI, Burris HA, et al. A Phase I-II Study of the Oral PARP Inhibitor Rucaparib in Patients with Germline BRCA1/2-Mutated Ovarian Carcinoma or Other Solid Tumors. *Clin Cancer Res* 2017; **23**(15): 4095-106.

11. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017; **18**(1): 75-87.

12. Watkins JA, Irshad S, Grigoriadis A, Tutt AN. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. *Breast Cancer Res* 2014; **16**(3): 211.

13. Abkevich V, Timms KM, Hennessy BT, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. *Br J Cancer* 2012; **107**(10): 1776-82.

14. Pedersen B, Konstantinopoulos PA, Spillman MA, De S. Copy neutral loss of heterozygosity is more frequent in older ovarian cancer patients. *Genes Chromosomes Cancer* 2013; **52**(9): 794-801.

15. Marquard AM, Eklund AC, Joshi T, et al. Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs. *Biomark Res* 2015; **3**: 9.

16. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**(2): 228-47.

17. Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer* 2011; **21**(2): 419-23.

18. Jensen SE, Rosenbloom SK, Beaumont JL, et al. A new index of priority symptoms in advanced ovarian cancer. *Gynecol Oncol* 2011; **120**(2): 214-9.

19. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999; **20**(2): 109-17.

20. NCI Term Browser, CTCAE. https://nciterms.nci.nih.gov/ncitbrowser/pages/vocabulary.jsf?dictionary=CTCAE&version=4.03 (accessed August 1 2017).

21. Maurer W, Hothorn L, Lehmacher W. Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In: Vollmar J, ed. Biometrie in der chemisch-pharmazeutischen Industrie: Testing Principles in Clinical and Preclinical Trials. Stuttgart: Fischer Verlag; 1995: 3-18.

22. Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *Journal of Statistical Planning and Inference* 2001; **99**(1): 25-40.

23. Kristeleit RS, Shapira-Frommer R, Oaknin A, et al. Clinical activity of the poly(ADP-Ribose) polymerase (PARP) inhibitor rucaparib in ratients with high-grade ovarian carcinoma and a *BRCA* mutation: analysis of pooled data from Study 10 (Parts 1, 2a, and 3) and ARIEL2 (Parts 1 and 2). *Ann Oncol* 2016; **27**(supp 6): abstr 856O.

24. LYNPARZA (olaparib) capsules [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2017.

25. Rubraca (rucaparib) tablets [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2017.

26. McCormick A, Swaisland H. In vitro assessment of the roles of drug transporters in the disposition and drug-drug interaction potential of olaparib. *Xenobiotica; the fate of foreign compounds in biological systems* 2016: 1-47.

27. Kikuchi R, Lao Y, Bow DA, et al. Prediction of clinical drug-drug interactions of veliparib (ABT-888) with human renal transporters (OAT1, OAT3, OCT2, MATE1, and MATE2K). *J Pharm Sci* 2013; **102**(12): 4426-32.

28. Konecny GE, Oza AM, Tinker AV, et al. Rucaparib in patients with relapsed, primary platinum-sensitive high-grade ovarian carcinoma with germline or somatic *BRCA* mutations: Integrated summary of efficacy and safety from the phase II study ARIEL2. 2017. https://www.sgo.org/education/annual-meeting-on-womens-cancer/annual-meeting-abstracts-2/ (accessed August 1 2017).

29. Oaknin A, Oza A, Tinker AV, et al. Integrated efficacy and safety analysis of the poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib in patients (pts) with high-grade ovarian carcinoma (HGOC). *ECCO2017 European Cancer Congress* 2017: abstr 710. http://www.eccocongress.org/en/Scientific-Programme/Abstract-search?abstractid=29845 (accessed August 1 2017).

30. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol* 2014; **15**(8): 852-61.

TABLES

Table 1. Baseline patient and disease characteristics.

Characteristic	Rucaparib (n=375)	Placebo (n=189)
Age (years)	61.0 (53.0-67.0)	62.0 (53.0-68.0)
Race		
White	302 (80.5%)	149 (78.8%)
Non-white	26 (6.9%)	13 (6.9%)
Unknown	47 (12.5%)	27 (14.3%)
ECOG Performance Status		
0	280 (74.7%)	136 (72.0%)
1	94 (25.3%)	53 (28.0%)
Diagnosis		
Epithelial ovarian cancer	312 (83.2%)	159 (84.1%)
Fallopian tube cancer	32 (8.5%)	10 (5.3%)
Primary peritoneal cancer	31 (8.3%)	19 (10.1%)
High grade serous adenocarcinoma*	0 (0%)	1 (0.5%)
Histology		
Serous	357 (95.2%)	179 (94.7%)
Endometrioid	16 (4.3%)	7 (3.7%)
Mixed	1 (0.3%)	3 (1.6%)

Transitional	1 (0.3%)	0 (0%)
BRCA mutation in the carcinoma		
BRCA mutant	130 (34.7%)	66 (34.9%)
BRCA1	80 (21.3%)	37 (19.6%)
BRCA2	50 (13.3%)	29 (15.3%)
Germline	82 (21.9%)	48 (25.4%)
Somatic	40 (10.7%)	16 (8.5%)
Unknown[†]	8 (2.1%)	2 (1.1%)
BRCA wild-type	245 (65.3%)	123 (65.1%)
LOH high	106 (28.3%)	52 (27.5%)
LOH low	107 (28.5%)	54 (28.6%)
LOH indeterminate[‡]	32 (8.5%)	17 (9.0%)
Number of prior chemotherapy regimens	2 (2-3)	2 (2-3)
2	231 (61.6%)	124 (65.6%)
≥3	144 (38.4%)	65 (34.4%)
Prior bevacizumab use[§]	83 (22.1%)	43 (22.8%)
Number of platinum-based regimens	2 (2-3)	2 (2-3)
2	236 (62.9%)	126 (66.7%)
≥3	139 (37.1%)	63 (33.3%)
Measurable disease at baseline (per investigator)	141 (37.6%)	66 (34.9%)
Bulky disease (any lesion >2 cm) at baseline	71 (18.9%)	29 (15.3%)
Randomisation stratification factors		

HRD gene mutation status		
BRCA mutant	130 (34.7%)	66 (34.9%)
Mutation in other, non-*BRCA* homologous recombination gene	28 (7.5%)	15 (7.9%)
No mutation detected	217 (57.9%)	108 (57.1%)
Time to progression with penultimate platinum (months)	13.8 (10.0-22.3)	14.6 (10.7-24.0)
6 to <12 months	151 (40.3%)	76 (40.2%)
≥12 months	224 (59.7%)	113 (59.8%)
Response to last platinum		
CR per RECIST	126 (33.6%)	64 (33.9%)
PR per RECIST or serologic response per GCIG CA-125 criteria	249 (66.4%)	125 (66.1%)

Data are median (IQR) or n (%). CA-125=cancer antigen 125; CR=complete response; ECOG=Eastern Cooperative Oncology Group; GCIG=Gynecologic Cancer InterGroup; HRD=homologous recombination deficiency; 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* positive 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.

