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

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

Declaration of interests

RLC reports grants from AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, Merck, Clovis Oncology, Esperance, and AbbVie and reports serving as an advisor to AstraZeneca, Roche/Genentech, Janssen, OncoMed, Millennium, Merck, Clovis Oncology, Esperance, Tesaro, GamaMabs, Pfizer, Genmab, Gradalis, Bayer, and AbbVie. AMO has served on advisory boards for Amgen, Verastem, Clovis Oncology, and Immunovaccine; received support for travel or accommodation from AstraZeneca; and received honoraria from WebRx. DL has served in a consulting or advisory role for AstraZeneca, Clovis Oncology, Roche, Tesaro, and PharmaMar and received support for travel or accommodation from Roche and PharmaMar. CA served on a steering committee for Mateon Therapeutics and has served on advisory boards for Clovis Oncology, Cerulean Pharma, Bayer, VentiRx, and AstraZeneca. AO has served on advisory boards for Roche, AstraZeneca, PharmaMar, Clovis Oncology, and Tesaro and received support for travel 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 served on advisory boards for AstraZeneca. AC has served on advisory boards for AstraZeneca and Roche and received research support from AstraZeneca. AL has served on an advisory board for Clovis Oncology, Pfizer, and PharmaMar; reports institutional research grant support from GamaMabs and Merus; and reports boarding and travel expenses for congress activities from AstraZeneca. RWH has served on a speakers bureau for AstraZeneca, Clovis Oncology, and Tesaro. PCF has served on advisory boards for Clovis Oncology and AstraZeneca and received honoraria from AstraZeneca. JCG has served on advisory boards for Roche, AstraZeneca, Janssen, Merck, and Bristol-Myers Squibb and received support for travel or accommodation from Roche, Bristol-Myers Squibb, and Astellas. DMO received research funding from Clovis Oncology; received institutional research support from Amgen, VentiRx, Regeneron, Immunogen, Array Biopharma, Janssen, Clovis Oncology, EMD Serono, Ergomed, Ajinomoto, and Genentech/Roche; served on an advisory board for Clovis Oncology, AstraZeneca, Janssen, Genentech/Roche, Eisai, Tesaro, and Novocure; served on steering committees for Amgen, Tesaro, and Novocure; and served as a consultant to Tesaro and Novocure. JG-D has received research funding from AstraZeneca and 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; received support for travel or accommodation from AstraZeneca, Clovis Oncology, and Roche; and received drugs for research from Eisai Australia; and her institution received in kind research support for parallel laboratory work using rucaparib. TC, LM, JI, SG, CG, TCH, KKL, and HG are employees of Clovis Oncology and 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 this trial. JAL has served in an advisory role for Clovis Oncology and AstraZeneca and served on a speakers bureau for and received research grants from AstraZeneca. All other authors declare no competing interests.

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Summary

Background—Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has anticancer activity in recurrent ovarian carcinoma harbouring a BRCA mutation or high percentage of genome-wide loss of heterozygosity. In this trial we assessed rucaparib versus placebo after response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma.

Methods—In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients from 87 hospitals and cancer centres across 11 countries. Eligible patients were aged 18 years or older, had a platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma, had received at least two previous platinum-based chemotherapy regimens, had achieved complete or partial response to their last platinum-based regimen, had a cancer antigen 125 concentration of less than the upper limit of normal, had a performance status of 0–1, and had adequate organ function. Patients were ineligible if they had symptomatic or untreated central nervous system metastases, had received anticancer therapy 14 days or fewer before starting the study, or had received previous treatment with a poly(ADP-ribose) polymerase inhibitor. We randomly allocated patients 2:1 to receive oral rucaparib 600 mg twice daily or placebo in 28 day cycles using a computer-generated sequence (block size of six, stratified by homologous recombination repair gene mutation status, progression-free interval after the penultimate platinum-based regimen, and best response to the most recent platinum-based regimen). Patients, investigators, site staff, assessors, and the funder were masked to assignments. The primary outcome was investigator-assessed progression-free survival evaluated with use of an ordered step-down procedure for three nested cohorts: patients with BRCA mutations (carcinoma associated with deleterious germline or somatic BRCA mutations), patients with homologous recombination deficiencies (BRCA mutant or BRCA wild-type and high loss of heterozygosity), and the intention-to-treat population, assessed at screening and every 12 weeks thereafter. This trial is registered with ClinicalTrials.gov, number NCT01968213; enrolment is complete.

Findings—Between April 7, 2014, and July 19, 2016, we randomly allocated 564 patients: 375 (66%) to rucaparib and 189 (34%) to placebo. Median progression-free survival in patients with a BRCA-mutant carcinoma was 16·6 months (95% CI 13·4–22·9; 130 [35%] patients) in the rucaparib group versus 5·4 months (3·4–6·7; 66 [35%] patients) in the placebo group (hazard ratio 0·23 [95% CI 0·16–0·34]; p<0·0001). In patients with a homologous recombination deficient carcinoma (236 [63%] vs 118 [62%]), it was 13·6 months (10·9–16·2) versus 5·4 months (5·1–5·6; 0·32 [0·24–0·42]; p<0·0001). In the intention-to-treat population, it was 10·8 months (8·3–11·4) versus 5·4 months (5·3–5·5; 0·36 [0·30–0·45]; p<0·0001). Treatment-emergent adverse events of grade 3 or higher in the safety population (372 [99%] patients in the rucaparib group vs 189 [100%] in the placebo group) were reported in 209 (56%) patients in the rucaparib group versus 28 (15%) in the placebo group, the most common of which were anaemia or decreased haemoglobin concentration (70 [19%] vs one [1%]) and increased alanine or aspartate aminotransferase concentration (39 [10%] vs none).

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. ARIEL3 provides further evidence that use of a poly(ADP-ribose) polymerase inhibitor in the maintenance treatment setting versus placebo could be considered a new standard of care for women with platinum-sensitive ovarian cancer following a complete or partial response to second-line or later platinum-based chemotherapy.

Funding—Clovis Oncology, Inc.

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, most of these patients will ultimately relapse.[2] 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 than without this treatment.[4, 5, 6, 7, 8, 9] However, clinical benefit is typically transient, hence the pursuit continues for new therapies and tools to identify patients who might benefit most from these therapies, as well as to identify the optimal therapeutic strategy.

The poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib is approved in the USA for treatment of patients with deleterious BRCA mutation (germline or somatic)-associated advanced ovarian carcinoma who have received two or more chemotherapy regimens. Approval of rucaparib was based on the proportion of patients with an objective response (57 [54%] of 106 patients) observed in a pooled population of patients with BRCA-mutant high-grade ovarian carcinoma from the Study 10[10] and ARIEL211 clinical trials.

