Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious *BRCA1* or *BRCA2* mutation (ARIEL4): an international, open-label, randomised, phase 3 trial

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Summary

Background Few prospective studies have compared poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors to chemotherapy for the treatment of *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma. We aimed to assess rucaparib versus platinum-based and non-platinum-based chemotherapy in this setting.

Methods In this open-label, randomised, controlled, phase 3 study (ARIEL4), conducted in 64 hospitals and cancer centres across 12 countries (Brazil, Canada, Czech Republic, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, the UK, and the USA), we recruited patients aged 18 years and older with *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and who had received two or more previous chemotherapy regimens. Eligible patients were randomly assigned (2:1), using an interactive response technology and block randomisation (block size of six) and stratified by progression-free interval after the most recent platinum-containing therapy, to oral rucaparib (600 mg twice daily) or chemotherapy (administered per institutional guidelines). Patients assigned to the chemotherapy group with platinum-resistant or partially platinum-sensitive disease were given paclitaxel (starting dose 60–80 mg/m² on days 1, 8, and 15); those with fully platinum-sensitive disease received platinum-based chemotherapy (single-agent cisplatin or carboplatin, or platinum-doublet chemotherapy). Patients were treated in 21-day or 28-day cycles. The primary endpoint was investigator-assessed progression-free survival, assessed in the efficacy population (all randomly assigned patients with deleterious *BRCA1* or *BRCA2* mutations without reversion mutations), and then in the intention-to-treat population (all randomly assigned patients). Safety was assessed in all patients who received at least one dose of assigned study treatment. This study is registered with ClinicalTrials.gov, NCT02855944; enrolment is complete, and the study is ongoing.

Findings Between March 1, 2017, and Sept 24, 2020, 930 patients were screened, of whom 349 eligible patients were randomly assigned to rucaparib (n=233) or chemotherapy (n=116). Median age was 58 years (IQR 52–64) and 332 (95%) patients were White. As of data cutoff (Sept 30, 2020), median follow-up was 25·0 months (IQR 13·8–32·5). In the efficacy population (220 patients in the rucaparib group; 105 in the chemotherapy group), median progression-free survival was 7·4 months (95% CI 7·3–9·1) in the rucaparib group versus 5·7 months (5·5–7·3) in the chemotherapy group (hazard ratio [HR] 0·64 [95% CI 0·49–0·84]; p=0·0010). In the intention-to-treat population (233 in the rucaparib group; 116 in the chemotherapy group), median progression-free survival was 7·4 months (95% CI 6·7–7·9) in the rucaparib group versus 5·7 months (5·5–6·7) in the chemotherapy group (HR 0·67 [95% CI 0·52–0·86]; p=0·0017). Most treatment-emergent adverse events were grade 1 or 2. The most common grade 3 or worse treatment-emergent adverse event was anaemia or decreased haemoglobin (in 52 [22%] of 232 patients in the rucaparib group *vs* six [5%] of 113 in the chemotherapy group). Serious treatment-emergent adverse events occurred in 62 (27%) patients in the rucaparib group versus 13 (12%) in the chemotherapy group; serious adverse events considered related to treatment by the investigator occurred in 32 (14%) patients in the rucaparib group and six (5%) in the chemotherapy group. Three deaths were considered to be potentially related to rucaparib (one due to cardiac disorder, one due to myelodysplastic syndrome, and one with an unconfirmed cause).

Interpretation Results from the ARIEL4 study support rucaparib as an alternative treatment option to chemotherapy for patients with relapsed, *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma.

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Research in context

Evidence before this study

Patients with high-grade ovarian carcinoma who have received several previous lines of therapy have greatly diminished treatment-free intervals and responses. These patients have few therapeutic options because the benefit–risk profile of treatment might not be favourable. Therefore, the development of targeted therapies, based on disease molecular characteristics, that improve the benefit–risk ratio of chemotherapy is of crucial importance. Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors are a targeted treatment option for patients with relapsed ovarian carcinoma associated with a *BRCA1* or *BRCA2* mutation, although little prospective randomised data comparing the efficacy and safety of PARP inhibitors with standard-of-care chemotherapy in this population exist, with no randomised data comparing PARP inhibitor monotherapy with platinum-based chemotherapy. We searched PubMed, with no language restrictions, for articles published from database inception up to July 1, 2021, using the search terms ("PARP inhibitor" OR "rucaparib" OR "olaparib" OR "niraparib" OR "veliparib" OR "talazoparib") AND "chemotherapy" AND ("ovarian" AND ["cancer" OR "carcinoma"]) AND ("BRCA" OR "BRCA1" OR "BRCA2" OR "BRCA1/2") and we found that data have been published in a PubMed-indexed journal for only two randomised clinical trials comparing PARP inhibitor monotherapy with chemotherapy as treatment for ovarian cancer. In a phase 2, open-label, randomised study in 97 patients with germline *BRCA* mutations and relapsed ovarian carcinoma, progression-free survival was non-significantly longer with olaparib monotherapy than with pegylated liposomal doxorubicin. In a confirmatory, open-label, randomised, phase 3 study in 266 patients with germline *BRCA1* or *BRCA2* mutations and platinum-sensitive, relapsed ovarian carcinoma, the proportion of patients with objective responses and the length of progression-free survival significantly favoured olaparib monotherapy versus investigator's choice of single-agent nonplatinum chemotherapy (pegylated liposomal doxorubicin, paclitaxel, gemcitabine, or topotecan).

Added value of this study

To our knowledge, ARIEL4 is the first study to compare a PARP inhibitor with standard-of-care platinum and non-platinum-based chemotherapy in patients with germline or somatic *BRCA1* or *BRCA2* mutations and relapsed ovarian carcinoma. Our patient population is also distinct from that of previous studies because it included patients with platinum-resistant, partially platinum-sensitive, and fully platinum-sensitive disease. In this broad population, rucaparib significantly improved progression-free survival versus chemotherapy. Finally, our study was the first randomised trial designed to prospectively evaluate the effect of *BRCA* reversion mutations present before study treatment on the efficacy of a PARP inhibitor and chemotherapy.

Implications of all the available evidence

Our study supports the use of rucaparib as an alternative treatment choice to chemotherapy for patients with relapsed, *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma. Additional research is needed to understand the factors that confer sensitivity to platinum-based chemotherapy and PARP inhibitors, and the optimal treatment strategy for patients with *BRCA* reversion mutations.

Introduction

Rucaparib is a potent and selective oral poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor.[1,2] Inhibition of PARP causes accumulation of unrepaired DNA single-strand breaks, leading to replication fork collapse and increased double-strand breaks.[3] Tumour cells with defects in the homologous recombination repair (HRR) pathway (eg, due to *BRCA1* or *BRCA2* mutations) are selectively sensitive to PARP inhibition through an interaction known as synthetic lethality.[4] *BRCA1* and *BRCA2* reversion mutations that restore BRCA protein function have been associated with reduced benefit from PARP inhibitors and platinum-based chemotherapy when present before treatment (probably linked to primary resistance to these treatments).[5–7]

Rucaparib is approved in the USA and Europe as a monotherapy treatment for patients with *BRCA1*-mutated or *BRCA2*-mutated, relapsed ovarian carcinoma who have received two or more previous lines of platinum-based chemotherapy (and in Europe for patients who are unable to tolerate further platinum-based chemotherapy), on the basis of data from two open-label, single-arm, phase 1/2 studies: Study 10 (NCT01482715) and ARIEL2 (NCT01891344).[8,9] Approval in the USA was based on a pooled analysis of data from 106 patients with platinum-sensitive, platinum-resistant, or platinum-refractory disease. In this population, 53·8% (95% CI 43·8–63·5) of patients had an investigator-assessed confirmed objective response as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and median progression-free survival was 10·0 months (95% CI 7·3–12·5).[8,10] The European Commission's conditional marketing authorisation was based on an analysis of the subset of 79 patients with platinum-sensitive disease, among whom 64·6% (95% CI 53·0–75·0) had an investigator-assessed confirmed objective response per RECIST 1.1; and median progression-free survival was 10·9 months (95% CI 8·4–12·8).[9,11]

Although PARP inhibitors have shown consistent and robust clinical activity in single-arm studies of patients with relapsed *BRCA1*-mutated or *BRCA2*-mutated ovarian carcinoma,[11–14] only two randomised clinical trials have been published to date that compared PARP inhibitors with non-platinum chemotherapy as treatment for patients with ovarian carcinoma and a germline *BRCA1* or *BRCA2* mutation.[15,16] We did the phase 3 ARIEL4 study to compare

the efficacy and safety of rucaparib versus platinum and non-platinum chemotherapy as treatment for patients with germline or somatic *BRCA1*-mutated or *BRCA2*-mutated, relapsed ovarian carcinoma (including patients with platinum-resistant, partially platinum-sensitive, and fully platinum-sensitive disease) who had received two or more previous chemotherapy regimens.

