Rucaparib versus chemotherapy for treatment of relapsed ovarian cancer with deleterious *BRCA1* or *BRCA2* mutation (ARIEL4): final results of an international, open-label, randomised, phase 3 trial

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Summary

Background In the ARIEL4 trial of rucaparib versus standard-of-care chemotherapy in patients with relapsed *BRCA*-mutated ovarian carcinoma, the primary endpoint was met, showing improved investigator-assessed progression-free survival with rucaparib. Here, we present the final overall survival analysis of the trial and other post-progression outcomes.

Methods This open-label, randomised, controlled phase 3 trial was done at 64 hospitals and cancer centres in 12 countries, including Brazil, Canada, Czech Republic, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, the UK, and the USA. Eligible patients were women aged 18 or older with *BRCA1* or *BRCA2*-mutated ovarian carcinoma and had received at least two previous chemotherapy regimens. Patients had to have evaluable disease as per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) criteria and an Eastern Cooperative Oncology Group performance status of 0 or 1. 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 receive oral rucaparib (600 mg twice daily administered in 28-day cycles) or chemotherapy on the basis of platinum-sensitivity status. In the chemotherapy group, patients with platinum-resistant disease (progression-free interval ≥1 to <6 months) or partially platinum-sensitive disease (progression-free interval ≥6 to <12 months) received weekly paclitaxel (starting dose 60–80 mg/m² on days 1, 8, and 15). Patients with fully platinum-sensitive disease (progression-free interval ≥12 months) received the investigator's choice of platinum-based chemotherapy (single-agent cisplatin or carboplatin, or platinum-doublet chemotherapy), in 21-day or 28-day cycles. The primary endpoint (previously reported) 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 in the intention-to-treat population (all randomly assigned patients). Overall survival was a prespecified secondary endpoint and was analysed in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of assigned study treatment. The cutoff date was April 10, 2022. This study is registered with ClinicalTrials.gov, NCT02855944; enrolment is complete and the study is closed.

Findings Between March 1, 2017, and Sept 24, 2020, 349 eligible patients were randomly assigned to receive rucaparib (n=233) or chemotherapy (n=116). 332 (95%) of 349 patients were white and 17 (5%) patients were other or of unknown race. In the chemotherapy group, 80 (69%) of 116 patients crossed over to receive rucaparib. Median follow-up was 41·2 months (IQR 37·8–44·6). At data cutoff for this final analysis (April 10, 2022), 244 (70%) of 349 patients had died: 167 (72%) of 233 in the rucaparib group and 77 (66%) of 116 in the rucaparib group. Median overall survival was 19·4 months (95% CI 15·2–23·6) in the rucaparib group versus 25·4 months (21·4–27·6) in the chemotherapy group (hazard ratio 1·3 [95% CI 1·0–1·7], p=0·047). No new safety signals were observed, including during crossover to rucaparib. The most common grade 3–4 adverse events across treatment groups included anaemia or decreased haemoglobin (reported in 59 [25%] of 232 patients in the rucaparib group and seven [6%] of 113 in the chemotherapy group), and neutropenia or decreased neutrophil count (in 26 [11%] of 232 in the rucaparib group and 16 [14%] of 113 patients in the chemotherapy group). Serious adverse events were reported in 66 (28%) of 232 patients in the rucaparib group and 14 (12%) of 113 patients in the chemotherapy group. Ten treatment-related deaths were reported in the rucaparib group, two of which were linked to judged to be related to rucaparib (cardiac disorder and myelodysplastic syndrome), and one death related to treatment was reported in the chemotherapy group, with no specific cause linked to the treatment.

Interpretation These data highlight the need for a better understanding of the most appropriate treatment for patients who have progressed on a poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor, and the optimal sequencing of chemotherapy and PARP inhibitors in advanced ovarian cancer.

Lancet Oncol 2025; 26: 249–64

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Funding Clovis Oncology.