In part 1 of the ARIEL2 trial,[11] 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 those with BRCA wild-type carcinomas with high genomic loss of heterozygosity (LOH), a potential marker of homologous recombination deficiency (HRD) and thus PARP inhibitor activity.[12, 13, 14, 15] The next-generation sequencing (NGS) assay used in ARIEL2 combines mutation analysis of BRCA1 and BRCA2 genes with measurement of the percentage of genome-wide LOH in the cancer tissue as a biomarker for sensitivity to rucaparib treatment. In this randomised, double-blind, placebo-controlled, phase 3 trial (ARIEL3), our objective was to assess the efficacy and safety of rucaparib versus placebo after 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 prospectively test the genomic LOH cutoff discriminator that was optimised on the basis of results of ARIEL2 part 1 as a predictive biomarker for sensitivity to rucaparib treatment.

Methods

Study design and patients

In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients from 87 hospitals and cancer centres in Australia, Belgium, Canada, France, Germany, Israel, Italy, New Zealand, Spain, the UK, and the USA. Eligible patients were aged 18 years or older, had platinum-sensitive (ie, documented radiological disease progression more than

6 months after the last dose of the penultimate platinum administered), high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma and had received at least two previous platinum-based chemotherapy regimens. We permitted previous treatment with bevacizumab, with the exception of bevacizumab maintenance treatment after the most recent platinum-based regimen. On Nov 4, 2014, after 91 patients had been randomly allocated, we made an amendment to the protocol requiring that the most recent platinum-based regimen was to be administered as a chemotherapy doublet and for a minimum of four cycles. Patients must have achieved either a complete response according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1[16] or a partial response, defined as either a RECIST partial response or a serological response according to 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, we placed no restriction on residual carcinoma size at study entry; we defined those who had persistent lesions of greater than 2 cm as established by independent radiological review as having bulky residual disease. Responses must have been maintained through completion of chemotherapy and during the interval period between completion of chemotherapy and entry into the trial. Additionally, we required CA 125 to be less than the upper limit of normal. Patients had an Eastern Cooperative Oncology Group Performance Status of 0–1 and adequate organ function. Patients were ineligible if they had symptomatic or untreated central nervous system metastases, received anticancer therapy 14 days or fewer before starting the study, or received previous treatment with a PARP inhibitor. A complete list of inclusion and exclusion criteria is provided in the appendix (pp 6–7).

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

Randomisation and masking

Within 8 weeks of their last dose of platinum, we randomly allocated eligible patients 2:1 to receive rucaparib or placebo. Randomisation was computer generated by Almac Clinical Technologies (Souderton, PA, USA) using a block size of six. Randomisation stratification factors included homologous recombination repair gene mutation status (based on gene mutation only; mutation in BRCA1 or BRCA2, mutation in a non-BRCA gene associated with homologous recombination, or no mutation in BRCA or a homologous recombination gene; additional details in the appendix [p 3]); progression-free interval following penultimate platinum-based regimen (6–12 months or >12 months); and best response to most recent platinum-based regimen (complete or partial response). Patients were assigned to the rucaparib or placebo group in a masked manner with use of Almac Clinical Technologies' interactive web and voice response system (IXRS); patients, investigators, site staff, assessors, and the funder were masked to assignments. To ensure masking was maintained, rucaparib and placebo tablets were manufactured to have identical appearances.

Procedures

Central testing of DNA derived from patient archival tumour tissue samples was done to detect mutations in homologous recombination pathway genes (appendix p 8) and assess genomic LOH with use of Foundation Medicine's T5 NGS assay (Cambridge, MA, USA). On the basis of retrospective analysis of data from ARIEL2 part 1,[11] we prespecified a cutoff of 16% or greater for ARIEL3 as a discriminator for high genomic LOH. We identified germline mutations with a BRCAnalysis CDx test (Myriad Genetics, Salt Lake City, UT, USA). Further details of the tumour tissue testing are provided in the appendix (p 2). The independent data monitoring committee surveyed enrolment of patients with a BRCA mutation and informed the funder when the target enrolment number for the BRCA-mutant cohort was anticipated to be reached. Once notified, patients who were in the screening process were allowed to complete screening and enrol in the study if they met all eligibility criteria.

Patients received oral rucaparib (600 mg twice daily) or matched placebo in continuous 28 day cycles until disease progression, death, or other reason for discontinuation. We permitted dose reductions (in decrements of 120 mg) if a patient had a grade 3 or greater or persistent grade 2 adverse event (additional details in the appendix [p 3]). We discontinued treatment for a toxicity-related treatment interruption lasting for more than 14 consecutive days (unless otherwise agreed on between the investigator and the funder).

We did disease assessments at screening, every 12 weeks during treatment (and after treatment for patients who discontinued for any reason other than disease progression), following clinical symptoms (eg, rising CA 125 levels, patient deterioration), and at treatment discontinuation. We established disease progression with RECIST. We only considered patients with a complete response at study entry to have disease progression if we identified an unequivocal new lesion. We did not consider increased CA 125 concentrations alone to indicate disease progression unless confirmed by RECIST. We provided all computed tomography scans and other imaging to a blinded, independent, central radiology review (BICR). We used the National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy Ovarian Symptom Index 18 (FOSI-18)[18] questionnaire to assess patient-reported outcomes at screening and throughout treatment.

Outcomes

The primary endpoint was investigator-assessed progression-free survival, defined as the time from randomisation to investigator-assessed disease progression according to RECIST or death. Secondary endpoints were progression-free survival according to BICR, patient-reported outcomes as assessed 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.

We assessed safety by monitoring for adverse events, laboratory testing, assessing vital signs, and physical examinations. We classified adverse events 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] We classified serious adverse events as those that result in death, are immediately life-threatening, require admission to hospital or prolongation of an existing hospital stay, result in incapacity or disruption of the ability to carry out normal life functions, result in a congenital anomaly or birth defect, or are important medical events on the basis of appropriate medical judgment.

Statistical analysis

ARIEL3 was designed to enrol approximately 540 patients, including between 180 and 200 with a BRCA mutation in their carcinoma (with no more than 150 with a known deleterious germline BRCA mutation) and no more than 360 without. We calculated these subgroup sizes to result in a 90% power to establish a significant difference between rucaparib and placebo at a one-sided α level of 0·025 given the following assumptions for investigator-assessed median 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 group vs 6·0 months in the placebo group; hazard ratio [HR] 0·5), HRD (BRCA-mutated carcinoma or BRCA wild-type and high-LOH carcinomas; 10·0 months vs 6·0 months; HR 0·6), and the intention-to-treat population (all randomly allocated patients; 8·5 months vs 6·0 months; HR 0·7). We classified HRD status in the carcinoma (on the basis of BRCA mutation or LOH) for the efficacy analysis before database lock and final efficacy analysis. The primary analysis was to be done after the independent data monitoring committee established that investigator-assessed disease progression or death had occurred in at least 70% of expected patients in the BRCA-mutant cohort.