Methods

Study design and patients

ARIEL4 is an open-label, randomised, controlled, phase 3 study that was conducted in 64 hospitals and cancer centres in Brazil, Canada, Czech Republic, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, the UK, and the USA (appendix pp 3–6). We enrolled patients with a histologically confirmed diagnosis of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Eligible patients were women aged 18 years or older; with a deleterious germline or somatic *BRCA1* or *BRCA2* mutation, confirmed by a central or local laboratory; with evaluable disease per RECIST 1.1; with an Eastern Cooperative Oncology Group performance status of 0 or 1; who had received two or more previous chemotherapy regimens (including one or more platinum regimen); and who had relapsed or progressive disease confirmed by radiological assessment before enrolment. Patients were required to have a documented treatment-free interval of at least 6 months after the first chemotherapy regimen they had received. Patients with platinum-refractory disease (ie, with progression during or within 4 weeks after the last dose of platinum-based chemotherapy) or who had received a previous PARP inhibitor, single-agent paclitaxel, or nab-paclitaxel were excluded. Full eligibility criteria are in the appendix (pp 10–11). Patients provided written informed consent before participating in the study.

The study was approved by national or local institutional review boards and performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation. The protocol is available online.

Randomisation and masking

After confirmation of *BRCA1* or *BRCA2* mutation status, patients were randomly assigned (2:1) to receive rucaparib or chemotherapy with a central randomisation procedure using interactive response technology. Randomisation was done by Endpoint Clinical (San Francisco, CA, USA) using block randomisation (block size of six). Patients were stratified by progression-free interval after most recent platinum-containing therapy upon study entry, classified as having platinum-resistant (progression ≥1 month to <6 months after last dose of platinum-based chemotherapy), partially platinum-sensitive (progression within ≥6 months to <12 months), or fully platinum-sensitive (progression ≥12 months) disease. The study was open label; no patients or investigators were masked to treatment allocation due to the nature of the intervention, but the sponsor was blinded to treatment allocation when viewing aggregate data.

Procedures

DNA extracted from patient archival tumour or screening biopsy were tested at a central laboratory (Foundation Medicine, Cambridge, MA, USA) and *BRCA* mutation status was confirmed for patients who had been enrolled on the basis of a local result, using Foundation Medicine's FoundationOne next-generation sequencing (NGS) assay to detect deleterious *BRCA* mutations (Cambridge, MA, USA). *BRCA* reversion mutations were prospectively analysed after randomisation by testing of cell-free DNA derived from plasma samples collected before rucaparib treatment, using Guardant Health's Guardant360 NGS assay (Redwood City, CA, USA). Central germline *BRCA* testing of DNA derived from whole blood or buffy coat was done with Ambry Genetics' CancerNext test (Aliso Viejo, CA, USA). A *BRCA* mutation was classified as germline if either the central or local germline testing result was *BRCA*-positive.

Patients assigned to the rucaparib group were given oral rucaparib 600 mg twice daily in 28-day cycles, regardless of platinum sensitivity status. Patients in the chemotherapy group were given weekly intravenous paclitaxel as chemotherapy (starting dose 60–80 mg/m² according to institutional standard of care, on days 1, 8, and 15 in 28-day cycles) if they had platinum-resistant or partially platinum-sensitive disease, or investigator's choice of platinum-based chemotherapy (single-agent cisplatin or carboplatin, or platinum-doublet chemotherapy [carboplatin plus paclitaxel, carboplatin plus gemcitabine, or cisplatin plus gemcitabine], administered in 21-day or 28-day cycles according to institutional guidelines) if they had fully platinum-sensitive disease. Investigators made their choice of chemotherapy for patients with fully platinum-sensitive disease before randomisation. No other anticancer therapies were permitted in combination with rucaparib or chemotherapy, except for hormonal treatment for previous breast cancer. Treatment with rucaparib or chemotherapy continued until investigator-assessed disease progression by RECIST 1.1, unacceptable toxicity, death, or another appropriate reason for discontinuation occurred. Patients allocated to receive platinum monotherapy or doublet therapy received a maximum of eight cycles. There was no cap on the number of paclitaxel cycles. After disease progression, eligible patients who were randomly assigned to the chemotherapy group could cross over to rucaparib treatment, after sponsor approval of the radiology report confirming disease progression, and confirmation that eligibility criteria for cross-over were met.

Rucaparib dose interruptions or reductions in 100 mg twice daily decrements were permitted in the event of grade 3 or 4 adverse events, or a grade 2 adverse event not

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See **Online** for appendix

For the **ARIEL4 protocol** see https://clinicaltrials.gov/ProvidedDocs/44/NCT02855944/Prot_000.pdf

adequately controlled by concomitant medications or supportive care (appendix p 7). If a patient continued to experience an adverse event despite three dose-reduction steps (ie, to a rucaparib dose of 300 mg twice daily), or if rucaparib dosing was interrupted for more than 14 consecutive days because of toxicity, treatment was to be discontinued, unless otherwise agreed between the investigator and the sponsor. For chemotherapy, dose interruptions and modifications were permitted according to institutional guidelines and local prescribing information.

Efficacy measures included tumour assessments using CT per RECIST 1.1, Gynecologic Cancer InterGroup cancer antigen 125 (CA-125 [MUC-16]) measurement, and clinical examination; other studies (MRI, x-ray, PET, and ultrasound) could also be done if required. Tumours were assessed during screening, then at 8-week intervals for 18 months, and then at 16-week intervals until radiological disease progression by RECIST 1.1, death, loss to follow-up, withdrawal of consent, study closure, or initiation of subsequent treatment. We collected patient-reported outcomes using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) instruments via an electronic tablet (iPad, Apple) during screening, on day 1 of each treatment cycle, at treatment discontinuation, and at the 28-day safety follow-up visit.

We followed up patients for safety and efficacy assessments for 28 days after the last dose of study drug, with additional long-term follow-up assessments (subsequent treatments, secondary malignancies, and survival) every 12 weeks until death, loss to follow-up, consent withdrawal, or study closure. Patient-reported outcomes were assessed during screening, on day 1 of every treatment cycle, at the treatment discontinuation visit, and at the 28-day safety follow-up visit. Treatment-emergent adverse events were defined as those with an onset date on or after the date of first dose of randomised study drug until the date of the last dose of study drug plus 28 days, or up to the date of first dose of rucaparib for those patients who crossed over from chemotherapy, whichever was first. Adverse events were considered related to treatment on the basis of investigators' medical judgment. Treatment-emergent adverse events were classified using Medical Dictionary for Drug Regulatory Activities (version 23.0) terms and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). We also assessed safety via physical examinations, laboratory assessments, electrocardiogram, and vital signs. Myelodysplastic syndrome and acute myeloid leukaemia were monitored as adverse events of special interest.

Outcomes

The primary endpoint was investigator-assessed progression-free survival per RECIST 1.1 for rucaparib versus chemotherapy. Key secondary endpoints were objective response rate per RECIST 1.1, duration of response per RECIST 1.1, objective response rate per RECIST 1.1 or CA-125, and patient-reported outcomes per EORTC QLQ-C30 Global Health Status. Further secondary endpoints were blinded, independent, central review-assessed progression-free survival per RECIST 1.1, overall survival, and patient-reported outcomes per EORTC QLQ-OV28. EORTC QLQ-OV28 data will be presented separately.

EORTC QLQ-C30 Global Health Status scores range from 0 to 100, with higher scores indicating better health-related quality of life; a difference of 10 points is considered to represent a clinically meaningful difference.[17] Progression-free survival assessed via blinded, independent, central review was a prespecified secondary endpoint; however, evaluation of this secondary endpoint was considered not necessary due to new evidence generated during the course of this study. We also assessed the safety and tolerability of rucaparib versus chemotherapy.

Statistical analysis

A sample size of 345 patients (230 randomly assigned to the rucaparib group and 115 to the chemotherapy group) was required to yield at least 80% power at a two-sided 0·05 significance level, to show a significant difference in investigator-assessed progression-free survival, assuming a median of 12 months for rucaparib and 8 months for chemotherapy, a hazard ratio (HR) of 0·65, and a 2% dropout rate.