	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* (100.0%)	163 (43.8%)	179 (48.1%)	24 (6.5%)	182† (96.3%)	154 (81.5%)	24 (12.7%)	2 (1.1%)
Blood and lymphatic system disorders								
Anaemia; decreased haemoglobin	139 (37.4%)	69 (18.5%)	67 (18.0%)	3 (0.8%)	11 (5.8%)	10 (5.3%)	0	1 (0.5%)
Neutropenia; neutrophil count decreased	67 (18.0%)	42 (11.3%)	19 (5.1%)	6 (1.6%)	9 (4.8%)	7 (3.7%)	1 (0.5%)	1 (0.5%)
Thrombocytopenia; platelet count decreased	104 (28.0%)	85 (22.8%)	13 (3.5%)	6 (1.6%)	5 (2.6%)	5 (2.6%)	0	0
Gastrointestinal disorders								
Abdominal distension	41 (11.0%)	41 (11.0%)	0	0	22 (11.6%)	22 (11.6%)	0	0
Abdominal pain	111 (29.8%)	102 (27.4%)	9 (2.4%)	0	49 (25.9%)	48 (25.5%)	1 (0.5%)	0
Abdominal pain (upper)	52 (14.0%)	50 (13.4%)	2 (0.5%)	0	10 (5.3%)	10 (5.3%)	0	0
Constipation	136 (36.6%)	129 (34.7%)	7 (1.9%)	0	45 (23.8%)	43 (22.8%)	2 (1.1%)	0
Diarrhoea	118 (31.7%)	116 (31.2%)	2 (0.5%)	0	41 (21.7%)	39 (7.9%)	2 (1.1%)	0
Dyspepsia	54 (14.5%)	53 (14.2%)	1 (0.3%)	0	9 (4.8%)	9 (4.8%)	0	0
Nausea	280 (75.3%)	266 (71.5%)	14 (3.8%)	0	69 (36.5%)	68 (36.0%)	1 (0.5%)	0
Vomiting	136 (36.6%)	121 (32.5%)	15 (4.0%)	0	28 (14.8%)	26 (13.8%)	2 (1.1%)	0
General disorders and administration site conditions								
Asthenia; fatigue	258 (69.4%)	233 (62.6%)	25 (6.7%)	0	83 (43.9%)	78 (41.3%)	5 (2.6%)	0
Oedema peripheral	39 (10.5%)	38 (10.2%)	1 (0.3%)	0	14 (7.4%)	14 (7.4%)	0	0
Pyrexia	44 (11.8%)	44 (11.8%)	0	0	8 (4.2%)	8 (4.2%)	0	0
Infections and infestations								
Upper respiratory tract infection	41 (11.0%)	41 (11.0%)	0	0	6 (3.2%)	4 (2.1%)	2 (1.1%)	0
Investigations								
Increase in alanine aminotransferase or aspartate aminotransferase‡	126 (33.9%)	87 (23.4%)	39 (10.5%)	0	7 (3.7%)	7 (3.7%)	0	0
Increase in blood creatinine	57 (15.3%)	56 (15.1%)	1 (0.3%)	0	3 (1.6%)	3 (1.6%)	0	0
Metabolism and nutrition disorders								
Decreased appetite	87 (23.4%)	85 (22.8%)	2 (0.5%)	0	26 (13.8%)	26 (13.8%)	0	0

Hypomagnesaemia	40 (10.8%)	39 (10.5%)	1 (0.3%)	0	11 (5.8%)	11 (5.8%)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	57 (15.3%)	55 (14.8%)	2 (0.5%)	0	24 (12.7%)	24 (12.7%)	0	0
Back pain	45 (12.1%)	45 (12.1%)	0	0	28 (14.8%)	28 (14.8%)	0	0
Nervous system disorders								
Dizziness	54 (14.5%)	54 (14.5%)	0	0	15 (7.9%)	14 (7.4%)	1 (0.5%)	0
Dysgeusia	146 (39.2%)	146 (39.2%)	0	0	13 (6.9%)	13 (6.9%)	0	0
Headache	67 (18.0%)	66 (17.7%)	1 (0.3%)	0	30 (15.9%)	29 (15.3%)	1 (0.5%)	0
Psychiatric disorders								
Insomnia	53 (14.2%)	53 (14.2%)	0	0	15 (7.9%)	15 (7.9%)	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	54 (14.5%)	54 (14.5%)	0	0	25 (13.2%)	25 (13.2%)	0	0
Dyspnoea	50 (13.4%)	50 (13.4%)	0	0	14 (7.4%)	14 (7.4%)	0	0
Skin and subcutaneous tissue disorders								
Photosensitivity reaction	64 (17.2%)	62 (16.7%)	2 (0.5%)	0	1 (0.5%)	1 (0.5%)	0	0
Pruritus	47 (12.6%)	47 (12.6%)	0	0	19 (10.1%)	19 (10.1%)	0	0
Rash	46 (12.4%)	45 (12.1%)	1 (0.3%)	0	17 (9.0%)	17 (9.0%)	0	0

Data are n (%) in the safety population, all patients who received at least one dose of protocol-specified treatment. *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.

FIGURES

Figure 1: CONSORT diagram

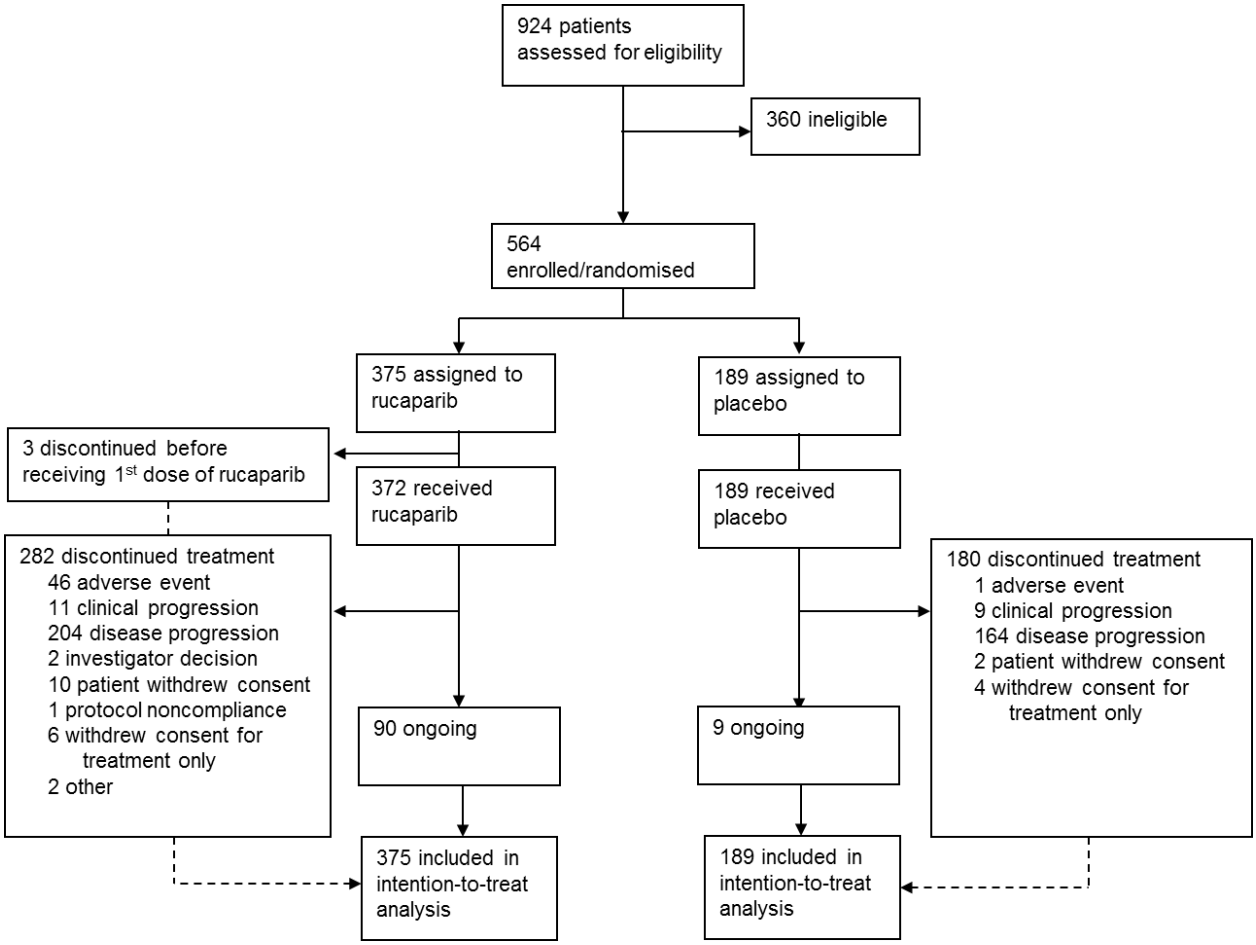
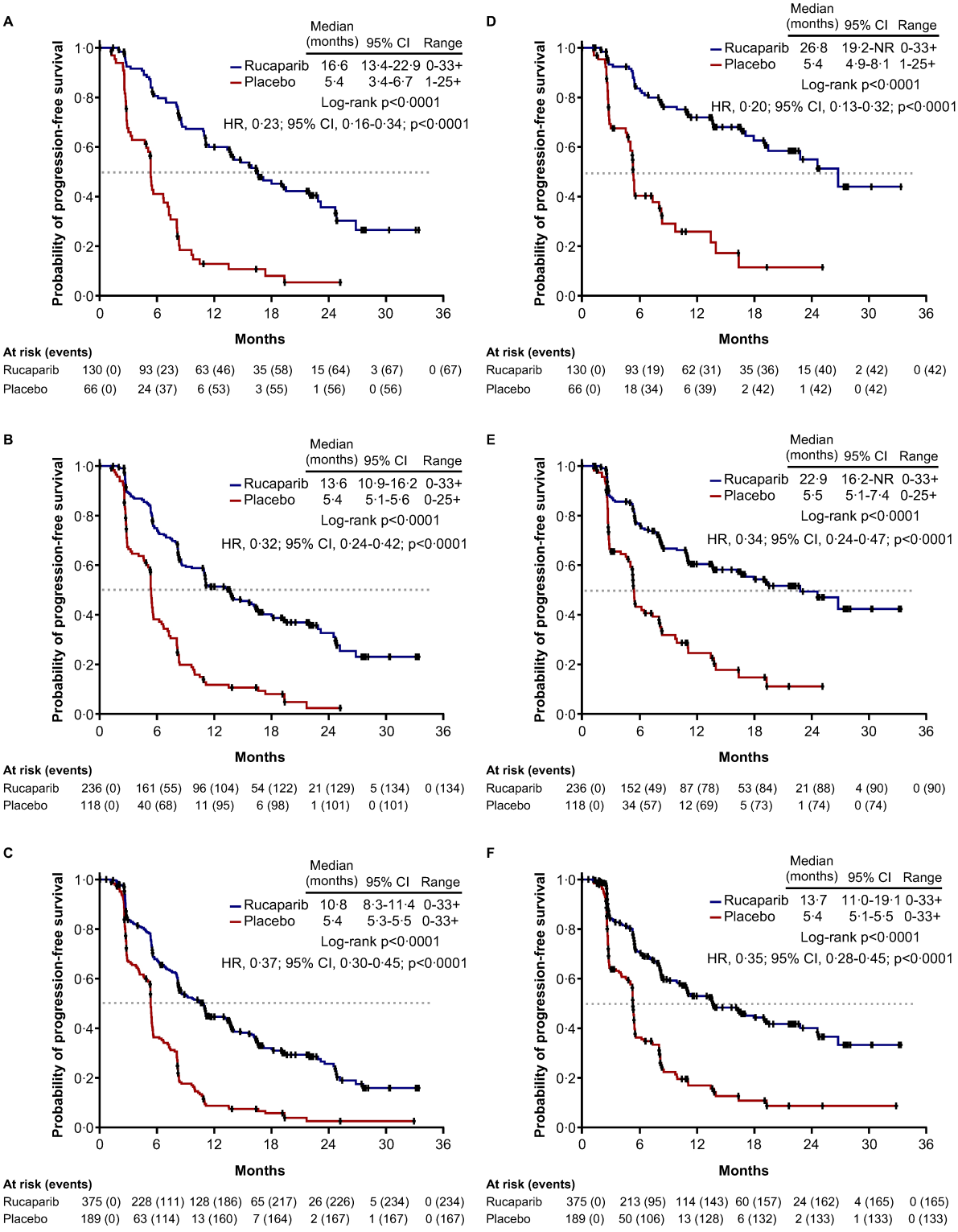