Introduction

Most patients with advanced high-grade serous ovarian cancer respond to initial treatment, but the majority relapse. Recurrent disease is generally incurable, and despite additional lines of therapy, patients have progressively shorter median progression-free survival and overall survival.[1] Rucaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has demonstrated efficacy as monotherapy treatment for patients with platinum-sensitive, *BRCA1* or *BRCA2* (*BRCA*)-mutated recurrent ovarian cancer who have received at least two previous therapies, and as maintenance treatment in the first-line and recurrent settings.[2–5] In the SOLO3 trial, olaparib monotherapy was more effective than non-platinum

Research in context

Evidence before this study

Patients with advanced high-grade ovarian carcinoma often have reduced treatment-free intervals and inadequate responses following multiple lines of therapy. There is a crucial need for targeted therapies that consider the molecular characteristics of the disease, aiming to improve the benefit-to-risk ratio of chemotherapy. One example of such targeted therapies are poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, which have shown promise as a treatment option for patients with relapsed ovarian carcinoma harbouring *BRCA1* or *BRCA2* mutations. However, there is a paucity of prospective randomised data comparing the efficacy and safety of PARP inhibitors with standard-of-care chemotherapy in this patient population, with no randomised studies comparing PARP inhibitor monotherapy with platinum-based chemotherapy. Before initiating the ARIEL4 study, we searched PubMed from database inception to July 1, 2021, without language restrictions, 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"). Our search yielded two randomised clinical trials comparing PARP inhibitor monotherapy with chemotherapy for ovarian cancer treatment. In a phase 2, open-label, randomised study including 97 patients with germline *BRCA* mutations and relapsed ovarian carcinoma, patients treated with olaparib monotherapy had longer progression-free survival than patients treated with pegylated liposomal doxorubicin, however, this difference was not statistically significant. A confirmatory, open-label, randomised, phase 3 study of 266 patients with germline *BRCA1* or *BRCA2* mutations and platinum-sensitive, relapsed ovarian carcinoma, olaparib monotherapy demonstrated significantly better objective response rates and longer progression-free survival compared with single-agent non-platinum chemotherapy. The first results of the randomised phase 3 ARIEL4 study, comparing olaparib monotherapy versus platinum and non-platinum-based chemotherapy, were published in March, 2022.

Added value of this study

To our knowledge, ARIEL4 represents 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 cohort differs from previous studies because it comprises individuals with platinum-resistant, partially platinum-sensitive, and fully platinum-sensitive disease. ARIEL4 aimed to confirm the efficacy and safety of rucaparib versus standard chemotherapy in heavily pretreated patients with *BRCA*-mutated ovarian carcinoma. The published report of ARIEL4 demonstrated that progression-free survival was improved with rucaparib versus chemotherapy across various patient subgroups, and showed similar or longer progression-free survival in the platinum-sensitive population. In this updated analysis, final overall survival data and other post-progression outcomes were analysed, in addition to safety assessments in both the randomised and crossover populations on the basis of platinum sensitivity status.

Implications of all the available evidence

The ARIEL4 efficacy data confirms the sensitivity of platinum-sensitive ovarian cancer to PARP inhibitors. Further research is needed to optimise chemotherapy and PARP inhibitor sequencing and understand resistance mechanisms. Our study shows that rucaparib significantly improves progression-free survival in patients with advanced, relapsed *BRCA*-mutated ovarian cancer when compared with chemotherapy. Chemotherapy seems to be associated with longer overall survival in the intention-to-treat (ITT) population, but overall survival is similar between rucaparib and platinum chemotherapy groups in patients with platinum-sensitive disease. Overall survival within the ITT population seems to be influenced by the platinum-resistant subgroup who had benefit from chemotherapy and complicated by substantial crossover to rucaparib after randomisation. Restrictions placed on the use of PARP inhibitors by regulatory agencies such as the US Food and Drug Administration highlight the urgency of determining the best treatment for patients who have disease progression on these inhibitors. The study also helps clarify the potential sequencing of platinum and non-platinum chemotherapies with rucaparib, and the evolution of resistance mechanisms.

chemotherapy in patients with platinum-sensitive ovarian cancer who had had received at least two previous lines of therapy.[6] Additionally, when used as second-line or third-line therapy in patients with germline *BRCA*-positive ovarian cancer, olaparib monotherapy has been shown to have significant anti-tumour activity compared with historical controls.[7]