The primary endpoint and key secondary endpoints were originally planned to be assessed in the efficacy population only (defined as all patients randomly assigned to treatment with deleterious *BRCA* mutations, excluding those with *BRCA* reversion mutations). The protocol was amended on Oct 23, 2020, to also include the intention-to-treat (ITT) population (ie, all patients randomly assigned to treatment) for these endpoints. The revision allowed us to fully assess efficacy in patients with or without *BRCA* reversion mutations present before treatment, because a *BRCA* reversion mutation might confer resistance to a PARP inhibitor or platinum-based chemotherapy.[6] We used a hierarchical step-down procedure to analyse the primary and key secondary endpoints and preserve the overall type 1 error rate, testing the primary efficacy endpoint first in the efficacy population and, if found to be significant at a 0·05 significance level, then testing the primary endpoint in the ITT population. The secondary efficacy endpoints were tested first in the efficacy population, and then in the ITT population only if the primary and previous secondary endpoints were significant. They were tested in the following order: objective response rate per RECIST 1.1, duration of response per RECIST 1.1, objective response rate per RECIST 1.1 or CA-125, and EORTC QLQ-C30 Global Health Status score.

We analysed the primary endpoint of investigator-assessed progression-free survival using stratified Cox

proportional hazards methods. We verified the proportional hazard assumption for the Cox proportional model (ie, constant relative hazard) graphically using log-log plots (appendix p 24). Patients without a documented event of progression were censored on the date of their last tumour assessment (ie, radiological assessment) or date of randomisation if no tumour assessments were done.

We analysed investigator-assessed objective response rate per RECIST 1.1 in patients who were response-evaluable at baseline (ie, with measurable target lesions), comparing it between treatments using a stratified Cochran-Mantel-Haenszel test. We analysed investigator-assessed objective response rate per RECIST 1.1 and CA-125 in patients who were either response-evaluable or CA-125 response-evaluable at baseline, using a stratified Cochran-Mantel-Haenszel test to compare between treatments (appendix p 7). We analysed duration of response using stratified Cox proportional hazards methods. Overall survival will be assessed once 70% maturity is reached.

We assessed patient-reported outcomes as the change from baseline in EORTC QLQ-C30 Global Health Status score during the first six treatment cycles using an ANCOVA model. At a given timepoint, the change from baseline was compared between the randomised treatment groups using the baseline value for the parameter as a continuous covariate and the treatment and randomisation stratification variables as categorical factors. Patients without a baseline measurement and at least one measurement after baseline were excluded.

We did exploratory analyses of progression-free survival in prespecified and post-hoc subgroups of the efficacy population. The prespecified subgroups were based on platinum sensitivity status as determined by the investigator (platinum resistant, partially platinum sensitive, and fully platinum sensitive), age (<65 years and ≥65 years), and race (White and not White or unknown). The post-hoc subgroups were based on *BRCA* mutation status (germline and somatic), progression-free interval (≥1 to <6 months, ≥6 to <12 months, and ≥12 months), number of previous chemotherapy regimens (two or three or more), and geographical region (central or eastern Europe, northern or southern Europe, and North or South America).

We summarised safety data descriptively in the safety population (ie, all patients who received at least one dose of randomly assigned treatment). We did post-hoc, exploratory, time-adjusted safety analyses of the incidence of treatment-emergent adverse events per 100 patient-years (ie, by total exposure time for all patients). Patients with protocol deviations were not excluded from any efficacy or safety analyses (appendix p 8).

All data were used to their maximum possible extent without any imputations for missing data. The analyses presented here do not include results after patient cross-over from chemotherapy to rucaparib treatment.

We did prespecified, exploratory analyses assessing circulating cell-free tumour DNA collected before rucaparib treatment as a molecular marker of efficacy, and explored the primary endpoint of progression-free survival using a treatment-by-*BRCA* mutation type variable in the model. We also had several prespecified exploratory endpoints that will be reported separately.

p values of less than 0·05 were considered to be statistically significant. We did all statistical analyses using SAS (version 9.4). This ongoing study is registered

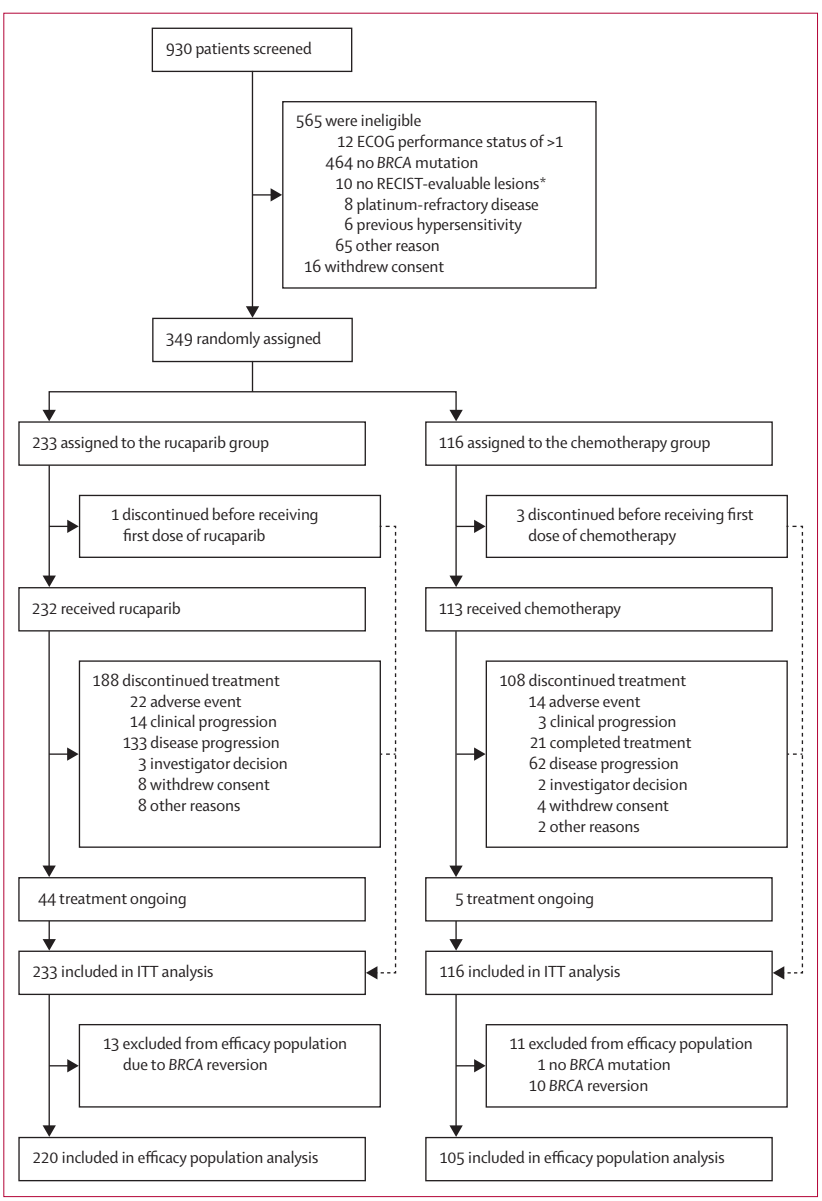

Figure 1: **Trial profile**
A full description of protocol deviations is in the appendix (p 8); these protocol deviations are reported as of data cutoff (Sept 30, 2020). Protocol deviations did not result in exclusion from efficacy or safety analyses (except for one patient with non-*BRCA*-mutated ovarian carcinoma who was excluded from the efficacy population analysis). ECOG=Eastern Cooperative Oncology Group. ITT=intention-to-treat. RECIST=Response Evaluation Criteria in Solid Tumors version 1.1. *Target or non-target lesions.

with ClinicalTrials.gov, NCT02855944, and enrolment is complete. The independent data monitoring committee reviewed the efficacy and safety data, including maturity of progression-free survival events, approximately every 6 months. The sponsor was unblinded to aggregate study data on Dec 15, 2020.