We did all efficacy analyses for the intention-to-treat population. The efficacy analyses are presented separately for the nested cohorts: BRCA mutant, HRD, and the intention-to-treat population; we used an ordered step-down multiple comparisons procedure.[21] We tested investigator-assessed progression-free survival in patients with a BRCA-mutant carcinoma 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 intention-to-treat population was contingent on a 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 significance was not achieved for one test, significance was not declared for all subsequent analyses.

Progression-free survival by BICR was evaluated as a key stand-alone secondary endpoint, separate from the step-down procedure described above. We analysed time to progression-free survival (by investigator and BICR) and to worsening according to the FOSI-18 DRS-P subscale using a stratified Kaplan-Meier method with which we compared distributions between the rucaparib and placebo groups using a stratified log-rank test. We used a stratified Cox proportional hazards model to estimate the HR between the groups. We verified the proportionality of hazards for the Cox proportional hazard assumption (ie, constant relative hazard) graphically using log-log plots. We did exploratory analyses of

progression-free survival in subgroups based on patient characteristics (eg, randomisation stratification factors, demographics, and disease burden at baseline). For patients with measurable disease at study entry, the proportion of patients achieving a confirmed complete or partial response according to RECIST as assessed by the investigator was a prespecified exploratory endpoint. We assessed safety, including adverse events and clinical laboratory investigations, in all patients who received at least one dose of study treatment.

We did statistical analyses using SAS version 9.4. Additional details are available in the appendix (pp 4–5). The independent data monitoring committee monitored enrolment and reviewed the safety and efficacy of the trial approximately every 6 months, including maturity of progression-free survival events. This trial is registered with ClinicalTrials.gov, number NCT01968213; enrolment is complete.

Role of the funding source

The study was designed by the funder and the coordinating investigators (RLC and JAL). Data were collected by the investigators, analysed by the funder, and interpreted by all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. Writing and editorial assistance were supported by the funder.

Results

Between April 7, 2014, and July 19, 2016, we randomly allocated 564 patients: 375 (66%) to rucaparib and 189 (34%) to placebo (figure 1, figure 2). At the visit cutoff date (April 15, 2017), 90 (24%) patients in the rucaparib group and nine (5%) in the placebo group were still receiving treatment. Baseline characteristics were generally well balanced between the treatment groups (table 1).

Following the ordered step-down multiple comparisons procedure, we evaluated investigator-assessed progression-free survival first in patients with a BRCA-mutant carcinoma (130 [35%] in the rucaparib group vs 66 [35%] in the placebo group, figure 2). Median progression-free survival was 16·6 months (95% CI 13·4–22·9) in the rucaparib group versus 5·4 months (3·4–6·7) in the placebo group (HR 0·23 [95% CI 0·16–0·34]; p<0·0001; figure 3). In patients with an HRD carcinoma (236 [63%] in the rucaparib group vs 118 [62%] in the placebo group), median progression-free survival was 13·6 months (10·9–16·2) versus 5·4 months (5·1–5·6; 0·32 [0·24–0·42]; p<0·0001). Median progression-free survival in the intention-to-treat population was 10·8 months (8·3–11·4) in the rucuparib group versus 5·4 months in the placebo group (5·3–5·5; 0·36 [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 patients with a BRCA-mutant carcinoma (median 26·8 months [95% CI 19·2 to not reached] vs 5·4 months [4·9–8·1]; HR 0·20 [95% CI 0·13–0·32]; p<0·0001), the patients with an HRD carcinoma (22·9 months [16·2 to not reported] vs 5·5 months [5·1–7·4]; 0·34 [0·24–0·47]; p<0·0001), and the intention-to-treat population (13·7 months [11·0–19·1] vs 5·4 months [5·1–5·5]; 0·35 [0·28–0·45]; p<0·0001; figure 3). For the

three nested cohorts, the plot of the log of the cumulative hazard for each treatment group resulted in parallel curves for both investigator-assessed and BICR-assessed progression-free survival, indicating that no violation of the proportionality of hazards assumption occurred (appendix pp 13–15). The probability of being progression free at 6, 12, and 18 months is in the appendix (p 9).

We analysed the secondary endpoint of time to worsening according to the FOSI-18 DRS-P subscale using the step-down procedure for the three nested subgroups. In patients with a BRCA-mutant carcinoma, we noted no significant difference between groups (HR 1·24 [95% CI 0·82–1·86]; p=0·30). As significance was not reached in this group, in accordance with the prespecified step-down procedure, significance could not be established for the remaining secondary analyses. Patient-reported health outcomes will be shown in a secondary publication. At the visit cutoff date (April 15, 2017), overall survival data were not mature (81 [22%] patients in the rucaparib arm and 42 [22%] patients in the placebo arm had died). A follow-up analysis will be done when approximately 70% of patients have died (approximately 395 overall survival events).

Preplanned subgroup analyses of investigator-assessed progression-free survival showed that all clinical subgroups had a progression-free survival benefit for rucaparib versus placebo, irrespective of measurable or bulky disease at baseline, response to last platinum-based regimen, LOH, or BRCA mutation (figure 4, appendix p 16). Further supporting the efficacy observed in the intention-to-treat population, in the non-nested subgroups of patients with carcinomas that were BRCA wild-type, we observed an investigator-assessed progression-free survival benefit with rucaparib in patients with high-LOH (median 9·7 months [95% CI 7·9–13·1] vs 5·4 months [4·1–5·7]; HR 0·44 [95% CI 0·29–0·66]; p<0·0001) and low-LOH (6·7 months [5·4–9·1] vs 5·4 months [5·3–7·4]; 0·58 [0·40–0·85]; p=0·0049) carcinomas (figure 5, appendix p 9). We observed similar results for BICR-assessed progression-free survival, for which a benefit was also seen with rucaparib in patients with both high-LOH and low-LOH carcinomas (appendix p 17).

Most patients (374 [66%]) in ARIEL3 had achieved a partial response to platinum-based therapy before randomisation. For 207 (37%) of 564 patients with measurable disease per investigator at study entry, a prespecified exploratory analysis of confirmed response was done. In the subgroup of patients with measurable disease at study entry with a BRCA-mutant carcinoma, the exploratory analysis showed that 15 (38% [95% CI 23–54]) of 40 patients in the rucaparib group and two (9% [1–28]) of 23 in the placebo group achieved a confirmed RECIST response (appendix p 10). In patients with an HRD carcinoma, the objective response was also higher in the rucaparib group (23 [27% (18–38)] of 85 patients) than in the placebo group (three [7% (1–20)] of 41). We observed a similar result in the intention-to-treat population (26 [18% (12–26)] of 141 in the rucaparib group; five [8% (2–17)] of 66 in the placebo group). We observed complete responses in the rucaparib group in seven (18%) patients with measurable disease at baseline in the nested BRCA-mutant cohort, ten (12%) in the HRD cohort, and ten (7%) in the intention-to-treat population. We only observed one (2%) complete response in the placebo group; this response occurred in the intention-to-treat population.