Figure 2: Investigator-assessed and blinded, central independent radiology review-assessed progression-free survival

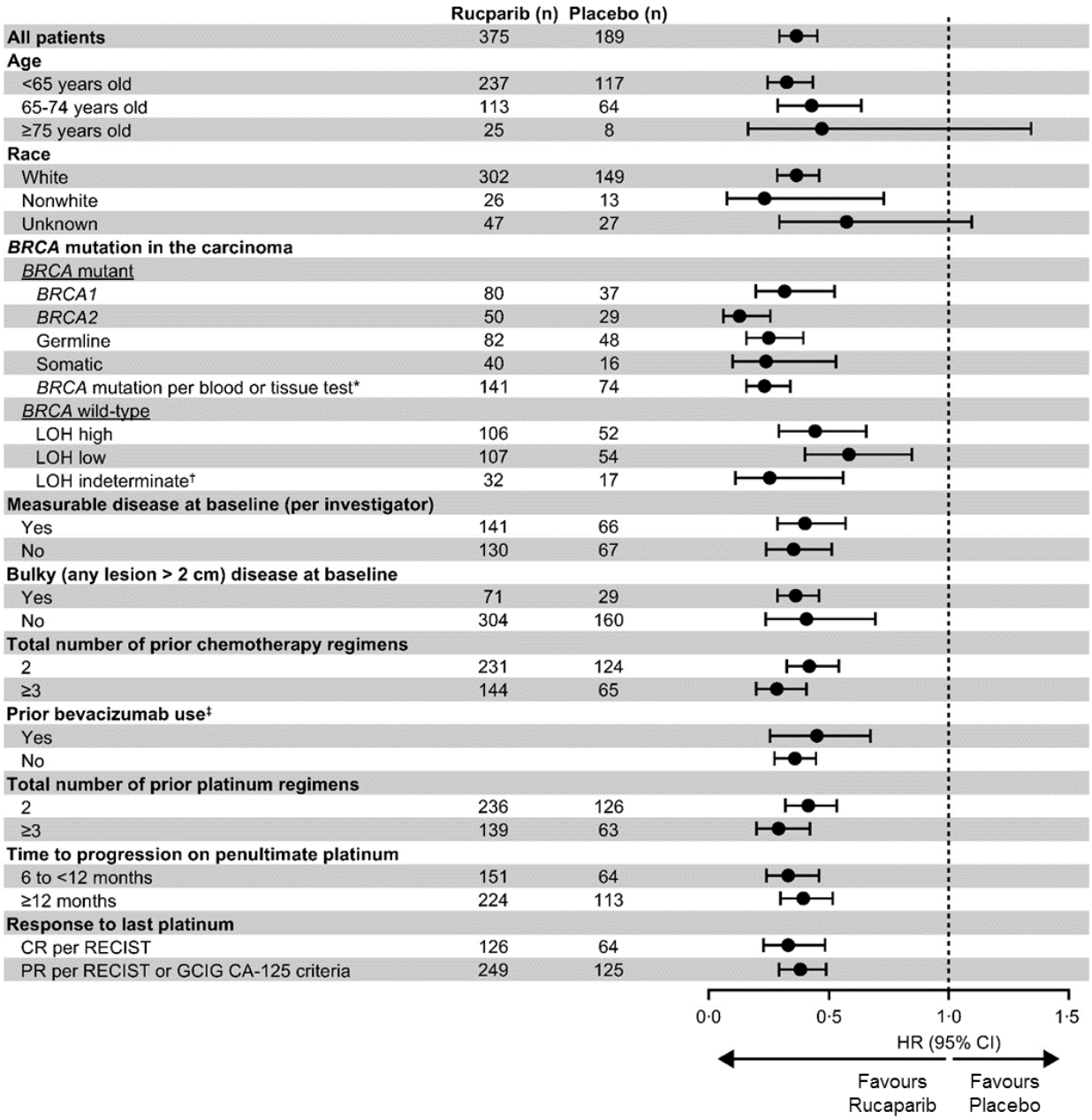
Kaplan-Meier estimates of progression-free survival as assessed by the investigator (A-C) and by BICR (D-F) in the rucaparib (blue) and placebo (red) arms for (A, D) patients with a *BRCA*-mutant carcinoma, (B, E) patients with an HRD carcinoma, and (C, F) the intent-to-treat population.



BICR=blinded, independent central radiology review; CI=confidence interval;

HRD=homologous recombination deficient; NR=not reached.

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

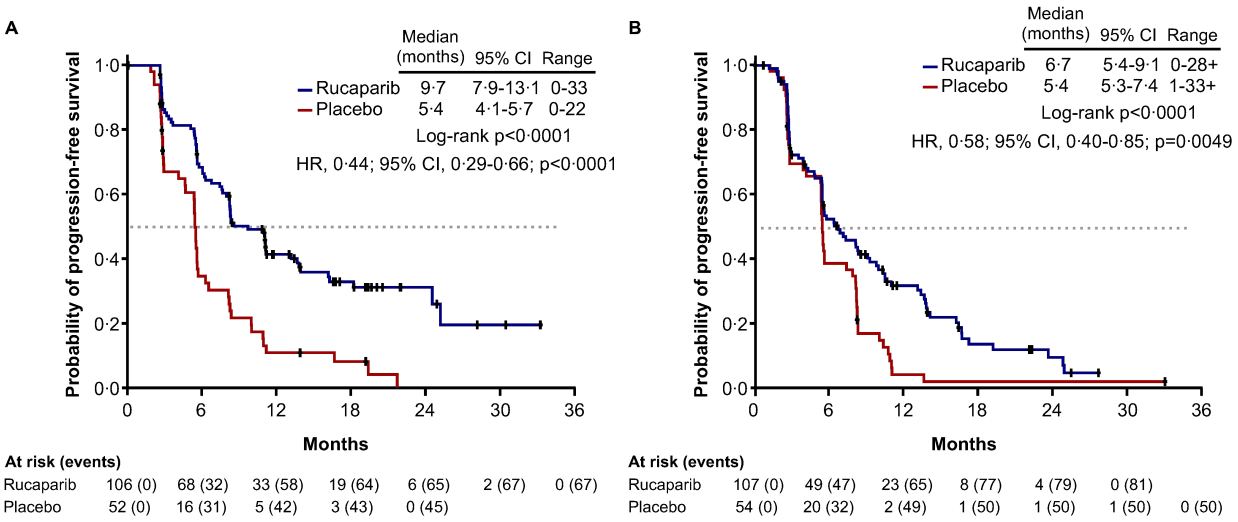


CA-125=cancer antigen 125; CI=confidence interval; CR=complete response; GCIG=Gynecologic Cancer InterGroup; HR=hazard ratio; ITT=intent-to-treat; LOH=loss of heterozygosity; PR=partial response; RECIST=Response Evaluation Criteria In Solid

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 (A) LOH high and (B) LOH low.