	Efficacy population		ITT population	
	Rucaparib group (n=220)	Chemotherapy group (n=105)	Rucaparib group (n=233)	Chemotherapy group (n=116)
Age, years	58 (50–63)	58 (52–65)	58 (50–63)	59 (52–64)
Race				
White	206 (94%)	102 (97%)	219 (94%)	113 (97%)
Other or unknown*	14 (6%)	3 (3%)	14 (6%)	3 (3%)
Geographical region				
Central and eastern Europe	130 (59%)	62 (59%)	135 (58%)	67 (58%)
Northern and southern Europe	53 (24%)	31 (30%)	59 (25%)	35 (30%)
North and South America	37 (17%)	12 (11%)	39 (17%)	14 (12%)
ECOG performance status				
0	119 (54%)	66 (63%)	125 (54%)	72 (62%)
1	101 (46%)	39 (37%)	108 (46%)	44 (38%)
Diagnosis				
Epithelial ovarian cancer	209 (95%)	101 (96%)	220 (94%)	111 (96%)
Primary peritoneal cancer	4 (2%)	1 (1%)	6 (3%)	2 (2%)
Fallopian tube cancer	7 (3%)	3 (3%)	7 (3%)	3 (3%)
Histology				
Serous	195 (89%)	95 (90%)	208 (89%)	105 (91%)
Endometrioid	18 (8%)	5 (5%)	18 (8%)	6 (5%)
Mixed	2 (1%)	2 (2%)	2 (1%)	2 (2%)
Other	5 (2%)	3 (3%)	5 (2%)	3 (3%)
BRCA mutation				
BRCA1†	173 (79%)	74 (70%)	181 (78%)	79 (68%)
BRCA2†	47 (21%)	31 (30%)	52 (22%)	36 (31%)
Non-*BRCA*†	0	0	0	1 (1%)
Germline	187 (85%)	88 (84%)	198 (85%)	95 (82%)
Somatic	33 (15%)	16 (15%)	35 (15%)	19 (16%)
Germline or somatic status not available	0	1 (1%)	0	2 (2%)
BRCA reversion mutation	0	0	13 (6%)	10 (9%)
Number of previous chemotherapy regimens	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)
2	130 (59%)	62 (59%)	134 (58%)	68 (59%)
3–5	80 (36%)	41 (39%)	88 (38%)	44 (38%)
≥6	10 (5%)	2 (2%)	11 (5%)	4 (3%)
Number of previous non-platinum regimens without intervening platinum before randomisation	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
0	170 (77%)	84 (80%)	179 (77%)	92 (79%)
≥1	50 (23%)	21 (20%)	54 (23%)	24 (21%)
Previously received bevacizumab	63 (29%)	32 (30%)	66 (28%)	35 (30%)
Time to progression with last platinum-based regimen‡				
≥1 to <6 months	113 (51%)	51 (49%)	123 (53%)	59 (51%)
≥6 to <12 months	63 (29%)	29 (28%)	66 (28%)	32 (28%)
≥12 months	44 (20%)	25 (24%)	44 (19%)	25 (22%)

(Table 1 continues on next page)

Role of the funding source

ARIEL4 was designed by the funder in collaboration with the coordinating investigators (RK and AMO). Data were collected by the investigators, analysed by the funder, and interpreted by all authors. Writing and editorial assistance were supported by the funder.

Results

Between March 1, 2017, and Sept 24, 2020, 930 patients were screened and 349 were enrolled and randomly assigned to the rucaparib group (n=233) or the chemotherapy group (n=116; ITT population; figure 1). The median age was 58 years (IQR 52–64) and 332 (95%) patients were White. 179 (51%) of 349 patients had platinum-resistant disease, 96 (28%) had partially platinum-sensitive disease, and 74 (21%) had fully platinum-sensitive disease (table 1). In the chemotherapy group, 90 (78%) of 116 patients were allocated to receive weekly paclitaxel; the remainder were to receive platinum monotherapy (ten [9%]) or platinum-doublet therapy (16 [14%]) by investigator's choice (appendix p 9). Of 349 patients in the ITT population, 24 (7%) were excluded from the efficacy population due to *BRCA* mutation status: 23 (7%) of 349 patients had *BRCA* reversion mutations before treatment (of whom 17 had platinum-resistant and six had partially platinum-sensitive disease), and one patient (assigned to chemotherapy) was found to not have a deleterious *BRCA* mutation on central review (figure 1). At data cutoff (Sept 30, 2020), 44 (19%) of 233 patients in the rucaparib group and five (4%) of 116 patients in the chemotherapy group were still receiving their assigned treatment. Median follow-up was 25·0 months (IQR 13·8–32·5). The protocol allowed patients in the chemotherapy group to cross over to open-label rucaparib treatment after they had completed the randomised portion of the study, and 74 (64%) of 116 patients crossed over. No patients discontinued treatment as a result of the COVID-19 pandemic. Baseline characteristics were generally well balanced between the treatment groups (table 1).

In the efficacy population (n=220 patients in the rucaparib group, n=105 patients in the chemotherapy group), median progression-free survival was 7·4 months (95% CI 7·3–9·1) in the rucaparib group versus 5·7 months (5·5–7·3) in the chemotherapy group (hazard ratio [HR] 0·64 [95% CI 0·49–0·84]; p=0·0010; figure 2A). In the ITT population (n=233 in the rucaparib group, n=116 in the chemotherapy group), median progression-free survival was 7·4 months (95% CI 6·7–7·9) in the rucaparib group versus 5·7 months (5·5–6·7) in the chemotherapy group (HR 0·67 [95% CI 0·52–0·86]; p=0·0017; figure 2B). Plots of the log of the cumulative hazard confirming the appropriateness of the Cox model assumption for the primary endpoint in the efficacy and ITT populations are in the appendix (p 24). In a prespecified exploratory analysis of patients with *BRCA*

reversion mutations before treatment (n=13 in the rucaparib group, n=10 in the chemotherapy group), median progression-free survival was 2·9 months (95% CI 1·8–4·2) in the rucaparib group versus 5·5 months (1·9–6·6) in the chemotherapy group (HR 2·77 [95% CI 0·99–7·76]; treatment-by-*BRCA* reversion interaction test p=0·0097; appendix p 25). Prespecified and post-hoc subgroup analyses are shown in figure 3 and in the appendix (p 26).

There was no significant difference in the objective response rate as per RECIST 1.1 between the two groups, in both the efficacy population and ITT population (table 2). Therefore, according to the hierarchical step-down approach, significance was not assessed for the other secondary endpoints. In the efficacy population, median duration of response was longer in the rucaparib group than in the chemotherapy group (table 2; appendix p 27). A higher proportion of patients in the rucaparib group than in the chemotherapy group had a response as per RECIST 1.1 or CA-125 criteria. Overall survival data are not mature; as of data cutoff, 51% of death events had occurred.

Change from baseline in EORTC QLQ-C30 Global Health Status during the first six cycles of treatment was similar between rucaparib and chemotherapy groups (difference in least squares mean for rucaparib *vs* chemotherapy in the efficacy population was 0·2 [SE 1·0; 95% CI –1·8 to 2·2]; appendix p 28). Results for the secondary efficacy endpoints in the ITT population were similar to those in the efficacy population (table 2; appendix pp 27–28).

The safety population included 232 (>99%) of 233 patients in the rucaparib group and 113 (97%) of 116 patients in the chemotherapy group who received at least one dose of study treatment. Three patients randomly assigned to chemotherapy (two with platinum-resistant disease and one with fully platinum-sensitive disease) and one patient assigned to rucaparib with platinum-resistant disease did not receive treatment (figure 1). The median duration of treatment (time on study drug in the treatment portion of the study—ie, excluding cross-over) in the safety population was 7·3 months (IQR 2·8–12·8) in the rucaparib group versus 3·6 months (1·9–5·3) in the chemotherapy group. Treatment-emergent adverse events of any grade occurred in 222 (96%) patients in the rucaparib group and 106 (94%) patients in the chemotherapy group; the most common treatment-emergent adverse events are shown in table 3. Treatment-emergent adverse events of grade 3 or worse occurred in 136 (59%) patients in the rucaparib group and 43 (38%) patients in the chemotherapy group, the most common of which were anaemia or decreased haemoglobin (52 [22%] patients in the rucaparib group *vs* six [5%] in the chemotherapy group) and neutropenia or decreased neutrophil count (24 [10%] *vs* 17 [15%] patients; table 3; appendix pp 12–13). For the majority of frequently reported treatment-emergent adverse events of any grade, median time to first onset was less than 2 months from the beginning of treatment (appendix p 29). A table of treatment-related adverse events is in the appendix (p 14).

	Efficacy population		ITT population	
	Rucaparib group (n=220)	Chemotherapy group (n=105)	Rucaparib group (n=233)	Chemotherapy group (n=116)
(Continued from previous page)				
Platinum status§				
Platinum resistant	110 (50%)	51 (49%)	120 (52%)	59 (51%)
Partially platinum sensitive	62 (28%)	28 (27%)	65 (28%)	31 (27%)
Fully platinum sensitive	48 (22%)	26 (25%)	48 (21%)	26 (22%)
Measurable disease	211 (96%)	96 (91%)	224 (96%)	106 (91%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. ITT=intention-to-treat. *Includes Native American or Alaska native, Black or African American, and patients of multiple or unknown races. †Combined local and central laboratory *BRCA* mutation results. ‡Derived from records of the patients' previous anticancer treatment submitted during screening. §Randomisation stratification factor.