Based on the results observed in the phase 2 Study 10 and ARIEL2 single-arm studies,[8,9] the phase 3 ARIEL4 study[10] was conducted to confirm the efficacy and safety of rucaparib versus standard-of-care chemotherapy in patients with advanced, relapsed, heavily pretreated, *BRCA*-mutated ovarian carcinoma. In the ARIEL4 efficacy population (which included all patients randomly assigned to treatment with deleterious *BRCA* mutations, with the exception of those with reversion mutations), the primary endpoint was met; patients in the rucaparib group had significantly improved investigator-assessed progression-free survival (median 7·4 months [95% CI 6·7–8·3]) versus those treated with standard-of-care chemotherapy (5·7 months [5·5–7·2]; hazard ratio [HR] 0·64 [95% CI 0·49–0·84], p=0·0010). In the intention-to-treat (ITT) population (which included all patients randomly assigned to treatment), the investigator-assessed progression-free survival was also improved with rucaparib (median 7·1 months [95% CI 6·3–7·8]) versus chemotherapy (5·4 months [5·1–6·0]; HR 0·67 [95% CI 0·52–0·86], p=0·0017).[10] Additionally, progression-free survival in the subgroups of the efficacy population with platinum-resistant, partially platinum-sensitive, and fully platinum-sensitive disease was also similar or longer with rucaparib versus chemotherapy. Here, we present final overall survival data and other post-progression outcomes from the ARIEL4 study of rucaparib compared with chemotherapy.

Methods

Study design and participants

ARIEL4 is a randomised, open-label, phase 3 study done at 64 hospitals and cancer centres in 12 countries (Brazil, Canada, Czech Republic, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, the UK, and the USA). Eligible patients were women aged 18 years or older who had a histologically confirmed diagnosis of high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, with a deleterious germline or somatic *BRCA1* or *BRCA2* mutation, confirmed by either a central or local laboratory. Patients had to have evaluable disease as per Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) criteria, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a documented treatment-free interval of at least 6 months after their initial chemotherapy regimen. Additionally, patients must have received two or more previous chemotherapy regimens, including at least one platinum-based regimen, and have confirmed relapsed or progressive disease by radiological assessment before enrolment. Exclusion criteria included platinum-refractory disease (defined as disease progression during or within 4 weeks after the last dose of platinum-based chemotherapy) and previous treatment with a PARP inhibitor, single-agent paclitaxel, or nab-paclitaxel. The study was approved by all national or local institutional review boards and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council for Harmonisation. Comprehensive details regarding the study design, eligibility criteria, randomisation procedures, schedule of assessments, and dosing have been previously published.[10] This study is registered with ClinicalTrials.gov, NCT02855944.

Randomisation and masking

After confirmation of *BRCA1* or *BRCA2* mutation status, eligible patients were randomly assigned (2:1) to receive oral rucaparib (600 mg twice daily) or chemotherapy, with central randomisation performed by Endpoint Clinical (San Francisco, CA, USA) using interactive response technology and block randomisation with a block size of six. Patients were stratified based on their progression-free interval after the most recent platinum-containing therapy at study entry, categorised as having platinum-resistant (progression ≥1 month to <6 months after the last dose of platinum-based chemotherapy), partially platinum-sensitive (progression ≥6 months to <12 months), or fully platinum-sensitive (progression ≥12 months) disease. The study was open-label; neither patients nor investigators were masked to treatment allocation due to the nature of the intervention. However, the sponsor was masked to treatment allocation when reviewing aggregate data.

Procedures

Patients assigned to the rucaparib group received 600 mg oral rucaparib twice daily, administered in 28-day cycles, regardless of platinum sensitivity status. In the chemotherapy group, patients with platinum-resistant disease (progression-free interval ≥1 to <6 months) or partially platinum-sensitive disease (progression-free interval ≥6 to <12 months) were treated with weekly intravenous paclitaxel at a starting dose of 60–80 mg/m², administered on days 1, 8, and 15 of each 28-day cycle. Patients with fully platinum-sensitive disease (progression-free interval ≥12 months) received investigator's choice of platinum-based chemotherapy, which could be single-agent cisplatin or carboplatin, or platinum doublet chemotherapy, including carboplatin plus paclitaxel, carboplatin plus gemcitabine, or cisplatin plus gemcitabine, administered in 21-day or 28-day cycles according to institutional guidelines. The number of cycles for chemotherapy was limited to eight for platinum

monotherapy or doublet therapy, with no limit on the number of paclitaxel cycles.

No other anti-cancer therapies were permitted in combination with rucaparib or chemotherapy, with the exception of hormonal treatment for previous breast cancer. Treatment continued until investigator-assessed disease progression per RECIST (version 1.1), unacceptable toxicity, death, or other appropriate reasons for discontinuation. Patients who had disease progression and were allocated to the chemotherapy group could cross over to rucaparib treatment on sponsor approval of the radiology report confirming disease progression and if they met eligibility criteria for crossover.