CI=confidence interval; HR=hazard ratio; LOH=loss of heterozygosity.

ONLINE SUPPLEMENTARY APPENDIX

Rucaparib for recurrent ovarian cancer after response to platinum therapy (ARIEL3): an international, randomised, double-blind study, phase 3 trial

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

This appendix has been provided by the authors to give readers additional information about their work.

TABLE OF CONTENTS

ARIEL3 collaborators

Australia – M. Buck, A. Dean, M. L. Friedlander, J. Goh, P. Harnett, G. Kichenadasse, C. L. Scott; **Belgium –** H. Denys, L. Dirix, I. Vergote; **Canada –** L. Elit, P. Ghatage, A. M. Oza, M. Plante, D. Provencher, J. I. Weberpals, S. Welch; **France –** A. Floquet, L. Gladieff, F. Joly, A. Leary, A. Lortholary, J. Lotz, J. Medioni, O. Tredan, B. You; **Germany –** A. El-Balat, C. Hänle, P. Krabisch, T. Neunhöffer, M. Pölcher, P. Wimberger; **Israel –** A. Amit, S. Kovel, M. Leviov, T. Safra, R. Shapira-Frommer, S. Stemmer; **Italy –** A. Bologna, N. Colombo, D. Lorusso, S. Pignata, R. F. Sabbatini, G. Scambia, S. Tamberi, C. Zamagni; **New Zealand –** P. C. Fong, A. O'Donnell; **Spain –** M. Amenedo Gancedo, A. Casado Herraez, J. Garcia-Donas, E. M. Guerra, A. Oaknin, I. Palacio, I. Romero, A. Sanchez; **United Kingdom –** S. N. Banerjee, A. Clamp, Y. Drew, H. G. Gabra, D. Jackson, J. A. Ledermann, I. A. McNeish, C. Parkinson, M. Powell; **United States –** C. Aghajanian, D. K. Armstrong, M. J. Birrer, M. K. Buss, S. K. Chambers, L-m. Chen, R. L. Coleman, R. W. Holloway, G. E. Konecny, L. Ma, M. A. Morgan, R. T. Morris, D. G. Mutch, D. M. O'Malley, B. M. Slomovitz, E. M. Swisher, T. Vanderkwaak, M. Vulfovich

SUPPLEMENTAL METHODS

Patient inclusion/exclusion criteria

A full list of inclusion and exclusion criteria are provided in Table S1. Patients must have achieved either a complete response by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST) 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) response criteria, to their last platinum-based regimen. All responses required that CA-125 be less than the upper limit of normal.

Next-generation sequencing of tumour biopsies

Patients were required to provide sufficient archival formalin-fixed paraffin-embedded tumour tissue (1 × 4 μm section for haematoxylin and eosin stain and approximately 8 to 12 × 10 μm sections, or equivalent) for analyses of mutations in homologous recombination pathway genes (Table S2) and assessment of genomic loss of heterozygosity (LOH) using Foundation Medicine's T5 next-generation sequencing assay performed at the central testing facility (Cambridge, MA). A cutoff of 16% or greater was defined as the optimum cutoff following a retrospective analysis of data from ARIEL2 Part 1[1] and was prespecified for high genomic LOH. The most recently collected tumour tissue sample was preferred. *BRCA1* or *BRCA2 (BRCA)* mutation results were provided to patients and investigators upon availability; results for other mutations were provided upon study treatment discontinuation. Investigators were not blinded to *BRCA* mutation status because patients could enrol with a known germline *BRCA* mutation (limited to 150 patients), and presence of a *BRCA* mutation detected upon analysis of tumour tissue during the study was provided to consenting patients and investigators. Germline mutations were identified by BRCAnalysis CDx test (Myriad Genetics).

Tumours were designated in the following ways:

- Germline *BRCA* mutant: deleterious *BRCA* mutation detected by both next-generation sequencing of tumour tissue and central germline blood test
- Somatic *BRCA* mutant: deleterious *BRCA* mutation detected by next-generation sequencing of tumour tissue but not by central germline blood test
- *BRCA* wild type: deleterious *BRCA* mutation not detected by next-generation sequencing of tumour tissue
- LOH high: genomic LOH of 16% or greater as detected by next-generation sequencing of tumour tissue
- LOH low: genomic LOH of less than 16% as detected by next-generation sequencing of tumour tissue
- LOH indeterminate: not evaluable for percent of genomic LOH due to low tumour content or low aneuploidy in the biopsy

These designations were used to categorise patients into the following non-nested, non-overlapping subgroups:

- *BRCA* mutant (a deleterious germline or somatic *BRCA* mutation in the carcinoma)
- *BRCA* wild type/LOH high
- *BRCA* wild type/LOH low
- *BRCA* wild type/LOH indeterminate

Randomisation stratification

Randomisation stratification factors included: homologous recombination deficiency (HRD) status (based on gene mutation only); progression-free interval following penultimate platinum-based regimen (6 to 12 or more than 12 months); and best response to most recent platinum-based regimen (complete or partial response). Stratification based on HRD as assessed by gene mutation status of tumour tissue was as follows: mutation in *BRCA1* or *BRCA2* (*BRCA* mutant), mutation in a non-*BRCA* gene associated with homologous recombination from a 28-gene panel (Table S2), or no mutation in *BRCA* or a homologous recombination panel gene.

Treatment and assessments

Study drug could be taken with or without food. Supportive care (eg, analgesics for pain control or antiemetics) was permitted at the investigator's discretion. Patients who discontinued treatment for a reason other than disease progression or death continued to have tumour scans performed at 12-week intervals (up to 1 week prior was permitted) until disease progression, as assessed by the investigator. Patient-reported outcomes using the Functional Assessment of Cancer Therapy Ovarian Symptom Index 18 (FOSI-18) instrument were assessed at screening, day 1 of every treatment cycle, and treatment discontinuation. All patients who discontinued from treatment (regardless of reason) were followed for 28 days for assessment of adverse events and patient reported outcomes. Patients were also 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.

Dose modification criteria

Rucaparib was to be reduced if any of the following were observed: grade 3 or 4 haematologic toxicity; grade 3 or 4 nonhaematologic toxicity (except for alopecia, nausea, vomiting, or diarrhoea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study centre routines). Additionally, rucaparib may have been held and/or reduced at the discretion of the investigator for grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care. Rucaparib was to be held until the toxicity resolved to grade 2 or less.

Secondary endpoint definitions

The time to an event of worsening in the FOSI-18 disease-related symptoms–physical (DRS-P) subscale was defined as time from randomisation to a 4-point reduction in the DRS-P subscale. The time to an event of worsening in the total score of the FOSI-18 was defined as the time from randomisation to an 8-point reduction in the total score. Overall survival is defined as the number of days from the date of randomisation to the date of death (due to any cause). Progression-free survival by independent radiology review was defined as the time from randomisation to disease progression, according to RECIST criteria as assessed by independent radiology review, or death due to any cause, whichever occurs first. Safety endpoints included incidence of adverse events, clinical laboratory abnormalities, and dose modifications. The population pharmacokinetics endpoint included individual model parameter estimates of rucaparib and covariates identification.