Table 1: **Baseline demographic and clinical characteristics in the intention-to-treat and efficacy populations**

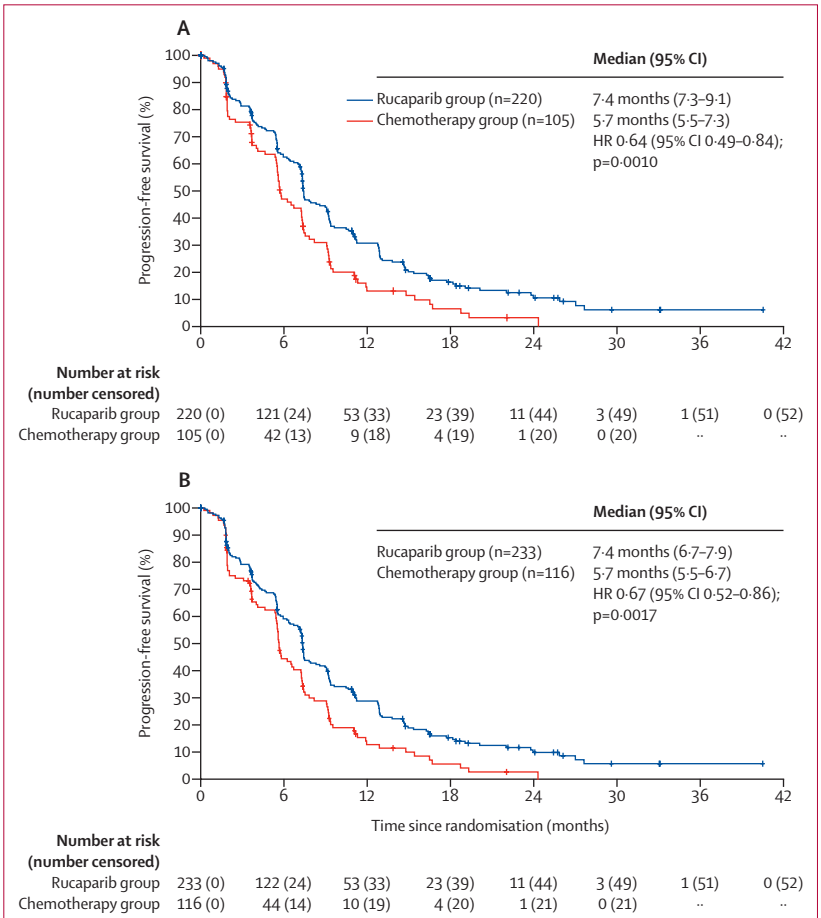

Figure 2: **Investigator-assessed progression-free survival in the efficacy (A) and intention-to-treat (B) populations**
Hazard ratios (HRs) and p values were calculated using a stratified Cox proportional hazards model.

A

	Rucaparib group (events/patients)	Chemotherapy group (events/patients)	Median progression-free survival, months (95% CI)		HR (95% CI)	p value
			Rucaparib group	Chemotherapy group		
***BRCA* reversion mutation**						
Yes (n=23)	13/13	9/10	2·9 (1·8–4·2)	5·5 (1·9–6·6)	2·77 (0·99–7·76)	0·053
No (efficacy population) (n=325)	168/220	85/105	7·4 (7·3–9·1)	5·7 (5·5–7·3)	0·64 (0·49–0·84)	0·0010
ITT population (N=349)	**181/233**	**95/116**	**7·4 (6·7–7·9)**	**5·7 (5·5–6·7)**	**0·67 (0·52–0·86)**	**0·0017**

B

Platinum sensitivity status						
Platinum resistant (n=161)	87/110	44/51	6·4 (5·5–7·4)	5·7 (3·7–7·3)	0·78 (0·54–1·13)	0·19
Partially platinum sensitive (n=90)	50/62	26/28	8·0 (7·0–11·0)	5·5 (2·0–5·6)	0·40 (0·24–0·65)	0·0002
Platinum sensitive (n=74)	31/48	15/26	12·9 (9·2–14·8)	9·6 (7·5–15·4)	0·69 (0·37–1·29)	0·25
Age, years						
<65 (n=259)	141/181	62/78	7·4 (7·2–8·6)	5·8 (5·5–7·4)	0·68 (0·50–0·93)	0·015
≥65 (n=66)	27/39	23/27	9·4 (6·5–12·9)	5·6 (2·0–9·3)	0·53 (0·29–0·94)	0·031
Race						
White (n=308)	156/206	83/102	7·4 (7·3–9·2)	5·7 (5·5–7·3)	0·63 (0·48–0·82)	0·0008
Not White or unknown (n=17)	12/14	2/3	7·5 (2·9–12·9)	5·7 (4·1–7·3)	0·60 (0·10–3·76)	0·59
Efficacy population (n=325)	**168/220**	**85/105**	**7·4 (7·3–9·1)**	**5·7 (5·5–7·3)**	**0·64 (0·49–0·84)**	**0·0010**

C

***BRCA* gene mutation**						
BRCA1 (n=247)	136/173	59/74	7·4 (7·2–9·1)	5·7 (4·7–7·4)	0·68 (0·49–0·92)	0·013
BRCA2 (n=78)	32/47	26/31	8·3 (6·5–16·3)	5·6 (4·1–7·9)	0·51 (0·29–0·89)	0·017
***BRCA* germline status**						
Germline (n=275)	146/187	70/88	7·4 (7·3–9·2)	5·7 (4·1–7·3)	0·60 (0·45–0·80)	0·0006
Somatic (n=49)	22/33	14/16	7·5 (5·6–11·2)	7·3 (1·8–9·3)	0·67 (0·32–1·40)	0·29
Progression-free interval						
≥1 to <6 months (n=164)	92/113	44/51	6·2 (5·5–7·4)	5·7 (3·7–7·3)	0·79 (0·55–1·14)	0·21
≥6 to <12 months (n=92)	48/63	27/29	9·1 (7·3–12·8)	5·5 (3·5–5·8)	0·38 (0·23–0·62)	0·0001
≥12 months (n=69)	28/44	14/25	12·9 (9·1–15·4)	9·6 (6·7–15·4)	0·69 (0·36–1·34)	0·27
Previous chemotherapy regimens						
2 (n=192)	91/130	49/62	9·1 (7·4–11·0)	6·7 (5·6–7·9)	0·58 (0·40–0·83)	0·0027
≥3 (n=133)	77/90	36/43	7·2 (5·6–7·5)	5·5 (3·5–7·3)	0·66 (0·44–0·99)	0·046
Geographical region						
Central and eastern Europe (n=192)	100/130	50/62	7·5 (7·2–9·2)	5·6 (3·7–5·8)	0·53 (0·37–0·76)	0·0006
Northern and southern Europe (n=84)	43/53	27/31	7·4 (5·3–9·3)	7·3 (5·5–9·4)	0·75 (0·45–1·24)	0·26
North and South America (n=49)	25/37	8/12	9·1 (5·8–12·9)	9·3 (1·8–15·4)	0·94 (0·41–2·16)	0·88
Efficacy population (n=325)	**168/220**	**85/105**	**7·4 (7·3–9·1)**	**5·7 (5·5–7·3)**	**0·64 (0·49–0·84)**	**0·0010**

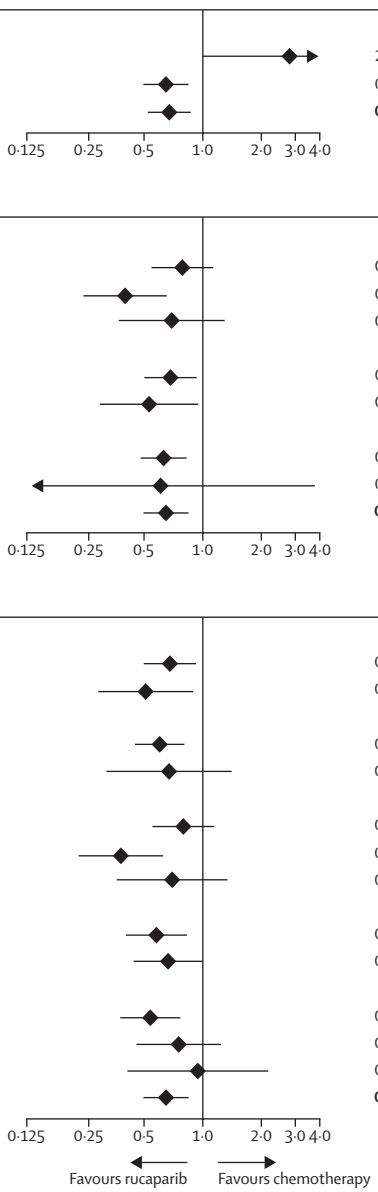

Figure 3: **Investigator-assessed progression-free survival in subgroups of the intention-to-treat population (A) and in prespecified (B) and non-prespecified (C) subgroups of the efficacy population**

HRs and p values were calculated using a stratified Cox proportional hazards model. *BRCA* germline status was not available for one patient assigned to the chemotherapy group. HR=hazard ratio. ITT=intention-to-treat.