The safety population included 372 (99%) patients who received rucaparib (three [1%] patients withdrew before receiving rucaparib) and 189 (100%) who received placebo. For the safety population, the median treatment duration was 8·3 months (IQR 3·4–16·1) in the rucaparib group and 5·5 months (2·8–8·3) in the placebo group. A treatment-emergent adverse event of any grade occurred in 372 (100%) patients in the rucaparib group and 182 (96%) in the placebo group (table 2). The most common treatment-emergent adverse events (reported in at least 35% of patients in either group) were nausea, asthenia or fatigue, dysgeusia, anaemia or decreased haemoglobin concentration, constipation, and vomiting. Treatment-emergent adverse events of grade 3 or greater were reported in 209 (56%) patients in the rucaparib group and 28 (15%) in the placebo group, the most common of which were anaemia or decreased haemoglobin concentration and increase in alanine aminotransferase or aspartate aminotransferase concentration. For patients in the rucaparib group, a decline in haemoglobin concentration from baseline generally occurred in the first few cycles (appendix p 18). Elevations in alanine aminotransferase or aspartate aminotransferase concentrations were generally transient, self-limiting, and not associated with other signs of liver toxicity (appendix pp 19–20).

One or more serious adverse events were reported in 78 (21%) patients in the rucaparib group and 20 (11%) in the placebo group. The most common serious adverse events (reported in at least 2% of patients in either group) were anaemia (16 [4%] patients in the rucaparib group vs one [1%] in the placebo group), pyrexia (six [2%] vs none), vomiting (six [2%] vs two [1%]), and small intestinal obstruction (three [1%] vs three [2%]).

Myelodysplastic syndrome and acute myeloid leukaemia were reported in three (1%) patients in the rucaparib group (two [1%] had a germline BRCA-mutant carcinoma and one [<1%] had a BRCA wild-type and low-LOH carcinoma). One (<1%) patient died from myelodysplastic syndrome and one (<1%) died from acute myeloid leukaemia. No patients reported myelodysplastic syndrome or acute myeloid leukaemia in the placebo group.

Treatment interruption due to a treatment-emergent adverse event occurred in 237 (64%) patients in the rucaparib group and 19 (10%) in the placebo group (appendix p 11). Dose reduction due to a treatment-emergent adverse event occurred in 203 (55%) patients in the rucaparib group and eight (4%) in the placebo group. 117 (31%) patients in the rucaparib group and six (3%) in the placebo group had both a treatment interruption and dose reduction due to a treatment-emergent adverse event. Of patients who received rucaparib, 50 (13%) discontinued because of a treatment-emergent adverse event (excluding disease progression) compared with three (2%) patients in the placebo group (appendix p 12). As of the visit cutoff date, in the rucaparib group, four (1%) deaths occurred because of adverse events considered unrelated to treatment by the investigator (two [1%] patients due to progressive disease, one [<1%] due to cardiac arrest, and one [<1%] due to haematophagic histiocytosis) and two (1%) deaths occurred that were considered treatment related by the investigator (one [<1%] due to acute myeloid leukaemia and one [<1%] due to myelodysplastic syndrome). In the placebo group, two (1%) patients died because of adverse events considered unrelated to treatment by the investigator (one [1%] due to progressive disease and one [1%] due to pulmonary embolism).

Discussion

Rucaparib maintenance treatment significantly improved progression-free survival compared with placebo in all primary analysis groups of patients with recurrent ovarian carcinoma after a complete or partial response to platinum-based therapy, as well as when assessed by the BICR and across all prespecified subgroups. Analysis of non-nested, non-overlapping patient subpopulations indicate that the significant improvement in progression-free survival observed in the intention-to-treat population was not driven only by the results in the nested HRD or BRCA-mutant cohorts.

We observed no significant difference in time to worsening in the FOSI-18 DRS-P subscale between the rucaparib and placebo groups. Further analyses of the patient-reported health outcome data gathered in ARIEL3 are planned and will be reported separately. Overall survival data were not mature at the time of the visit cutoff, with approximately 22% of the events needed for final analysis. Patient follow-up is continuing in a masked manner and overall survival will be assessed after about 70% maturity is reached.

Treatment-emergent adverse events in the rucaparib group were generally managed with dose modifications and not associated with increased mortality or morbidity compared with the placebo group. As reported in previous studies of rucaparib and other PARP inhibitors, [5, 6, 9, 10, 11] gastrointestinal side-effects, asthenia or fatigue, and myelosuppression were common treatment-emergent adverse events in the rucaparib group. Management of adverse events included supportive care and dose modifications (including treatment interruption or dose reduction). Common laboratory abnormalities observed in the rucaparib group included elevations in alanine aminotransferase or aspartate aminotransferase concentration and blood creatinine concentration. Alanine aminotransferase and aspartate aminotransferase concentration increases were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity and generally resolved over time. We considered no cases to meet Hy's law criteria for drug-induced liver injury.[22, 23] Similarly, elevations in creatinine, which have also been observed with olaparib,[24] were self-limiting and stabilised over time. Creatinine is secreted into urine via renal transporters (eg, multidrug and toxin extrusion 1, multidrug and toxin extrusion 2-K, organic cation transporter 1, and organic cation transporter 2), which have been shown to be inhibited in vitro by multiple PARP inhibitors, including rucaparib,[25] olaparib,[26] and veliparib.[27] Patterns of elevation and stabilisation of these laboratory abnormalities similar to those reported in this study 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 ENGOT-OV16/NOVA studying niraparib6 and Study 195, [30] and SOLO29 studying olaparib. However, direct comparisons with these other trials cannot be made because of differences in patient groups analysed (eg, SOLO2/ENGOT-Ov21 only enrolled patients with a germline BRCA mutation), definition of HRD (eg, in ENGOT-OV16/NOVA, HRD included patients with somatic mutations in BRCA and those with non-BRCA-related HRD), the method of primary endpoint assessment (eg, investigator vs BICR), and study design (eg, residual disease was restricted to <2 cm in ENGOT-OV16/NOVA).

Although having a CA 125 concentration of less than the upper limit of normal is not a requirement of response according to GCIG CA 125 criteria or a RECIST partial response, ARIEL3 did have this requirement to ensure that patients had controlled disease at study entry. Similar restrictions on CA 125 concentrations were included in the enrolment criteria of other studies investigating PARP inhibitors in the maintenance treatment setting, although how many patients in these studies had CA 125 concentrations of greater than the upper limit of normal at study entry is unknown.[5, 6, 9] Furthermore, whether or not inclusion of patients with CA 125 concentrations exceeding the upper limit of normal affects the efficacy of PARP inhibitors in the maintenance treatment setting is also unknown.

Although ARIEL3 extends the findings of previous studies of PARP inhibitors in this setting, some important differences exist between this study 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, a feature that is unique to ARIEL3 in this setting. Additionally, we did not restrict enrolment on the basis of target lesion size for patients with residual disease (partial response to previous platinum). A number of patients with measurable residual disease at study entry showed further reduction in carcinoma burden with rucaparib maintenance treatment, including conversion to a complete response.