Efficacy analysis of subgroups

The primary endpoint of investigator-assessed progression-free survival was further explored in prespecified categories, including the following:

- Randomization stratification factors
    - *BRCA* mutant, mutation in non-*BRCA* homologous recombination repair (HRR) gene on list used for randomisation stratification (Table S2), no mutation in HRR gene on list used for randomisation stratification
    - Interval between completion of the penultimate platinum-based regimen and disease progression (6 to 12 months or > 12 months)
    - Best response (complete response per RECIST or partial response per RECIST and/or GCIG CA-125 response) to platinum regimen received immediately prior to initiation of rucaparib maintenance therapy
- HRD definition used for efficacy analysis (*BRCA* mutant, *BRCA* wild-type/LOH high, *BRCA* wild-type/LOH low, *BRCA* wild-type/LOH indeterminate)

- Age groups (<65, 65-74, ≥75)
- Race (white, non-white)
- Subgroups based on disease burden at baseline
    - Measurable disease: all patients who have measurable disease (ie, target lesion of any size) at baseline as assessed by the investigator and/or independent radiology reviewer.
    - No disease: all patients who have no target lesions or non-target disease at baseline as assessed by the investigator and/or independent radiology reviewer.
    - No bulky disease: all patients with any/all lesions less than 2 cm in the shortest axis (lymph nodes) or longest axis (all other lesions) as assessed by the independent reviewer.
- Subgroups based on gene mutation and type
    - *BRCA* mutation (*BRCA1* or *BRCA2*)
    - *BRCA* mutation origin (germline, somatic, unknown)
    - Combining the patients with a tumour with a somatic *BRCA* mutation and the patients with a tumour with LOH high
    - Intent-to-treat population excluding patients with a tumour harbouring a *BRCA* mutation that is germline in origin

In addition, investigator-assessed PFS was explored in a retrospective analysis in patients with and without prior bevacizumab as part of their penultimate or earlier treatment.

Exploratory endpoint

The proportion of patients achieving an objective response was an exploratory endpoint of ARIEL3, and was determined by the proportion of patients with measurable disease at study entry who achieved a best response of complete or partial response per RECIST as assessed by both investigator and independent radiology review.

Statistical analysis

The primary endpoint was tested using an ordered step-down multiple comparisons procedure for 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 analysis of patients with a *BRCA*-mutant carcinoma. As with the primary endpoint, analysis of key secondary endpoints followed in an ordered step-down procedure, starting with patient-reported outcomes using DRS-P subscale of the FOSI-18, then patient-reported outcomes using total FOSI-18 score, and then overall survival. 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.

Time-to-event variables (eg, progression-free survival) were calculated with Kaplan-Meier methodology. For progression-free survival, patients without documented progression were censored as of their last tumour assessment. Patients without a 4-point reduction in the FOSI-18 DRS-P subscale score were censored on the date of their last patient-reported outcome evaluation. Time-to-event distributions between the randomised arms were using a stratified log-rank test. Hazard ratios were estimated using the Cox proportional hazards model. Exact 95% confidence intervals for the objective response rate were determined using the Clopper-Pearson method.

The primary and secondary efficacy endpoints were also evaluated in the non-nested, non-overlapping subgroups of *BRCA* mutant, *BRCA* wild type/LOH high, *BRCA* wild type/LOH low, and *BRCA* wild type/LOH indeterminate to ensure that the results in the HRD cohort were not solely driven by the results in the *BRCA*-mutant cohort and the results in the intent-to-treat population were not solely driven by the results of the HRD cohort. To claim a significant result in the HRD cohort, the size of the estimated effect in patients with carcinomas with *BRCA* wild type/LOH high was required to be clinically relevant and at least as large as what would be needed to achieve ‘‘statistical significance’’ in an analysis conducted in the entire HRD population. Similarly, for the results in the intent-to-treat population to be considered significant and not solely driven by the results of the *BRCA*-mutant or HRD cohorts, the size of the estimated effect in patients with carcinomas with *BRCA* wild type/LOH low and *BRCA* wild type/LOH indeterminate was required to be clinically relevant and at least as large as what would be needed to achieve ‘‘statistical significance’’ in an analysis conducted in the entire intent-to-treat population.

Table S1: Inclusion and exclusion criteria

All patients enrolled into the study must have met all of the following inclusion criteria:
1. Signed an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Were ≥18 years of age at the time the informed consent form was signed
3. Had 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 tumour must have been confirmed to be high-grade serous or endometrioid - Grade 2 tumours classified under a 3-tier system should have been 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 was permitted. Prior hormonal therapy was permitted; this treatment were not be counted as a non-platinum regimen. - There was 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 was considered 1 treatment regimen - Prior maintenance therapy following a prior treatment regimen was permitted, with the exception of the regimen received immediately prior to maintenance in this study. No anticancer therapy was 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 was randomised 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 was per Investigator' discretion. (This criterion was added through an amendment to the protocol on November 4, 2014, 7 months after enrolment had started) - A minimum of 4 cycles of platinum chemotherapy must have been administered. There was 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 randomisation within 8 weeks of the last platinum dose was not permitted. - A CR was defined as a complete radiologic response per RECIST v1.1, i.e. absence of any detectable disease and CA-125 <ULN - A PR was 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 have been <ULN for all responses classified as a PR - R0 surgery (no visible tumour) or R1 surgery (residual disease <1 cm) as a component of the most recent treatment regimen was not permitted. The response assessment must have been 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 was 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 have been adequately documented in the patient's medical record
6. Had sufficient archival formalin-fixed paraffin-embedded (FFPE) tumour tissue (1 x 4 µm section for haematoxylin and eosin [H&E] stain and approximately 8 – 12 x 10 µm sections, or equivalent) available for planned analyses. - The most recently collected tumour tissue sample should have been provided, if available - Submission of a tumour block was preferred; if sections were provided, these must all have been from the same tumour sample - Sample must have been received at the central laboratory at least 3 weeks prior to planned start of treatment in order to enable stratification for randomisation
7. Had CA-125 measurement that was < ULN
8. Had ECOG performance status of 0 to 1
9. Had 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) ≥1.5 × 10^9/L; platelets >100 × 10^9/L; haemoglobin ≥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 was 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

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

1. History of a prior malignancy except:
   - Curatively treated non-melanoma skin cancer
   - Breast cancer treated curatively >3 years ago, or other solid tumour 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 were 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 randomisation to maintenance treatment in this study
4. Symptomatic and/or untreated central nervous system (CNS) metastases. Patients with asymptomatic previously treated CNS metastases were 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 have, in the opinion of the Investigator, interfered 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 had 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 were unlikely to be exacerbated by treatment with study drug
   - Ongoing hormonal treatment for previously treated breast cancer was permitted
9. Received administration of strong CYP1A2 or CYP3A4 inhibitors ≤7 days prior to first dose of study drug or had 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 have been sufficiently recovered and stable before treatment administration
11. Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study

Table S2: Panel of 30 genes associated with homologous recombination utilised for stratification

BRCA	**Other Homologous Recombination Genes**	
BRCA1	*ATM*	*FANCI*
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*

Table S3: Objective response rates in patients with measurable disease at baseline

	***BRCA* Mutant**		**HRD**		**Intent-to-Treat Population**	
	Rucaparib (n=40)	**Placebo (n=23)**	**Rucaparib (n=85)**	**Placebo (n=41)**	**Rucaparib (n=141)**	**Placebo (n=66)**
Investigator-assessed RECIST ORR (confirmed CR+PR)	15 (37.5%) [22.7%-54.2%]	2 (8.7%) [1.1%-28.0%]	23 (27.1%) [18.0%-37.8%]	3 (7.3%) [1.5%-19.9%]	26 (18.4%) [12.4%-25.8%]	5 (7.6%) [2.5%-16.8%]
Complete response	7 (17.5%)	0 (0%)	10 (11.8%)	0 (0%)	10 (7.1%)	1 (1.5%)
Partial response	8 (20.0%)	2 (8.7%)	13 (15.3%)	3 (7.3%)	16 (11.3%)	4 (6.1%)
Stable disease	19 (47.5%)	8 (34.8%)	43 (50.6%)	17 (41.5%)	71 (50.4%)	29 (43.9%)
Progressive disease	5 (12.5%)	13 (56.5%)	18 (21.2%)	21 (51.2%)	38 (27.0%)	32 (48.5%)
Not evaluable	1 (2.5%)	0 (0%)	1 (1.2%)	0 (0%)	6 (4.3%)	0 (0%)

Data are n (%) [95% CI]. CI=confidence interval; HRD=homologous recombination deficient; ORR=objective response rate; RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

Table S4: Treatment-emergent adverse events leading to dose reduction and/or treatment interruption in ≥1% of patients