Because patients in the rucaparib group generally received assigned treatment longer than those in the chemotherapy group, we did a post-hoc exploratory analysis of treatment-emergent adverse events adjusted for time on treatment. We found that there were 127 events of any grade per 100 patient-years of treatment in the rucaparib group versus 255 events per 100 patient-years in the chemotherapy group, and 78 grade 3 or worse events per 100 patient-years in the rucaparib group versus 103 grade 3 or worse events per 100 patient-years in the chemotherapy group (appendix p 30). The safety profiles of rucaparib and chemotherapy were similar in an additional exploratory analysis of treatment-emergent adverse in patients with *BRCA* reversion mutations (appendix pp 15–16).

	Efficacy population			ITT population		
	Rucaparib group	Chemotherapy group	p value	Rucaparib group	Chemotherapy	p value
RECIST-evaluable patients	211/220 (96%)	96/105 (91%)	..	224/233 (96%)	106/116 (91%)	..
Objective response rate per RECIST	85 (40%; 95% CI 34–47)	31 (32%; 95% CI 23–43)	0·13	85 (38%; 95% CI 32–45)	32 (30%; 95% CI 22–40)	0·13
Complete response	10 (5%)	2 (2%)	..	10 (4%)	2 (2%)	..
Partial response	75 (36%)	29 (30%)	..	75 (33%)	30 (28%)	..
Stable disease	77 (36%)	38 (40%)	..	83 (37%)	43 (41%)	..
Progressive disease	25 (12%)	15 (16%)	..	31 (14%)	19 (18%)	..
Not evaluable	24 (11%)	12 (13%)	..	25 (11%)	12 (11%)	..
Median duration of objective response per RECIST, months	9·4 (95% CI 7·5–11·1)	7·2 (95% CI 4·0–11·4)	..	9·4 (95% CI 7·5–11·1)	7·2 (95% CI 3·9–9·4)	..
HR (95% CI)	0·59 (0·36–0·98)	..	..	0·56 (0·34–0·93)	..	..
RECIST-evaluable or CA-125-evaluable patients	217/220 (99%)	101/105 (96%)	..	230/233 (99%)	111/116 (96%)	..
Objective response rate per RECIST or CA-125	110 (51%; 95% CI 44–58)	44 (44%; 95% CI 34–54)	..	110 (48%; 95% CI 41–55)	45 (41%; 95% CI 31–50)	..

All data are n/N (%), n (%), or estimate with 95% CI in parentheses, unless otherwise stated. p values were calculated using a stratified Cochran-Mantel-Haenszel test. p values for objective response rate per RECIST or CA-125 and duration of objective response are not presented due to the hierarchical step-down analysis being broken (ie, because there was no significant difference in objective response rate between the groups). HR=hazard ratio. ITT=intention-to-treat. RECIST=Response Evaluation Criteria in Solid Tumors version 1.1.

Table 2: **Investigator-assessed objective response rates in patients who were evaluable for RECIST or CA-125 response with measurable disease at baseline in the efficacy and ITT population**

Serious treatment-emergent adverse events occurred in 62 (27%) of 232 patients in the rucaparib group versus 13 (12%) of 113 patients in the chemotherapy group. The most common serious treatment-emergent adverse events (occurring in ≥3% of patients in either group) were anaemia or decreased haemoglobin (19 [8%] in the rucaparib group *vs* two [2%] in the chemotherapy group) and thrombocytopenia or decreased platelet count (seven [3%] *vs* one [1%]; appendix pp 19–20). Serious treatment-emergent adverse events were considered related to treatment by the investigator for 32 (14%) patients in the rucaparib group and six (5%) in the chemotherapy group, the most common of which was anaemia or decreased haemoglobin (19 [8%] *vs* two [2%]; appendix p 21). When adjusted for time on treatment (post hoc), there were 36 serious treatment-emergent adverse events per 100 patient-years of treatment in the rucaparib group versus 31 serious treatment-emergent adverse events per 100 patient-years in the chemotherapy group.

Treatment interruption, dose reduction, or both, due to a treatment-emergent adverse event occurred in 115 (50%) of 232 patients in the rucaparib group and 50 (44%) of 113 patients in the chemotherapy group (appendix p 17). Treatment-emergent adverse events (excluding disease progression) leading to treatment discontinuation occurred in 19 (8%) patients in the rucaparib group and 14 (12%) in the chemotherapy group (appendix p 18).

Death as a result of treatment-emergent adverse events, excluding disease progression, occurred in ten (4%) of 232 patients in the rucaparib group (cardiac disorder, large intestine perforation, myelodysplastic syndrome, neutropenia, pneumonia, pulmonary embolism, septic shock and thrombocytopenia [n=1 each], and three patients died due to an unconfirmed cause [one of which was subsequently identified as disease progression]). Of these deaths as a result of treatment-related adverse events, three of the adverse events were considered to be potentially related to rucaparib treatment by the investigator (one each of cardiac disorder, myelodysplastic syndrome, and unconfirmed cause). One (1%) patient in the chemotherapy group died as a result of a treatment-emergent adverse event (pulmonary embolism), but was not considered to be related to study treatment (appendix p 22).

Myelodysplastic syndrome or acute myeloid leukaemia were reported in five (2%) patients in the rucaparib group (one during treatment, and four during long-term follow-up); no cases were reported in the chemotherapy group (appendix p 23).

Discussion

The results of this trial show that rucaparib significantly improved progression-free survival versus the active comparator of chemotherapy in a population of patients with relapsed, heavily pretreated, *BRCA1*-mutated or *BRCA2*-mutated ovarian cancer, including those with platinum-resistant, partially platinum-sensitive, and fully platinum-sensitive disease. This progression-free survival advantage was observed in both the efficacy population (patients with deleterious *BRCA* mutations, excluding reversion mutations) and in the ITT population. To our knowledge, ARIEL4 is the first study to compare a PARP inhibitor with both platinum and non-platinum-based chemotherapy in patients with *BRCA1*-mutated or *BRCA2*-mutated, relapsed ovarian carcinoma. Notably, in our study, cross-over from chemotherapy to rucaparib after disease progression was an option for patients. Additionally, we enrolled a broad range of patients, including those with either somatic or germline *BRCA* mutations and those with platinum-resistant, partially platinum-sensitive, and fully platinum-sensitive disease.

Prespecified and post-hoc subgroup analyses showed that rucaparib generally had a consistent progression-free