ARIEL3 is, to our knowledge, the first phase 3 trial to prospectively assess the primary endpoint of progression-free survival in patients with recurrent ovarian carcinoma associated with HRD. Preplanned analysis of progression-free survival in patients with a BRCA wild-type and high-LOH carcinoma—wherein patients receiving rucaparib had an increase in median progression-free survival compared with placebo—shows that the improvement observed in the HRD cohort was not driven solely by patients with a BRCA-mutant carcinoma. The benefit in progression-free survival seen in patients with a BRCA wild-type and high-LOH carcinoma compared with those with a BRCA wild-type and low-LOH carcinoma shows the use of HRD, in particular high genomic LOH as defined by Foundation Medicine's T5 assay, as a predictive biomarker for sensitivity to rucaparib treatment.

ARIEL3 had several limitations. Use of a placebo might not be the most appropriate control group for patients who entered the study with a partial response to their prior platinum-based regimen. Additionally, there was the potential for bias with regard to investigator-assessment of progression-free survival (ie, investigators may have used other clinical markers unrelated to RECIST to evaluate disease progression, including use of rising CA 125 levels).

In ARIEL2 part 1,[11] use of LOH helped discriminate which patients with platinum-sensitive ovarian carcinoma who received one or two prior lines of chemotherapy benefited from rucaparib; however, HRD assessment with genomic LOH was not completely predictive of clinical benefit because some patients with a BRCA wild-type and low-LOH carcinoma responded to rucaparib. Similarly, in ARIEL3, we also observed response to rucaparib in patients with a BRCA wild-type and low-LOH carcinoma, with more than 30% of patients in the rucaparib group achieving benefit of more than a year's duration compared with less than 5% in the placebo group. Taken together, results from ARIEL2 in the treatment setting and ARIEL3 in the maintenance setting demonstrate that although HRD and genomic LOH

can be an informative tool for clinicians making treatment decisions for patients with BRCA wild-type-associated platinum-sensitive ovarian carcinoma, the biomarker does not appear to be sufficiently precise to predict absence of benefit on an individual basis. As NGS-based assays become more common in routine clinical practice than at present, the cost-benefit ratio of use of these assays will need to be evaluated in the context of optimal response to preceding platinum therapy, the cost of maintenance therapy, and the potential magnitude of clinical benefit in a particular subgroup.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. International Agency for Reasearch on Cancer. [accessed Aug 1, 2017] GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/summary_table_pop_sel.aspx
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; 95:157–164. [PubMed: 15385126]
3. Herzog TJ, Holloway RW, Stuart GCE. Workshop: options for therapy in ovarian cancer. Gynecol Oncol. 2003; 90:S45–S50. [PubMed: 13129496]
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; 30:2039–45. [PubMed: 22529265]
5. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012; 366:1382–92. [PubMed: 22452356]
6. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016; 375:2154–64. [PubMed: 27717299]
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; 18:779–91. [PubMed: 28438473]
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; 387:1066–74. [PubMed: 27025186]

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. Lancet Oncol. 2017; 18:1274–1284. [PubMed: 28754483]
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; 23:4095–106. [PubMed: 28264872]
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; 18:75–87. [PubMed: 27908594]
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; 16:211. [PubMed: 25093514]
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; 107:1776–82. [PubMed: 23047548]
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; 52:794–801. [PubMed: 23716468]
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. [PubMed: 26015868]
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; 45:228–47. [PubMed: 19097774]
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; 21:419–23. [PubMed: 21270624]
18. Jensen SE, Rosenbloom SK, Beaumont JL, et al. A new index of priority symptoms in advanced ovarian cancer. Gynecol Oncol. 2011; 120:214–9. [PubMed: 21075440]
19. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999; 20:109–17. [PubMed: 10082069]
20. Rahma OE, Duffy A, Liewehr DJ, Steinberg SM, Greten TF. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. Ann Oncol. 2013; 24:1972–9. [PubMed: 23670093]
21. Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Plan Inference. 2001; 99:25–40.
22. Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006; 15:241–3. [PubMed: 16552790]
23. U.S. Department of Health and Human Services. [accessed Aug 22, 2017] Guidance for industry. Drug-induced liver injury: premarketing clinical evaluation. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/Guidances/UCM174090.pdf
24. AstraZeneca. Wilmington: 2017. Lynparza (olaparib) capsules (prescribing information). http://www.azpicentral.com/pi.html?product=lynparza_tb&country=us&popup=no [accessed Sept 7, 2017]
25. Clovis Oncology. Boulder: 2017. Rubraca (rucaparib) tablets (prescribing information). http://clovisoncology.com/files/rubraca-prescribing-info.pdf [accessed Sep 7, 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. 2017; 47:903–915. [PubMed: 27684210]
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; 102:4426–32. [PubMed: 24122511]
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. Annual Meeting on Women's Cancer; National Harbor, USA. March 12–15, 2017; 2017. abstract 1

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; Amsterdam, Netherlands. Jan 27–30, 2017; Abstract 710
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; 15:852–61. [PubMed: 24882434]

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 scarce. In a search of PubMed for articles published up to July 31, 2017, using the search terms ("PARP inhibitor" OR "rucaparib" OR "olaparib" OR "niraparib" OR "veliparib" OR "talazoparib") AND ("ovarian" AND ["cancer" OR "carcinoma"] AND "maintenance") with no language restrictions, we found that data have been published in a PubMed-indexed journal for only three clinical trials. Study 19 and SOLO2/ENGOT-Ov21 showed that patients with platinum-sensitive ovarian carcinoma who had received at least two previous platinum-based chemotherapies had significantly improved progression-free survival with olaparib maintenance treatment, and results from the ENGOT-OV16/NOVA trial showed that niraparib also showed a significant improvement.

Added value of this study

ARIEL3 is, to our knowledge, the first phase 3 trial to prospectively assess progression-free survival in patients with recurrent platinum-sensitive ovarian carcinoma who achieved a response to platinum-based therapy associated with homologous recombination deficiency (HRD) as a primary endpoint. We enrolled patients with or without a germline or somatic BRCA mutation, and the size of residual disease was not restricted. Our results show that rucaparib maintenance treatment significantly improved progression-free survival for patients across all primary analysis groups, not only for patients with ovarian carcinoma associated with a BRCA mutation, but also for those with BRCA wild-type ovarian carcinoma. A novel aspect of this trial was the prospective validation of the tumour-based, next-generation sequencing HRD assay that was used in the phase 2 ARIEL2 trial. Additionally, an exploratory analysis of progression-free survival in patients with BRCA wild-type and high loss of heterozygosity (LOH) or low LOH tumours revealed that patients with BRCA-mutant tumours did not solely drive rucaparib benefit in the HRD cohort or intention-to-treat population. Furthermore, an improvement in progression-free survival (assessed by investigator or a masked independent central radiology review committee) versus placebo was maintained in the BRCA wild-type and high LOH or low LOH groups.