See Online for appendix 1

Rucaparib dose interruptions or reductions were permitted in 100 mg twice daily decrements for grade 3 or 4 adverse events, or grade 2 adverse events not adequately controlled by concomitant medications or supportive care. If a patient continued to have an adverse event despite three dose-reduction steps (to a rucaparib dose of 300 mg twice daily) or if rucaparib dosing was interrupted for more than 14 consecutive days due to toxicity, treatment was discontinued unless otherwise agreed on by the investigator and sponsor. For chemotherapy, dose interruptions and modifications were permitted according to institutional guidelines and local prescribing information.

Tumour assessments using CT scans were performed during screening, then at 8-week intervals for the first 18 months, and subsequently at 16-week intervals until radiological disease progression per RECIST (version 1.1), death, loss to follow-up, withdrawal of consent, study closure, or initiation of subsequent treatment. Other imaging studies such as MRI, x-ray, PET, and ultrasound could be conducted if required.

Safety was assessed by monitoring adverse events, laboratory testing, and vital signs, 12-lead electrocardiograms, physical examination, and ECOG performance status. Serious treatment-emergent adverse events, defined as events leading to hospital admission or those deemed life-threatening, were also monitored. Patients were assessed for safety for as long as they were on protocol therapy. Further details about the safety and quality-of-life assessments are available in the primary report of this trial.[7]

Plasma samples were collected from patients at baseline (during screening or before the first cycle of treatment) and at the end of treatment (after progression). Circulating-free DNA (cfDNA) was extracted from plasma samples and sequenced using Guardant Health's Guardant360 next-generation sequencing assay (Redwood City, CA, USA). Guardant Health defined *BRCA1* and *BRCA2* reversion mutations as mutations that restore the open reading frame of the original deleterious mutation detected in the tumour.[10] The variant allele frequency of *BRCA* reverse mutation was normalised to the clonal *TP53* mutation, somatic *BRCA* mutation, or somatic mutation with the highest percentage variant allele frequency detected in the sample before and after treatment. Plasma samples were collected from patients at baseline (during screening or before the first cycle of treatment) and at the end of treatment (after progression) for genomic analysis (appendix 1 p 15).

Outcomes

The previously published report of ARIEL4[10] presented the primary endpoint of investigator-assessed progression-free survival per RECIST in the efficacy population (comprising all patients randomly assigned to treatment with deleterious *BRCA* mutations, except those with reversion mutations) and in the ITT population (encompassing all patients randomly assigned to treatment). Progression-free survival was calculated from the time a patient was randomly assigned until investigator-assessed progressive disease per RECIST or death, whichever occurred first.

Key secondary endpoints were objective response rate (the proportion of patients with a complete or partial response) as assessed by RECIST (version 1.1), duration of response, defined as time from documentation of response to progression according to RECIST (version 1.1), and the combined objective response rate assessed by either RECIST (version 1.1) or CA-125 Gynecological Cancer Intergroup Criteria.[11] Additionally, patient-reported outcomes were assessed using the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 items Global Health Status. Further secondary endpoints comprised progression-free survival assessed by masked independent central review per RECIST (version 1.1), overall survival (defined as the time from randomisation until death from any cause), patient-reported outcomes measured using the EORTC QLQ-OV28, and the safety and tolerability of rucaparib versus chemotherapy. Here, we report the secondary endpoints of overall survival, time to progression on the first subsequent therapy, and safety of rucaparib and chemotherapy, and report on overall survival, progression-free survival, and safety data with longer follow-up (data collected up to Sept 30, 2022 for progression-free survival and up to April 10, 2022 for overall survival); all other secondary outcomes will be reported elsewhere. Time from randomisation to investigator-assessed disease progression on first subsequent line of therapy (the time from randomisation to the second disease progression event on subsequent therapy, which could be a documented event per RECIST, symptomatic progression, or death due to any cause) and progression-free survival from the beginning of subsequent therapy in the ITT population and in platinum status subgroups were exploratory endpoints.

Statistical analysis

For the primary endpoint of progression-free survival (analysed in both the efficacy population and the ITT

population), 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. In progression-free survival analyses, only tumour scans and deaths up to and within 6 weeks of start of any subsequent anticancer treatment were included. Patients who did not have a disease progression event or death were censored at their last tumour assessment or the date of randomisation if no tumour assessments were done.