	Rucaparib group (n=232)				Chemotherapy group (n=113)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
At least one treatment-emergent adverse event	86 (37%)	104 (45%)	17 (7%)	15 (6%)	63 (56%)	33 (29%)	7 (6%)	3 (3%)
Anaemia or decreased haemoglobin	73 (31%)	46 (20%)	6 (3%)	0	30 (27%)	6 (5%)	0	0
Nausea	118 (51%)	6 (3%)	0	0	36 (32%)	0	0	0
Asthenia or fatigue	96 (41%)	19 (8%)	0	0	47 (42%)	3 (3%)	0	0
Increased ALT or AST	62 (27%)	18 (8%)	0	0	13 (12%)	0	0	0
Vomiting	68 (29%)	11 (5%)	0	0	19 (17%)	0	0	0
Abdominal pain	45 (19%)	9 (4%)	0	0	18 (16%)	0	0	0
Thrombocytopenia or platelet count decreased	35 (15%)	15 (6%)	4 (2%)	0	13 (12%)	0	0	0
Neutropenia or decreased neutrophil count	28 (12%)	16 (7%)	7 (3%)	1 (<1%)	15 (13%)	14 (12%)	3 (3%)	0
Diarrhoea	43 (19%)	4 (2%)	0	0	23 (20%)	1 (1%)	0	0
Decreased appetite	42 (18%)	2 (1%)	0	0	20 (18%)	0	0	0
Dysgeusia	39 (17%)	0	0	0	8 (7%)	0	0	0
Constipation	36 (16%)	1 (<1%)	0	0	19 (17%)	0	0	0
Blood creatinine increased	28 (12%)	5 (2%)	0	0	9 (8%)	0	0	0
Dyspnoea	22 (9%)	3 (1%)	0	0	7 (6%)	2 (2%)	0	0
Weight loss	23 (10%)	2 (1%)	0	0	3 (3%)	0	0	0
Pyrexia	22 (9%)	1 (<1%)	0	0	7 (6%)	0	0	0
Leukopenia	16 (7%)	4 (2%)	1 (<1%)	0	15 (13%)	3 (3%)	0	0
Hyperglycaemia	14 (6%)	2 (1%)	0	0	12 (11%)	3 (3%)	0	0
Ascites	7 (3%)	6 (3%)	0	0	1 (1%)	1 (1%)	0	0
Alopecia	12 (5%)	0	0	0	37 (33%)	1 (1%)	0	0
Intestinal obstruction	2 (1%)	8 (3%)	0	0	0	0	0	0
Neuropathy	10 (4%)	0	0	0	41 (36%)	0	0	0
Pneumonia	6 (3%)	3 (1%)	0	1 (<1%)	0	0	0	0
Hypertriglyceridaemia	6 (3%)	1 (<1%)	1 (<1%)	0	5 (4%)	2 (2%)	0	0
Hyponatraemia	7 (3%)	0	1 (<1%)	0	1 (1%)	1 (1%)	1 (1%)	0
Malignant neoplasm progression	0	3 (1%)	0	5 (2%)	0	0	1 (1%)	2 (2%)
Hypoalbuminaemia	2 (1%)	0	0	0	3 (3%)	2 (2%)	0	0
Pulmonary embolism	1 (<1%)	0	0	1 (<1%)	0	1 (1%)	0	1 (1%)
Nail disorder	0	0	0	0	3 (3%)	2 (2%)	0	0
Seizure	0	0	0	0	0	2 (2%)	0	0

Data are n (%) and sorted by decreasing incidence in the rucaparib group. Data presented are grade 1 or 2 events occurring in ≥10% (rounded) of patients, and grade 3 or 4 events occurring in ≥2% (rounded) of patients. MedDRA (version 23.0) preferred terms are combined for the following adverse events: anaemia or decreased haemoglobin, asthenia or fatigue, increased ALT or AST, neuropathy, neutropenia or decreased neutrophil count, and thrombocytopenia or platelet count decreased. Neuropathy includes neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, and toxic neuropathy. ALT=alanine aminotransferase. AST=aspartate aminotransferase. MedDRA=Medical Dictionary for Drug Regulatory Activities.

Table 3: **Treatment-emergent adverse events in the safety population**

survival benefit compared with chemotherapy across most clinical subgroups analysed, although the study was not powered to detect differences in progression-free survival benefit between subgroups. In clinical practice, healthcare professionals should weigh the potential progression-free survival benefits and risks of rucaparib versus chemotherapy treatment for each patient according to their individual disease status.

Reversion mutations that restore function to proteins involved in the HRR pathway, such as *BRCA1* and *BRCA2*, are a key mechanism of resistance to platinum-based chemotherapies and to PARP inhibitors as treatment for *BRCA1*-mutated and *BRCA2*-mutated cancers.[6] Although the small number of patients in this subgroup of our trial should be noted, to our knowledge, ARIEL4 is the first randomised study to indicate that patients with *BRCA* reversion mutations that are present before treatment are less likely to benefit from rucaparib than those without these mutations. The optimal therapy for these patients is an outstanding question in the field. The proportion of patients in ARIEL4 who had *BRCA* reversion mutations before treatment was consistent with that observed in pretreatment cell-free DNA samples from platinum-resistant or platinum-sensitive

patients in ARIEL2 (7% each).[6] Patients in ARIEL2 without *BRCA* reversion mutations treated with rucaparib had significantly longer progression-free survival than those with reversion mutations. Patients in ARIEL4 with *BRCA* reversion mutations who were then treated with rucaparib had a similar absence of progression-free survival benefit compared with chemotherapy. Reversion mutations in HRR genes such as *BRCA1* and *BRCA2* have also been observed as a resistance mechanism for other PARP inhibitors, including olaparib and talazoparib.[18] These data suggest a gap in commercial tests for *BRCA* reversion mutations to enable pretreatment genomic disease characterisation.

We found no difference in objective response rate between rucaparib and standard-of-care chemotherapy in this broad patient population. However, the longer progression-free survival recorded with rucaparib than with chemotherapy could be reflective of some degree of extended disease stabilisation with rucaparib. Furthermore, the higher proportion of patients with a complete response and the longer duration of response in the rucaparib group than in the chemotherapy group suggest that rucaparib can provide deep and sustained responses for patients who respond to treatment. On the basis of EORTC QLQ-C30 Global Health Status scores, we found no difference in health-related quality of life with rucaparib versus chemotherapy. Overall survival data were not mature at the time of the visit cutoff; 51% of death events had occurred. Patient follow-up is ongoing, and overall survival will be assessed once 70% maturity is reached. However, any overall survival results will be confounded by the high proportion of patients who crossed over from chemotherapy to rucaparib after disease progression (64% as of data cutoff for this analysis).

The PARP inhibitors olaparib and niraparib have also been assessed in the treatment of patients with relapsed ovarian carcinoma. SOLO3 is a randomised phase 3 study of olaparib, which differed from ARIEL4 by enrolling only patients with partially or fully platinum-sensitive relapsed ovarian carcinoma and those with a germline, but not somatic, *BRCA1* or *BRCA2* mutation.[16] Additionally, patients with platinum-sensitive disease were not offered platinum chemotherapy in the comparator group. In that study, olaparib significantly improved the proportion of patients with an objective response versus physician's choice of single-agent non-platinum chemotherapy (primary endpoint: 109 [72%] of 151 *vs* 37 [51%] of 72; odds ratio 2·53 [95% CI 1·40–4·58]; p=0·002) and progression-free survival (median 13·4 months *vs* 9·2 months; HR 0·62 [95% CI 0·43–0·91]; p=0·013).[16] In the phase 3 NRG Oncology GY004 study, median progression-free survival was 12·7 months with olaparib monotherapy versus 10·5 months with platinum-based chemotherapy in the subgroup of patients with partial or fully platinum-sensitive ovarian carcinoma associated with a germline *BRCA1* or *BRCA2* mutation (HR 0·63 [95% CI 0·37–1·07]).[19] Niraparib has been assessed in a single-arm, phase 2 study as treatment for patients with partially or fully platinum-sensitive relapsed ovarian carcinoma with *BRCA1*-mutated or *BRCA2*-mutated, or homologous recombination deficiency-positive tumours who had received three or more previous chemotherapy regimens (primary efficacy population), with 18 (29%) of 63 patients with *BRCA1*-mutated or *BRCA2*-mutated disease (unselected for platinum sensitivity) having a response.[13]

Treatment-emergent adverse events in the rucaparib and chemotherapy groups were consistent with the expected safety profiles for these agents, and no new safety signals were identified.[10,11,14,20,21] The median time to first onset for frequently reported treatment-emergent adverse events was generally early in treatment for both groups. Although the overall incidences of treatment-emergent adverse events and serious treatment-emergent adverse events were higher in the rucaparib group than in the chemotherapy group, this reflects the approximately two-times longer median duration of treatment with rucaparib than with chemotherapy. Reflective of the differences of time on treatment, in a post-hoc exploratory time-adjusted analysis of safety, we observed a lower incidence of treatment-emergent adverse events per 100 patient-years in the rucaparib group than in the chemotherapy group. Consistent with other PARP inhibitor studies in this setting,[16] myelodysplastic syndrome or acute myeloid leukaemia occurred in a small number of patients in ARIEL4; however, attribution for causality of these adverse events is complicated by the confounding effects of previous chemotherapy received, and further research in this area is needed.