Implications of all the available evidence

Combined with the evidence from previous studies, our study supports 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. Our results show that HRD as a predictive biomarker can be an informative tool for clinicians when making treatment decisions for this patient population. The targeted agents bevacizumab and cediranib have also proven useful in extending progression-free survival for patients in this setting. Our findings strengthen the rationale for continued investigation of targeted therapies, such as PARP inhibitors, for maintenance treatment as

either monotherapy or in combination with other agents in an effort to provide the best care for patients with advanced ovarian cancer.

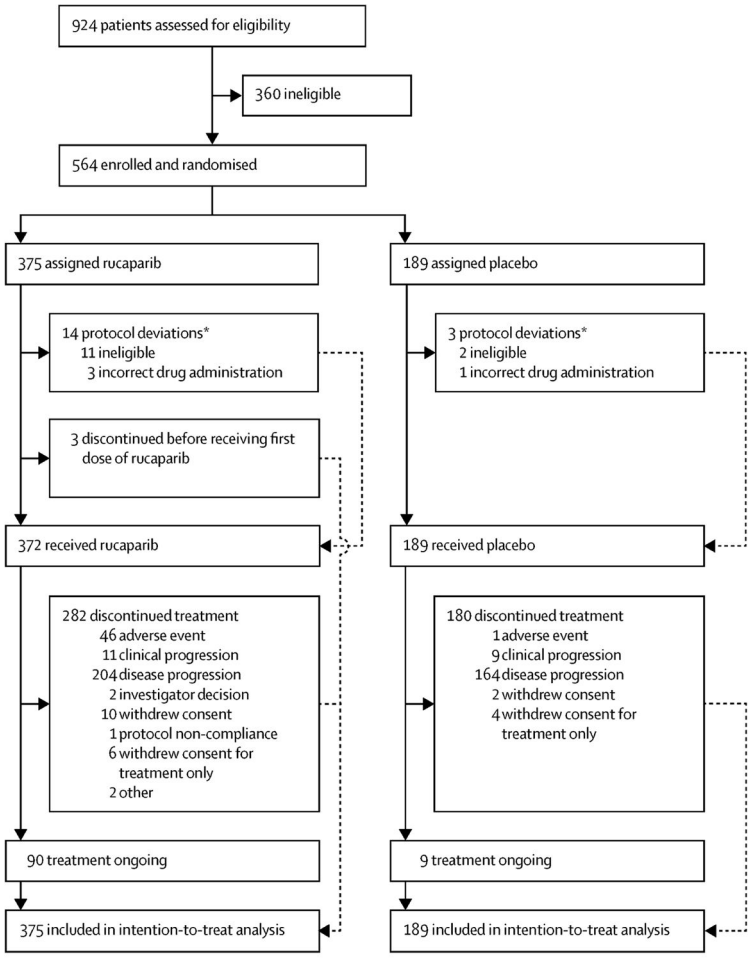

Figure 1.

Trial profile

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

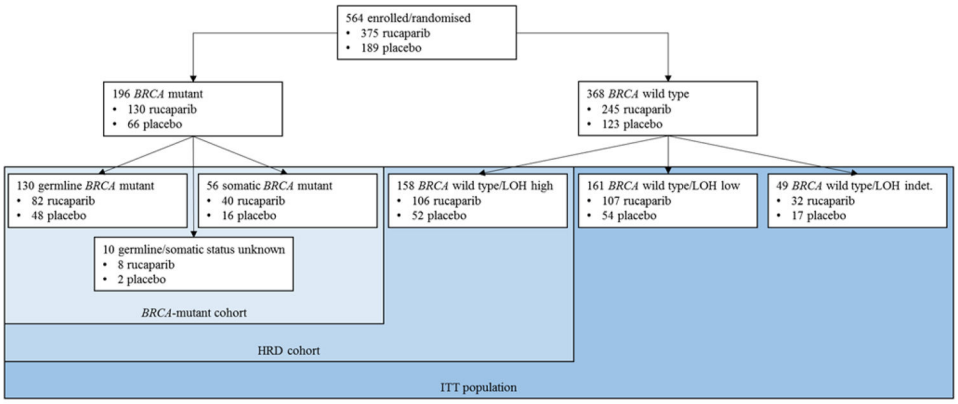

Figure 2.

Efficacy analysis cohorts

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

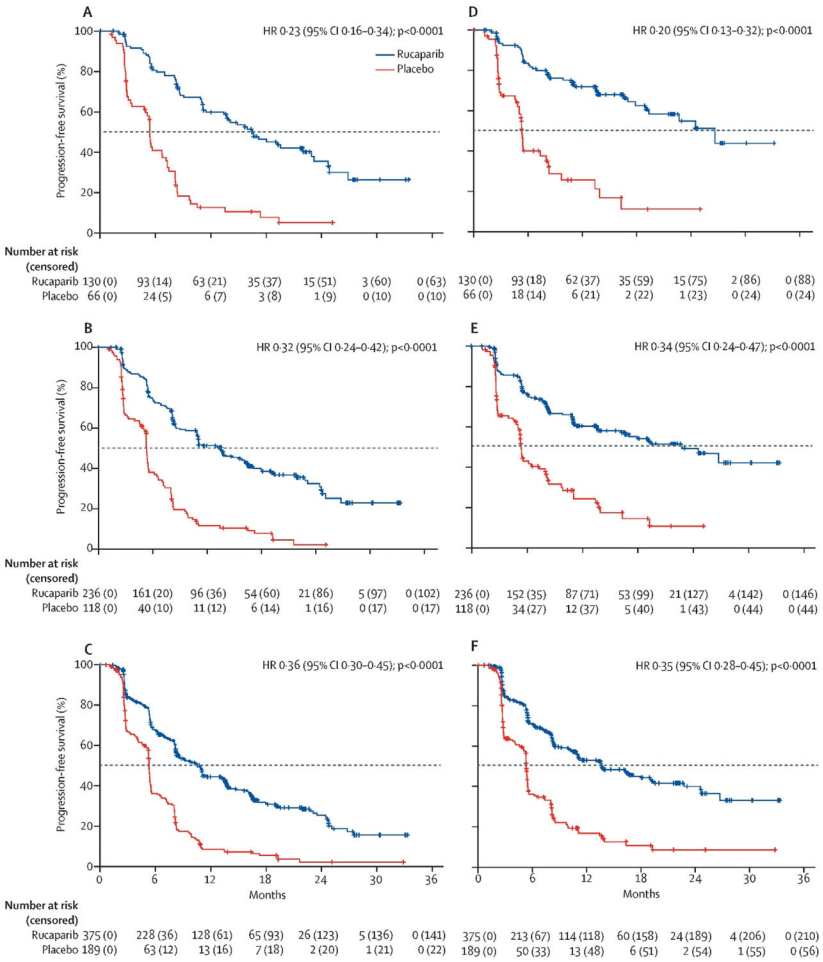

Figure 3.