The secondary endpoint of overall survival was not analysed within the pre-specified hierarchy step down testing of primary and key secondary endpoints,[12] and was analysed using stratified Cox proportional hazards methods and the Kaplan-Meier method. Patients who were alive were censored on the date of their last visit or last known date of being alive. The final analysis of overall survival was done when 70% of the expected death events (n=244) had occurred. Overall survival was analysed in the ITT population and in the platinum status subgroups. Analysis of overall survival was done to adjust for crossover using conventional methods: patients in the control group who crossed over to rucaparib were excluded, and patients in control group at the time of crossing over to rucaparib were censored.

In the analysis of the exploratory endpoint of time to disease progression on first subsequent line of therapy, patients without a second event (or death) were censored on the last date they were known to be alive, at a study visit, or on the date of randomisation if no post-baseline visits were performed. This endpoint was analysed using a stratified Cox proportional hazards methods and Kaplan-Meier methods. The secondary and exploratory analyses presented were not adjusted for multiplicity, therefore all p values are unadjusted.

In this updated analysis, prespecified analyses of progression-free survival, overall survival, and disease progression on first subsequent line of therapy in subgroups based on platinum sensitivity status (platinum-resistant, partially platinum-sensitive, or fully platinum-sensitive disease) were analysed in the ITT population. Prespecified outcomes were also assessed in the combined platinum-sensitive subgroup, which included patients with both partially platinum-sensitive disease and those with fully platinum-sensitive disease. Investigator-assessed progression-free survival in these subgroups was analysed using Kaplan-Meier methods and Cox proportional hazards methods. We also did prespecified genomic analyses of circulating free DNA to identify mutations, particularly in *BRCA1* and *BRCA2*, and reversion mutations that could affect the efficacy of rucaparib.

Safety was assessed in the safety population, which included all patients who received at least one dose of study drug, for 28 days after the last dose of the study drug during the randomised phase of the trial. Safety assessment in the crossover population was conducted for 28 days after the last dose of rucaparib during the crossover phase of the trial.

Additional details, including sample size calculations, safety data analysis, and the level of statistical significance, have been published previously.[8] All statistical analyses were done using SAS (version 9.4).

Role of the funding source

The funder of the study was involved in study design, data analysis, and writing of the report. The funders had no role in data collection or data interpretation.

Results

Between March 1, 2017, and Sept 24, 2020, 930 patients were screened, of whom 349 patients were enrolled and randomly assigned to receive either rucaparib (n=233) or chemotherapy (n=116; appendix 1 p 145). 332 (95%) of 349 patients were white and 17 (5%) were of other or unknown race. Among the 349 patients included in the ITT population, 179 (51%) patients had platinum-resistant disease (120 in the rucaparib group and 59 in the chemotherapy group), 96 (28%) patients had partially platinum-sensitive disease (65 in the rucaparib group and 31 in the chemotherapy group), and 74 (21%) patients had fully platinum-sensitive disease (48 in the rucaparib group and 26 in the chemotherapy group; table 1). Patients with fully platinum-sensitive disease were generally less heavily pretreated than those with platinum-resistant and partially platinum-resistant disease (table 1). Among the 272 patients who received a platinum regimen immediately before randomisation (141 in the rucaparib group and 131 in the chemotherapy group), 142 (52%) patients had platinum-resistant disease (73 in the rucaparib group and 69 in the chemotherapy group), 65 (24%) patients had partially platinum-sensitive disease (34 in the rucaparib group and 31 in the chemotherapy group), and 65 (24%) patients had fully platinum-sensitive disease (34 in the rucaparib group and 31 in the chemotherapy group).

At the data cutoff for progression-free survival analysis (Sept 30, 2020), in the platinum-resistant patient population (120 patients in the rucaparib group and 59 patients in the chemotherapy group), 108 (90%) patients in the rucaparib group and 56 (95%) patients in the chemotherapy group had disease progression (indicated by ≥1 subsequent anticancer treatments) or died. In the partially platinum-sensitive patient population (65 patients in the rucaparib group and 31 patients in the chemotherapy group), 57 (88%) patients in the rucaparib group and 30 (97%) patients in the chemotherapy group had disease progression or