	Dose Reduction		Treatment Interruption		Dose Reduction and/or Treatment Interruption	
Adverse event	**Rucaparib (n=372)**	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**	**Rucaparib (n=372)**	**Placebo (n=189)**
Any adverse event leading to dose reduction or interruption	203 (54.6%)	8 (4.2%)	237 (63.7%)	19 (10.1%)	263 (70.7%)	20 (10.6%)
Thrombocytopenia; platelet count decreased	39 (10.5%)	0	64 (17.2%)	0	67 (18.0%)	0
Anaemia; decreased haemoglobin	45 (12.1%)	0	51 (13.7%)	1 (0.5%)	62 (16.7%)	1 (0.5%)
Nausea	37 (9.9%)	1 (0.5%)	38 (10.2%)	2 (1.1%)	56 (15.1%)	2 (1.1%)
Increase in alanine aminotransferase or aspartate aminotransferase	41 (11.0%)	0	39 (10.5%)	0	50 (13.4%)	0
Asthenia; fatigue	33 (8.9%)	4 (2.1%)	32 (8.6%)	6 (3.2%)	46 (12.4%)	6 (3.2%)
Vomiting	12 (3.2%)	0	32 (8.6%)	2 (1.1%)	35 (9.4%)	2 (1.1%)
Neutropenia; neutrophil count decreased	13 (3.5%)	0	23 (6.2%)	1 (0.5%)	26 (7.0%)	1 (0.5%)
Increase in blood creatinine	14 (3.8%)	0	12 (3.2%)	0	17 (4.6%)	0
Diarrhoea	5 (1.3%)	0	11 (3.0%)	0	14 (3.8%)	0
Abdominal pain	2 (0.5%)	0	12 (3.2%)	0	12 (3.2%)	0
Constipation	5 (1.3%)	0	6 (1.6%)	1 (0.5%)	10 (2.7%)	1 (0.5%)
Abdominal pain upper	3 (0.8%)	0	5 (1.3%)	0	6 (1.6%)	0
Increase in transaminases	5 (1.3%)	0	4 (1.1%)	0	6 (1.6%)	0
Rash	2 (0.5%)	0	5 (1.3%)	0	6 (1.6%)	0
Dysgeusia	5 (1.3%)	0	3 (0.8%)	0	5 (1.3%)	0
Dyspepsia	4 (1.1%)	0	3 (0.8%)	1 (0.5%)	5 (1.3%)	1 (0.5%)
Urinary tract infection	0	1 (0.5%)	5 (1.3%)	0	5 (1.3%)	1 (0.5%)
Mucosal inflammation	1 (0.3%)	2 (1.1%)	4 (1.1%)	1 (0.5%)	4 (1.1%)	2 (1.1%)
Photosensitivity reaction	3 (0.8%)	0	3 (0.8%)	0	4 (1.1%)	0
Pyrexia	0	0	4 (1.1%)	0	4 (1.1%)	0
Small intestine obstruction	0	0	4 (1.1%)	1 (0.5%)	4 (1.1%)	1 (0.5%)
White blood count decreased	0	0	4 (1.1%)	0	4 (1.1%)	0
Decreased appetite	1 (0.3%)	1 (0.5%)	3 (0.8%)	2 (1.1%)	3 (0.8%)	2 (1.1%)
Dizziness	1 (0.3%)	0	1 (0.3%)	2 (1.1%)	2 (0.5%)	2 (1.1%)
Lung infection	0	1 (0.5%)	0	2 (1.1%)	0	2 (1.1%)

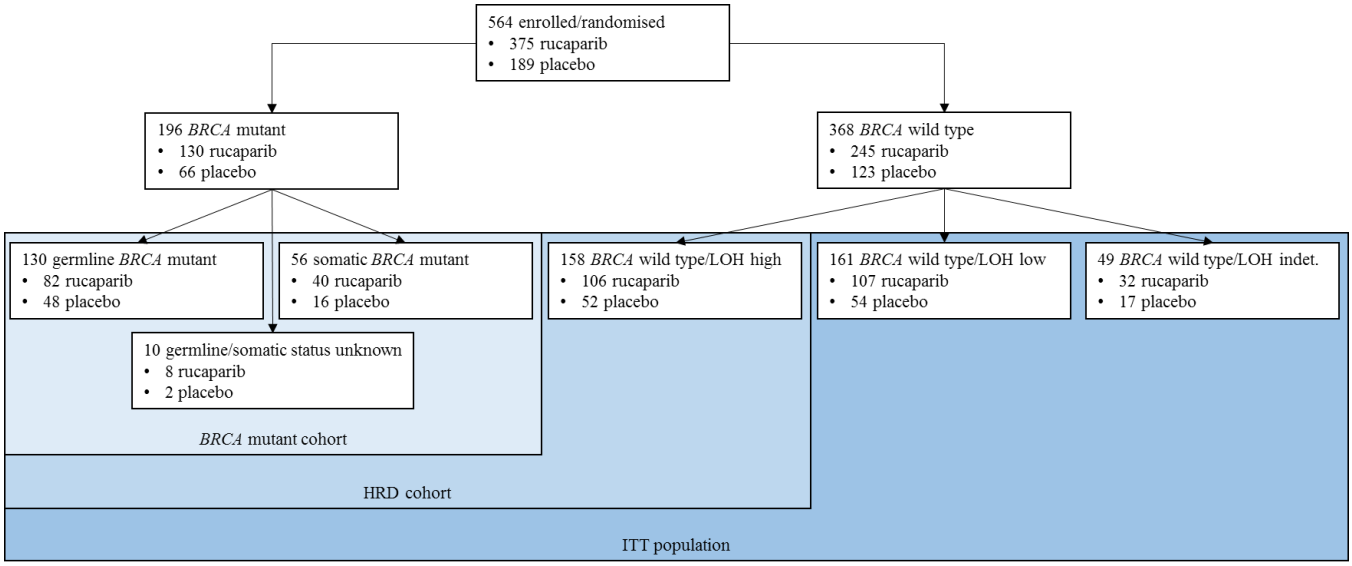
Data are n (%) in the safety population, all patients who received at least one dose of protocol-specified treatment; a patient may have had a dose reduction or interruption as a result of more than one adverse event. Data are sorted based on incidence of reduction and/or interruption in the rucaparib arm.

Table S5: Treatment-emergent adverse events leading to dose discontinuation

Adverse event	Rucaparib (n=372)	Placebo (n=189)
Any adverse event leading to discontinuation	50 (13.4%)	3 (1.6%)
Anaemia; decreased haemoglobin	11 (3.0%)	0
Thrombocytopenia; platelet count decreased	10 (2.7%)	0
Nausea	9 (2.4%)	1 (0.5%)
Asthenia; fatigue	6 (1.6%)	0
Vomiting	5 (1.3%)	1 (0.5%)
Febrile neutropenia	3 (0.8%)	0
Acute kidney injury	2 (0.5%)	0
Increase in alanine aminotransferase or aspartate aminotransferase	2 (0.5%)	0
Myelodysplastic syndrome	2 (0.5%)	0
Neutropenia; neutrophil count decreased	2 (0.5%)	0
Weight decreased	2 (0.5%)	0
Abdominal pain	1 (0.3%)	0
Acute myeloid leukaemia	1 (0.3%)	0
Acute respiratory distress syndrome	1 (0.3%)	0
Amnesia	1 (0.3%)	0
Cardiac arrest	1 (0.3%)	0
Confusional state	1 (0.3%)	0
Dyspepsia	1 (0.3%)	0
Dyspnoea	1 (0.3%)	0
Histiocytosis haematophagic	1 (0.3%)	0
Lethargy	1 (0.3%)	0
Leukopenia	1 (0.3%)	0
Mental status change	1 (0.3%)	0
Neutropenic colitis	1 (0.3%)	0
Pancytopenia	1 (0.3%)	0
Photosensitivity reaction	1 (0.3%)	0
Renal impairment	1 (0.3%)	0
Seizure	1 (0.3%)	0
Sepsis	1 (0.3%)	0
Swelling face	1 (0.3%)	0
Tachycardia	1 (0.3%)	0
Decreased appetite	0	1 (0.5%)
Intestinal obstruction	0	1 (0.5%)
Small intestinal obstruction	0	1 (0.5%)