Progression-free survival

Kaplan-Meier estimates of progression-free survival as assessed by the investigator for patients with a BRCA-mutant carcinoma (A), patients with a homologous recombination deficient carcinoma (B), and the intention-to-treat population (C) and as assessed by the blinded independent central radiology review for patients with a BRCA-mutant carcinoma (D), patients with a homologous recombination deficient carcinoma (E), and the intention-to-treat population (F). Tick marks denote censored patients. HR=hazard ratio.

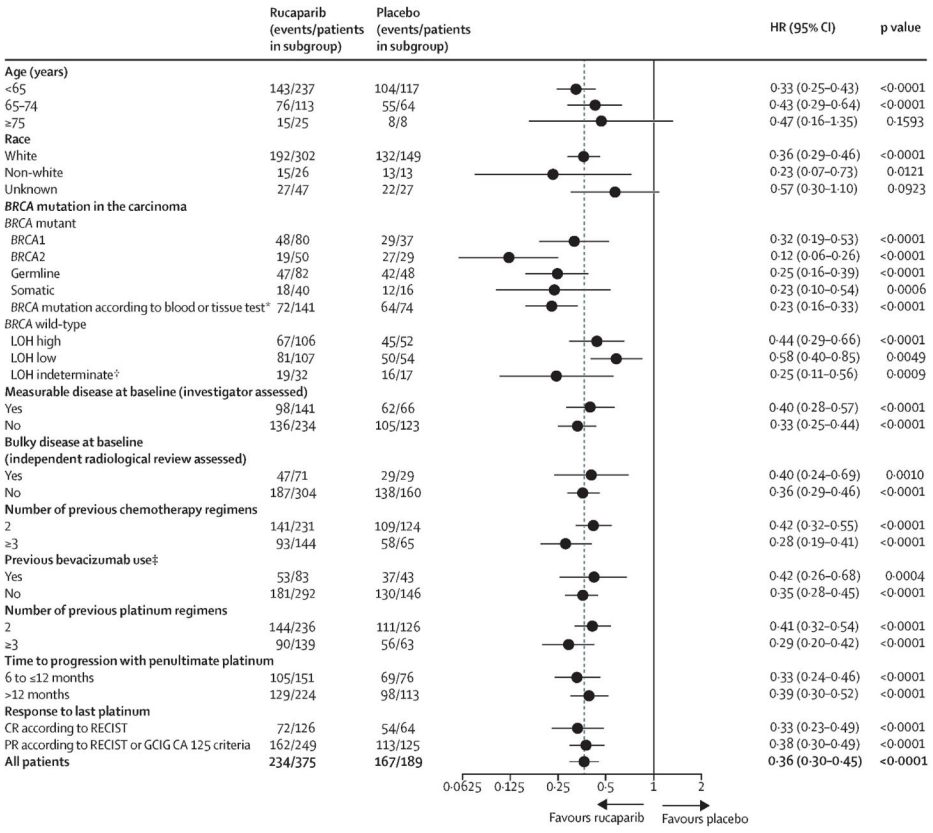

Figure 4.

Progression-free survival in subgroups

CA 125=cancer antigen 125. CR=complete response. GCIG=Gynecologic Cancer InterGroup. HR=hazard ratio. LOH=loss of heterozygosity. PR=partial response. RECIST=Response Evaluation Criteria In Solid Tumors. *By local germline testing, central germline testing, or tumour testing. †Tumour sample was not evaluable for percentage of genomic LOH because of low tumour content or aneuploidy. ‡We permitted previous treatment with bevacizumab as part of penultimate or earlier treatment.

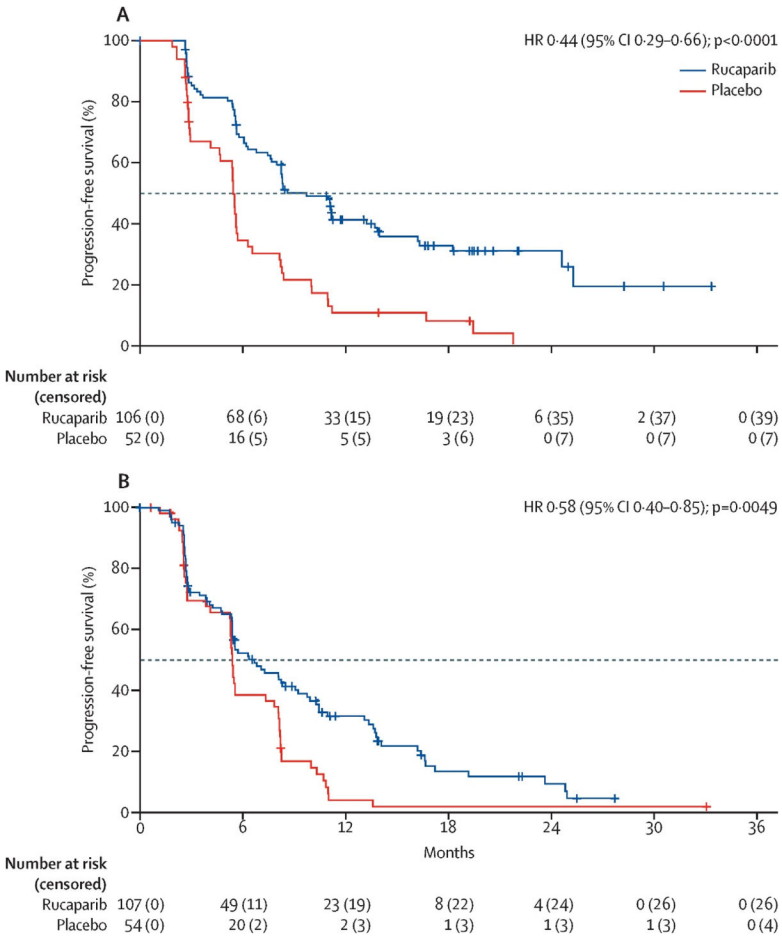

Figure 5.

Progression-free survival in patients with a BRCA wild-type carcinoma

Kaplan-Meier estimates of progression-free survival as assessed by the investigator for patients with a BRCA wild-type carcinoma with high (A) and low (B) loss of heterozygosity. HR=hazard ratio.