No established third-line standard of care for patients with ovarian cancer exists.[20,21] For the ARIEL4 study, the standard-of-care comparators we selected were chemotherapy agents that have activity in advanced ovarian cancer and are recommended by National Comprehensive Cancer Network and European Society for Medical Oncology guidelines.[20,21] A strength of this study is that rucaparib was compared with platinum-based chemotherapy for patients with fully platinum-sensitive disease. However, a potential limitation of the design of ARIEL4 is the comparison of rucaparib with a non-platinum-based chemotherapy for patients with partially platinum-sensitive disease. Weekly paclitaxel was selected as a platinum-sparing comparator treatment for these patients after consultations with regulatory authorities. However, although these patients might derive less clinical benefit from platinum-based chemotherapy than patients with fully platinum-sensitive disease, some studies have suggested that platinum-based chemotherapy is a reasonable alternative treatment option to paclitaxel in patients with partially platinum-sensitive disease. In the MITO-8 study (NCT00657878), treatment with platinum-based chemotherapy before non-platinum-based chemotherapy in patients with partially platinum-sensitive recurrent ovarian cancer resulted in

longer progression-free survival than in those treated with non-platinum-based chemotherapy followed by platinum-based chemotherapy.[22] However, notably, the MITO-8 study enrolled a different population than we did for ARIEL4. In MITO-8, patients must have received one or two previous chemotherapy regimens, and more than 90% of the patients enrolled had only received one previous chemotherapy regimen;[22] whereas in ARIEL4, patients must have received two or more previous chemotherapy regimens. Additionally, other studies have shown that, in patients with partially platinum-sensitive disease, second-line regimens incorporating non-platinum-based agents can yield response rates similar to or better than with platinum-based chemotherapy alone,[23,24] suggesting platinum might not always be the optimal choice for these patients.

A limitation of ARIEL4 was its open-label design. A blinded study design was considered to not be feasible because of the different administration routes and schedules of rucaparib and the chemotherapy regimens that were assessed; however, no data were reviewed by treatment group, except by the independent data monitoring committee, until unmasking of the sponsor to the aggregate data. The observed treatment effect (HR 0·67 in the ITT population) was consistent with the original power assumption of 0·65; this finding was despite enrolment of a higher proportion of patients with platinum-resistant disease (approximately 50%) then the anticipated even distribution across the platinum sensitivity status strata (ie, approximately 33% each), which might have contributed to shorter progression-free survival durations for the treatment groups than assumed in the initial statistical design. Finally, the distribution of patient population might not be considered ethnically diverse; the majority of patients were from central and eastern Europe.

Although progression-free survival assessment by blinded independent central review was originally planned as a secondary endpoint outside of the hierarchical step-down procedure, multiple studies have shown that, while there is a strong correlation in magnitude of treatment benefit observed with progression-free survival assessed by an investigator or blinded independent central review,[25,26] due to informative censoring, blinded independent central review might have a tendency to report a longer median progression-free survival than that reported by investigator assessment.[27] Given the clear and meaningful difference in investigator-assessed progression-free survival observed between rucaparib and chemotherapy, blinded independent central review assessment was ultimately not considered necessary by the sponsor after unblinding of the aggregate study data.

PARP inhibitors are approved in several countries as treatment for patients with relapsed ovarian carcinoma associated with a deleterious *BRCA* mutation or homologous recombination deficiency.[28] The results of ARIEL4 show that rucaparib might offer patients with *BRCA1*-mutated or *BRCA2*-mutated, relapsed ovarian carcinoma an orally administered therapeutic option with significantly improved progression-free survival versus intravenous non-platinum-based or platinum-based chemotherapy. PARP inhibitors are also approved as first-line and subsequent-line maintenance therapy to extend progression-free survival after a response to platinum-based chemotherapy in patients with ovarian carcinoma.[8,9] However, despite evidence of benefit in many settings, many patients with ovarian cancer might not receive appropriate treatment with a PARP inhibitor.[29,30] Further studies are required to more clearly define when patients should receive PARP inhibitors for optimal clinical benefit in both the treatment and maintenance settings, whether this is variable for different groups of patients (eg, those with *BRCA1*-mutated or *BRCA2*-mutated *vs* presence or absence of homologous recombination deficiency), and whether patients who had previous exposure to a PARP inhibitor and did not progress would still derive clinical benefit when rechallenged with another PARP inhibitor. Ideally, the molecular profile of the disease would be recharacterised on relapse to better inform treatment decision making, but this approach might have financial and practical considerations. Future research could also define optimal treatment strategies for patients with *BRCA* reversion mutations, improve understanding of additional factors that confer sensitivities to both platinum-based chemotherapy and to PARP inhibitors, and identify whether patients with mutations in other key genes involved in HRR derive similar benefit from PARP inhibitors compared with chemotherapy to those with *BRCA* mutations.

Contributors

RK, KKL, SG, and AMO designed the study. RK, AL, AF, MD, ACdM, YS, IR, IB, NC, VS, LB, MN, DL, GS, DC, RP, AO, TS, BM-M, LM, and AMO treated patients. RK, AL, AF, MD, ACdM, YS, IR, IB, NC, VS, LB, MN, DL, GS, DC, RP, AO, TS, BM-M, LM, DT, KKL, KM, SG, and AMO acquired data. RK, KKL, KM, SG, and AMO analysed or interpreted data. All authors contributed to manuscript review and revision, approved the final draft for submission, and are accountable for accuracy and integrity of any part of the work. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. RK, KKL, KM, SG, and AMO accessed and verified the underlying study data

Declaration of interests

RK has received institutional funding from Clovis Oncology for this clinical trial; reports clinical trial grants from Merck Sharp & Dohme; has served as a consultant for Basilea Pharmaceutica and Shattuck Pharma; has received honoraria from Clovis Oncology, AstraZeneca, GlaxoSmithKline, and Incyte; received travelling support from AstraZeneca, GlaxoSmithKline, and Sierra Oncology; has served on data safety monitoring boards or advisory boards for Clovis Oncology, AstraZeneca, BeiGene, Eisai, GlaxoSmithKline, Incyte, iTeos Therapeutics, PharmaMar, and Roche. AF is currently at P A Herzen Cancer Research Institute, Moscow, Russia and delcares no competing interests. ACdM has received institutional funding from Clovis Oncology for this cl.inical trial; reports institutional clinical trial grants from Amgen, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Regeneron, and Roche; has received honoraria for lectures from AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche, and Sanofi; has served on

advisory boards for AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Roche. YS has received honoraria from AstraZeneca, Merck Sharp & Dohme, and Roche. NC reports grants from AstraZeneca and Roche; has served as a consultant for Clovis Oncology, AstraZeneca, BIOCAD, Eisai, GlaxoSmithKline, Immunogen, Merck Sharp & Dohme/Merck, Mersana, Oncxerna, Pfizer, Pharmamar, Roche, Takeda, and Tesaro; has received honoraria from Clovis Oncology, AstraZeneca, Eisai, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, and Tesaro; received traveling support from Tesaro; and has served on data safety monitoring boards or advisory boards for Clovis Oncology, AstraZeneca, BIOCAD, Eisai, GlaxoSmithKline, Immunogen, Merck Sharp & Dohme/Merck, Mersana Therapeutics, OncXerna, Pfizer, PharmaMar, Roche, Takeda, and Tesaro. DL has received institutional funding from Clovis Oncology for this clinical trial; reports institutional research grants from Clovis Oncology, GlaxoSmithKline, and Merck Sharp & Dohme; has served as a consultant for Merck Serono and ParmaMar; has served on advisory boards for Amgen, AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, and PharmaMar; has received travelling support from AstraZeneca, GlaxoSmithKline, PharmaMar, and Roche; has served on data safety monitoring committee for Novartis; and has served on the board of directors for the Gynecological Cancer Academy, the Gynecological Cancer InterGroup, and Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies. GS reports grants and research support from Merck Sharp & Dohme Italia SRL; has served as a consultant for Tesaro Bio Italy SRL and Johnson & Johnson; and has received honoraria and served on a speakers' bureau for Clovis Oncology Italy SRL. DC has served as a consultant for Akeso Biopharma, AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, Novocure, Roche, Seagen, and SOTIO. DT, KKL, KM, and SG are employees of Clovis Oncology, and have stock and stock options. AMO reports institutional research grants from AstraZeneca; has served on an advisory board (uncompensated) for GlaxoSmithKline; has served on advisory boards and steering committees (uncompensated) for Clovis Oncology and AstraZeneca; and has served as a principal investigator on investigator-initiated trials for Clovis Oncology, AstraZeneca, and GlaxoSmithKline. All other authors declare no competing interests. Authors received writing support from Clovis Oncology during the conduct of the study. RK is currently at the Department of Oncology, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London, UK. AL is currently at the Department of Oncology, Almazov National Medical Research Center, Saint Petersburg, Russia. DL is currently at Gynecologic Oncology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS and Catholic University of Sacred Heart, Rome, Italy.

Data sharing

Requests for de-identified datasets for the results reported in this publication will be made available to qualified researchers after submission and approval of a methodologically sound proposal sent to medinfo@clovisoncology.com. Data will be made available for such requests following online publication of this Article and for 1 year thereafter, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymisation. Data will be provided by Clovis Oncology. Clovis Oncology does not share identified participant data or a data dictionary.

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