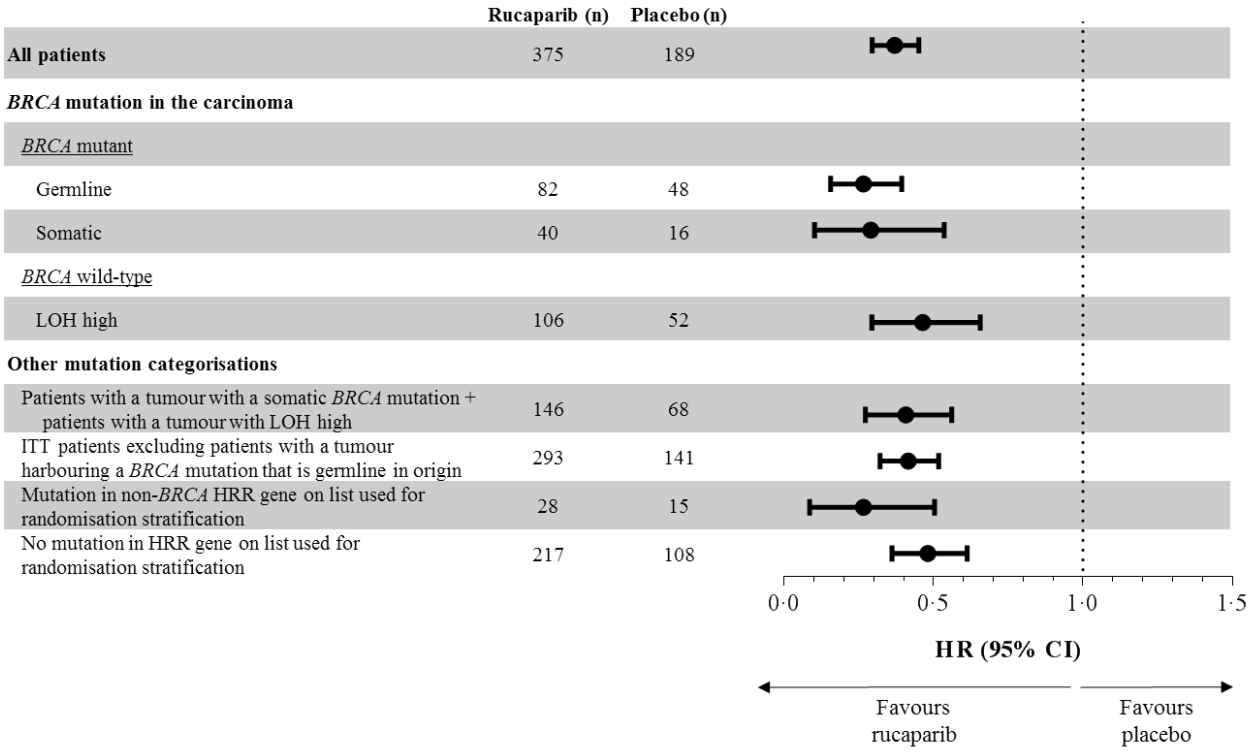
Data are n (%) in the safety population, all patients who received at least one dose of protocol-specified treatment; a patient may have discontinued as a result of more than one adverse event.

Figure S1. Diagram of efficacy analysis cohorts



HRD=homologous recombination deficient; Indet.=indeterminate; ITT=intent-to-treat; LOH=loss of heterozygosity.

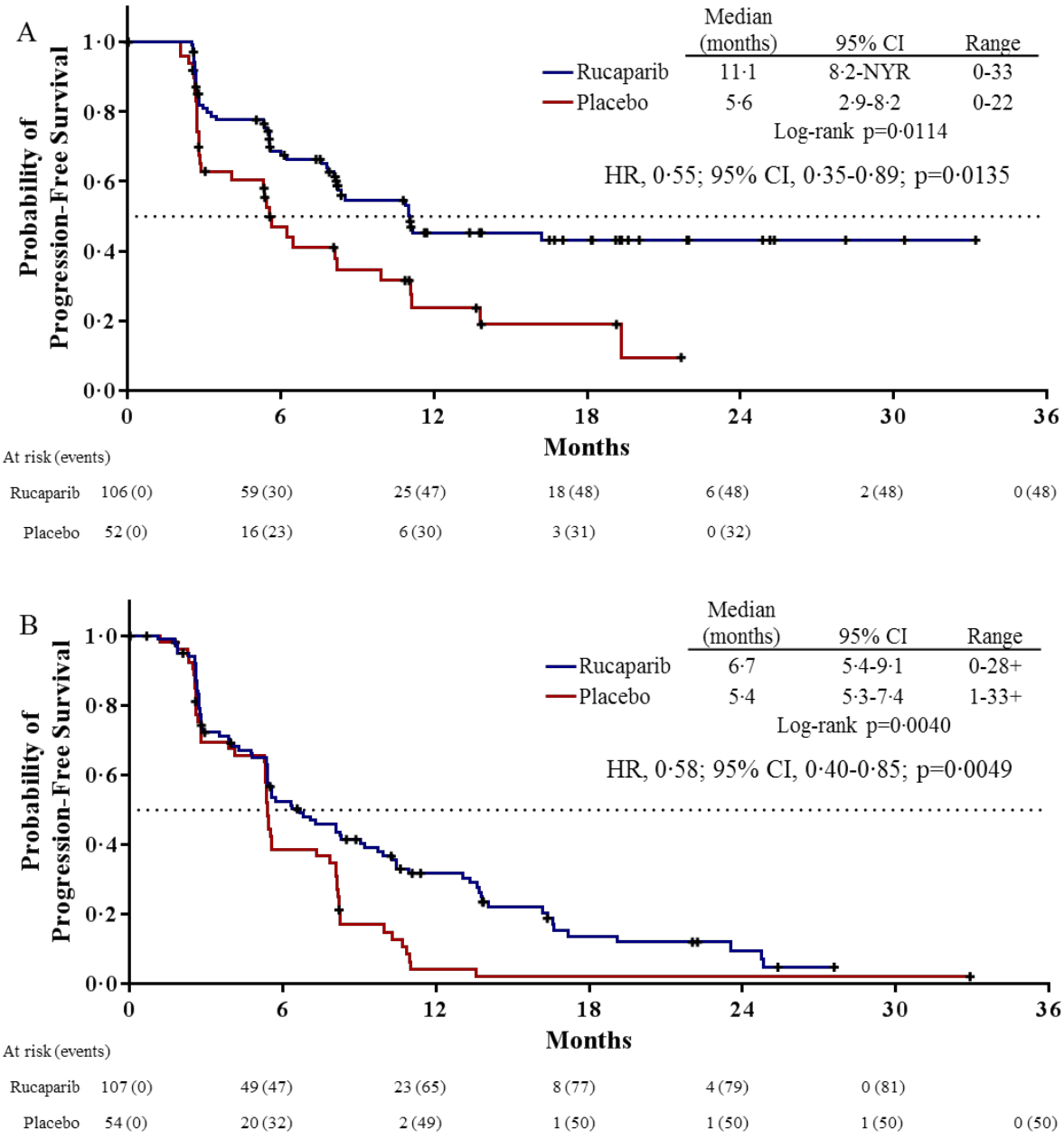
Figure S2. Investigator-assessed progression-free survival by other mutation categorisations



CI=confidence interval; HR=hazard ratio HRR=homologous recombination repair; ITT=intent-to-treat; LOH=loss of heterozygosity.

Figure S3. Blinded, independent central radiology review-assessed progression-free survival in patients with a *BRCA* wild-type carcinoma

Kaplan-Meier estimates of progression-free survival as assessed by BICR in the rucaparib (blue) and placebo (red) arms for patients with a *BRCA* wild-type carcinoma with (A) LOH high and (B) LOH low.



BICR=blinded, independent central radiology review; CI=confidence interval; HR=hazard ratio; LOH=loss of heterozygosity.

Figure S4. Mean baseline and on-treatment values for haematologic laboratory parameters

(**A**) Haemoglobin, (**B**) neutrophil, and (**C**) platelet values for patients in the safety population with baseline and postbaseline results. Horizontal lines in graphs represent the upper and lower limits of normal for each laboratory parameter. Error bars represent standard error of the mean.