Table 1

Baseline characteristics in the intention-to-treat population

	Rucaparib (n=375)	Placebo (n=1l89)
Ago (years)	61.0(53.0–67.0)	62.0(53.0–68.0)
Race		
White	302(81%)	149(79%)
Non-white	26(7%)	13(7%)
Unknown	47(13%)	27(14%)
ECOG performance status		
0	280(75%)	136(72%)
1	95(25%)	53(28%)
Diagnosis		
Epithelial ovarian cancer	312(83%)	159(84%)
Fallopian tube cancer	32(9%)	10(5%)
Primary peritoneal cancer	31(8%)	19(10%)
High grade serous adenocarcinoma	0	l 1%) *
Histology		
Serous	357(95%)	179(95%)
Endometrioid	16(4%)	7(4%)
Mixed	1(<1%)	3(2%)
Transitional	1(<1%)	0
BRCA mutation m the carcinoma		
BRCA mutant	130(35%)	66(35%)
*BRCA*1	80(21%)	37(20%)
*BRCA*2	50(13%)	29(15%)
Germline	82(22%)	48(25%)
Somatic	40(11%)	16(8%)
Unknown †	8(2%)	2(1%)
BRCA wild-type	245(65%)	123(65%)
LOH high	106(28%)	52(28%)
LOH low	107(29%)	54(29%)
LOH indeterminate ‡	32(9%)	17(9%)
Number of previous chemotherapy regimens	2(2–3)	2(2–3)
2	231(62%)	124(66%)
≥3	144(38%)	65(34%)
Previous bevacizumab use §	83(22%)	43(23%)
Number of plat mum-based regimens	2(2–3)	2(2–3)

	Rucaparib (n=375)	Placebo (n=1l89)
2	236(63%)	126(67%)
≥3	139(37%)	63(33%)
Measurable disease (investigator assessed)	141(38%)	66(35%)
Bulky disease (any lesion >2 cm) (independent radiological review assessed)	71(19%)	29(15%)
Randomisation stratification factors		
HRR gene mutation status		
BRCA mutant	130(35%)	66(35%)
Mutation in other, non-*BRCA* HKK gene	28(7%)	15(8%)
No mutation detected in *BRCA* or HRR gene	217(58%)	108(57%)
Time to progression with penultimate platinum (months)	13.8(10.0–22.3)	14.6(10.7–24.0)
6 to ≤12	151(40%)	76(40%)
>12	224(60%)	113(60%)
Response to last platinum		
CR according to RECIST	126(34%)	64(34%)
PR according to RECIST or serological response according to GCIG CA125 criteria	249(66%)	125(66%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. LOH=loss of heterozygosity. HRR=homologous recombination repair. CR=complete response.

RECIST=Response Evaluation Criteria In Solid Tumors. PR=partial response.

GCIG=Gynecologic Cancer InterGroup. CA 125=cancer antigen 125.

[*] According to the patient records, origin was fallopian tube or ovary.

[†] Tumour sample was BRCA mutant according to Foundation Medicine's T5 next-generation sequencing assay, but a blood sample was not available for central germline testing.

[‡] Tumour sample was not evaluable for percentage of genomic LOH because of low tumour content or aneuploidy.

[§] We permitted previous treatment with bevacizumab as part of penultimate or earlier treatment.

Table 2

Treatment-emergent adverse events of any grade reported in at least 10% of patients in either group in the safety population

	Rucaparib(n=372)				Placebo (n=189)			
	Any grade	**Grade 1–2**	**Grade 3**	**Grade 4**	**Any grade**	**Grade 1–2**	**Grade 3**	**Grade 4**
At least one AE	372(100%) *	163(44%)	179(48%)	24(6%)	182(96%) †	154(81%)	24(13%)	2(1%)
Blood and lymphatic system disorders								
Decreased haemoglobin concentration (anaemia)	139(37%)	69(19%)	67(18%)	3(1%)	11(6%)	10(5%)	0	1(1%)
Decreased neutrophil count (neutropenia)	67(18%)	42(11%)	19(5%)	6(2%)	9(5%)	7(4%)	1(1%)	1(1%)
Decreased platelet count (thrombocytopenia)	104(28%)	85(23%)	13(3%)	6(2%)	5(3%)	5(3%)	0	0
Gastrointestinal disorders								
Abdominal distension	41(11%)	41(11%)	0	0	22(12%)	22(12%)	0	0
Abdominal pain	111(30%)	102(27%)	9(2%)	0	49(26%)	48(25%)	1(1%)	0
Upper abdominal pain	52(14%)	50(13%)	2(1%)	0	10(5%)	10(5%)	0	0
Constipation	136(37%)	129(35%)	7(2%)	0	45(24%)	43(23%)	2(1%)	0
Diarrhoea	118(32%)	116(31%)	2(1%)	0	41(22%)	39(21%)	2(1%)	0
Dyspepsia	54(15%)	53(14%)	1(<1%)	0	9(5%)	9(5%)	0	0
Nausea	280(75%)	266(72%)	14(4%)	0	69(37%)	68(36%)	1(1%)	0
Vomiting	136(37%)	121(33%)	15(4%)	0	28(15%)	26(14%)	2(1%)	0
General disorders and administration site conditions								
Fatigue (asthenia)	258(69%)	233(63%)	25(7%)	0	83(44%)	78(41%)	5(3%)	0
Peripheral oedema	39(10%)	38(10%)	1(<1%)	0	14(7%)	14(7%)	0	0
Pyrexia	44(12%)	44(12%)	0	0	8(4%)	8(4%)	0	0
Infections and infestations								
Upper respiratory tract infection	41(11%)	41(11%)	0	0	6(3%)	4(2%)	2(1%)	0
Investigations								
Increase alanine aminotransferase oraspartate aminotransferase	126(34%)	87(23%)	39(10%)	0	7(4%)	7(4%)	0	0
Increase in blood creatinine concentration	57(15%)	56(15%)	1(<1%)	0	3(2%)	3(2%)	0	0
Metabolism and nutrition disorders								

	Rucaparib(n=372)				Placebo (n=189)			
	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4
Decreased appetite	87(23%)	85(23%)	2(1%)	0	26(14%)	26(14%)	0	0
Hypomagnesaemia	40(11%)	39(10%)	1(<1%)	0	11(6%)	11(6%)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	57(15%)	55(15%)	2(1%)	0	24(13%)	24(13%)	0	0
Back pain	45(12%)	45(12%)	0	0	28(15%)	28(15%)	0	0
Nervous system disorders								
Dizziness	54(15%)	54(15%)	0	0	15(8%)	14(7%)	1(1%)	0
Dysgeusia	146(39%)	146(39%)	0	0	13(7%)	13(7%)	0	0
Headache	67(18%)	66(18%)	1(<1%)	0	30(16%)	29(15%)	1(1%)	0
Psychiatric disorders								
Insomnia	53(14%)	53(14%)	0	0	15(8%)	15(8%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Cough	54(15%)	54(15%)	0	0	25(13%)	25(13%)	0	0
Dyspnoea	50(13%)	50(13%)	0	0	14(7%)	14(7%)	0	0
Skin and subcutaneous tissue disorders								
Photosensitivity reaction	64(17%)	62(17%)	2(1%)	0	1(1%)	1(1%)	0	0
Pruritus	47(13%)	47(13%)	0	0	19(10%)	19(10%)	0	0
Rash	46(12%)	45(12%)	1(<1%)	0	17(9%)	17(9%)	0	0

Data are n (%). AE=adverse event.

*Includes six patients who died from a treatment-emergent adverse event.

†Includes two patients who died from a treatment-emergent adverse event.

‡Elevations were generally transient, self-limiting, and not associated with other signs of liver toxicity.