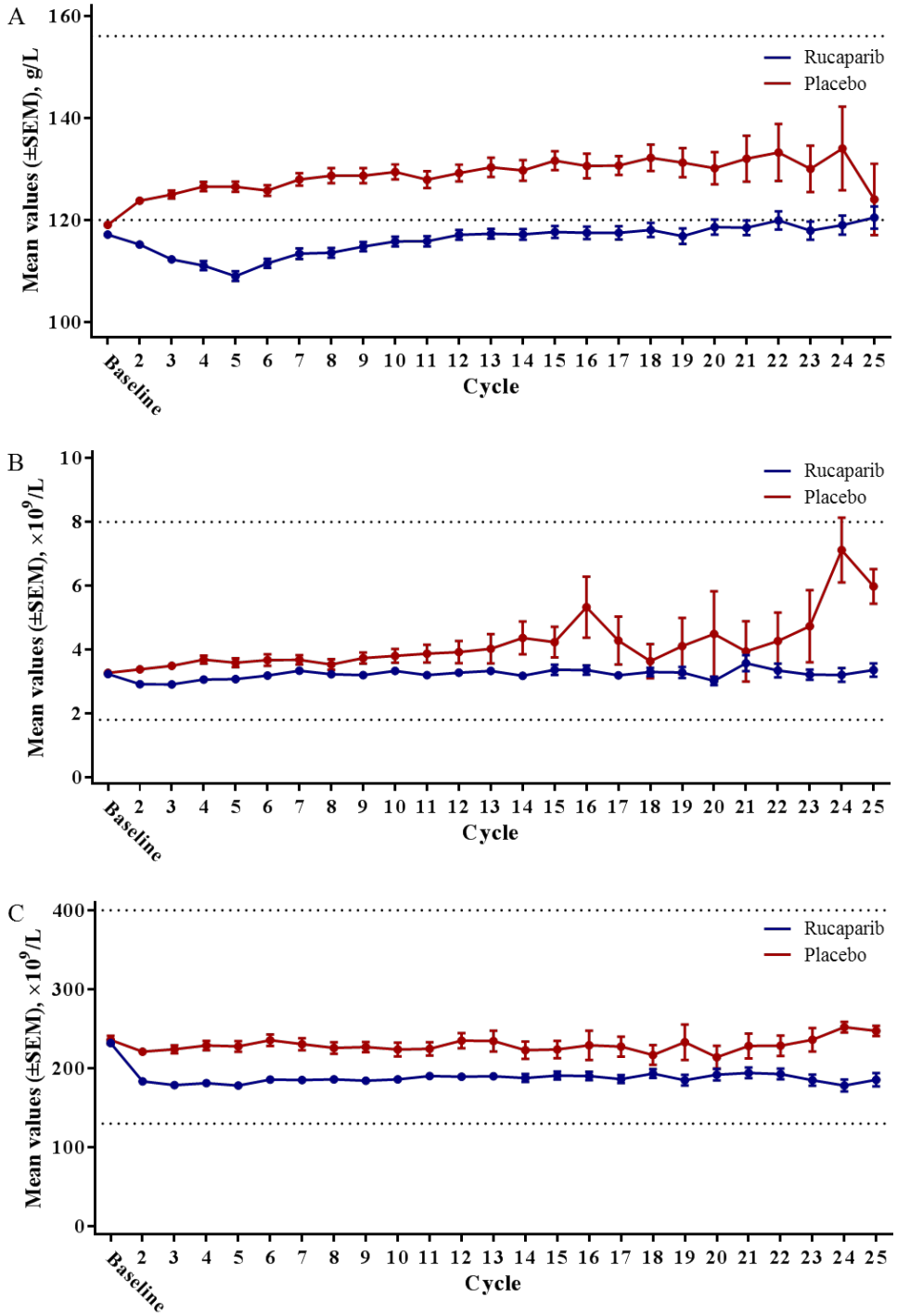
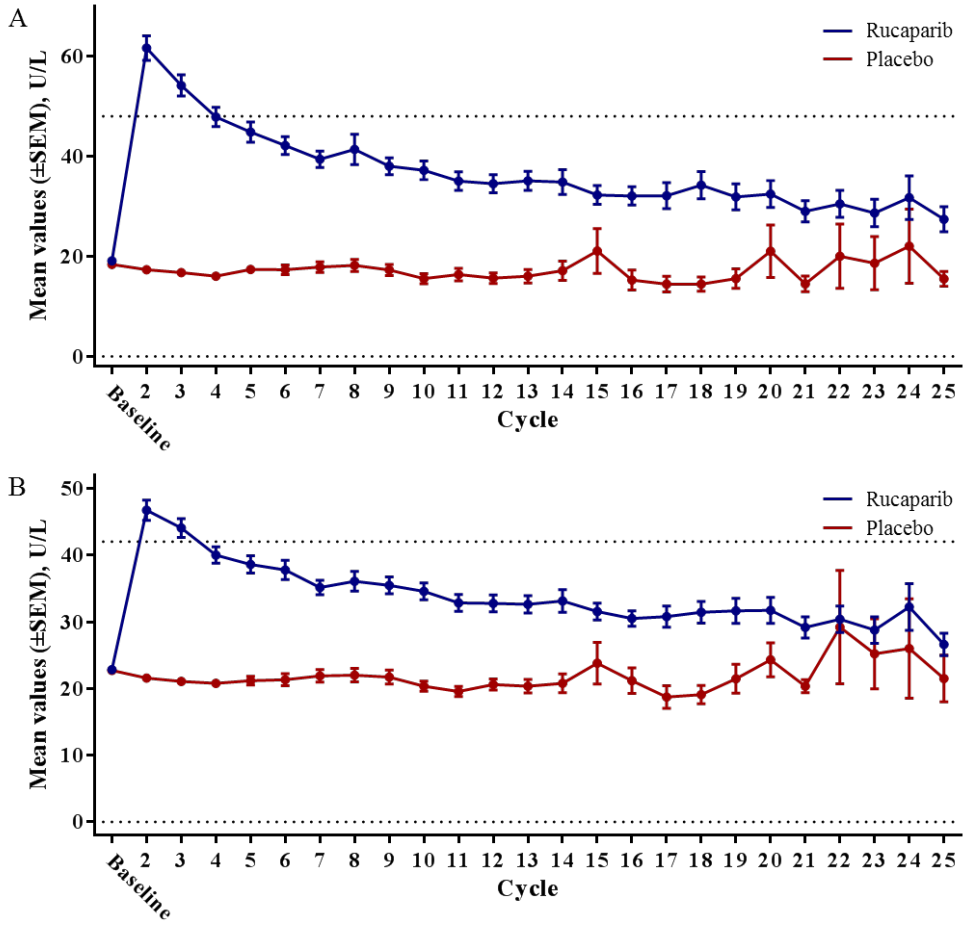
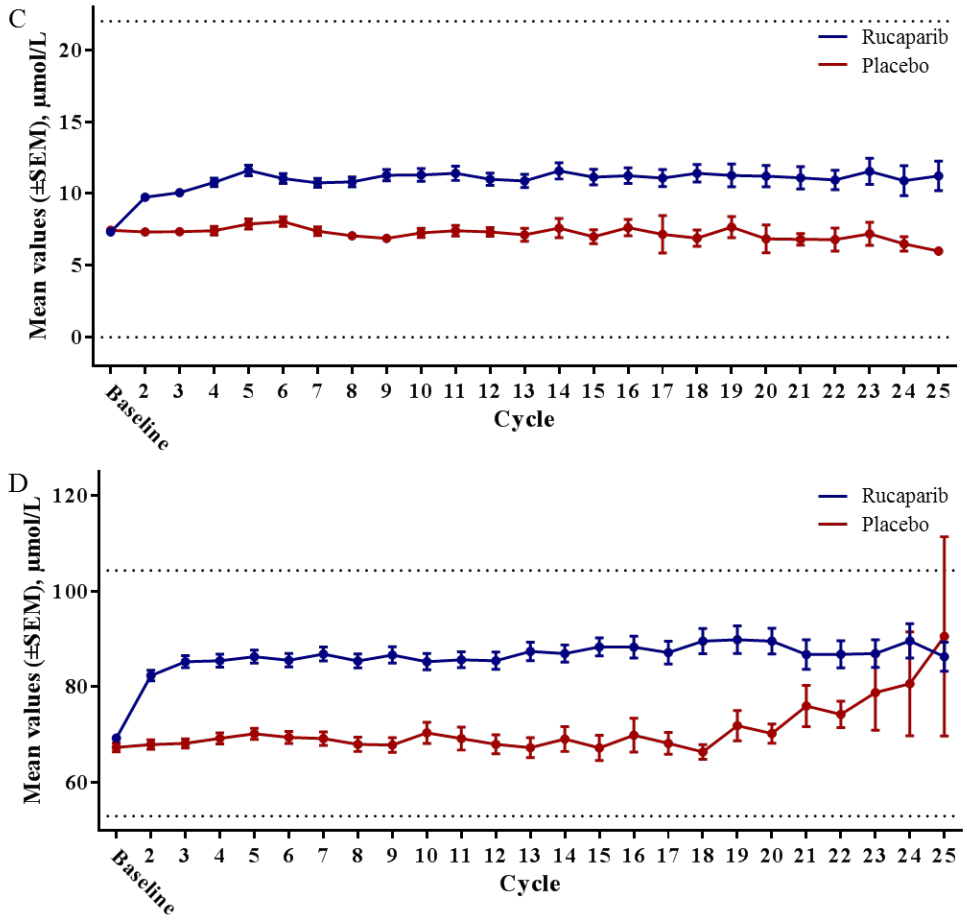


Figure S5. Mean baseline and on-treatment values for chemistry laboratory parameters

(**A**) Alanine aminotransferase, (**B**) aspartate aminotransferase, (**C**) bilirubin, and (**D**) creatinine values for patients in the safety population with baseline and postbaseline results. Horizontal lines in graphs represent the upper and lower limits of normal for each laboratory parameter. Error bars represent standard error of the mean.




C
Mean values (±SEM), µmol/L
20
15
10
5
0
Rucaparib
Placebo
Baseline
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Cycle
D
Mean values (±SEM), µmol/L
120
100
80
60
Rucaparib
Placebo
Baseline
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Cycle

References

1. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017; 18(1): 75-87.