	Platinum-resistant patients		Partially platinum-sensitive patients		Fully platinum-sensitive patients	
	Rucaparib (n=120)	Chemotherapy (n=59)	Rucaparib (n=65)	Chemotherapy (n=31)	Rucaparib (n=48)	Chemotherapy (n=26)
≥1 subsequent anticancer treatments						
Yes	69 (58%)	45 (76%)	40 (62%)	26 (84%)	26 (54%)	22 (85%)
No	51 (43%)	14 (24%)	25 (38%)	5 (16%)	22 (46%)	4 (15%)
Died	39 (76%)	11 (79%)	17 (68%)	4 (80%)	8 (36%)	1 (25%)
Withdrew consent	3 (6%)	2 (14%)	2 (8%)	0	0	0
Lost to follow-up	1 (2%)	0	0	0	0	0
Ongoing in randomised portion	4 (8%)	0	4 (16%)	0	6 (27%)	0
Discontinued but still missing subsequent data	4 (8%)	1 (7%)	2 (8%)	1 (20%)	8 (36%)	3 (75%)
Type of first subsequent therapy reported*						
Crossover to rucaparib	0	41 (91%)	0	25 (96%)	0	14 (64%)
Other PARP inhibitor	1 (1%)	0	1 (3%)	1 (4%)	1 (4%)	4 (18%)
Platinum-based chemotherapy	29 (42%)	1 (2%)	26 (65%)	0	20 (77%)	2 (9%)
Non-platinum-based chemotherapy	36 (52%)	2 (4%)	11 (28%)	0	5 (19%)	1 (5%)
Other	3 (4%)	1 (2%)	2 (5%)	0	0	1 (5%)
≥2 subsequent anticancer treatments reported						
Yes	33 (28%)	32 (54%)	22 (34%)	15 (48%)	17 (35%)	8 (31%)
No	87 (73%)	27 (46%)	43 (66%)	16 (52%)	31 (65%)	18 (69%)
Type of second subsequent therapy reported*						
PARP inhibitor	0	1 (3%)	2 (9%)	0	0	0
Platinum-based chemotherapy	8 (24%)	15 (47%)	3 (14%)	12 (80%)	3 (18%)	4 (50%)
Non-platinum-based chemotherapy	25 (76%)	12 (38%)	14 (64%)	3 (20%)	12 (71%)	4 (50%)
Other†	0	4 (13%)	3 (14%)	0	2 (12%)	0
≥3 subsequent anticancer treatments reported						
Yes	17 (14%)	12 (20%)	10 (15%)	10 (32%)	11 (23%)	3 (12%)
No	103 (86%)	47 (80%)	55 (85%)	21 (68%)	37 (77%)	23 (88%)
Type of third subsequent therapy reported*						
Other PARP inhibitor	2 (12%)	1 (8%)	0	0	0	1 (33%)
Platinum-based chemotherapy	5 (29%)	3 (25%)	1 (10%)	3 (30%)	3 (27%)	0
Non-platinum-based chemotherapy	6 (35%)	7 (58%)	9 (90%)	6 (60%)	7 (64%)	1 (33%)
Other‡	4 (24%)	1 (8%)	0	1 (10%)	1 (9%)	1 (33%)

Data are median (IQR) or n (%). PARP=poly(ADP-ribose) polymerase. *The denominator for the percentages is the number of patients with that particular number of regimens. †Treatments included monoclonal antibodies and hormonal therapies. ‡Other treatments included monoclonal antibodies, hormonal therapies, and investigational drugs.

Table 1: **Subsequent anticancer treatment in the platinum status subgroups in the intention-to-treat population**

died. In the fully platinum-sensitive patient population (48 patients in the rucaparib group and 26 patients in the chemotherapy group), 34 (71%) of 48 patients in the rucaparib group and 23 (88%) of 26 patients in the chemotherapy group had disease progression or died. In the combined partial and fully platinum-sensitive disease patient population (113 patients in the rucaparib group and 57 patients in the chemotherapy group), 91 (81%) patients in the rucaparib group and 53 (93%) patients in the chemotherapy group had disease progression or died. The median time since diagnosis was longer in the fully platinum sensitive subgroup than the other two subgroups (appendix 1 p 144). At data cutoff (April 10, 2022), median follow-up for progression-free survival was 25·0 months (IQR 13·8–32·5).

After disease progression, 80 (69%) of 116 patients in the chemotherapy group crossed over to receive rucaparib. Among the 80 patients who crossed over, 41 (51%) patients had platinum-resistant disease, 25 (31%) had partially platinum-sensitive disease, and 14 (18%) had fully platinum-sensitive disease before initial randomisation in the study. Overall, 314 (90%) of 349 patients who participated in ARIEL4 received rucaparib at any time after randomisation regardless of crossover. At the data cutoff for this final analysis (April 10, 2022), 14 (6%) of 233 patients in the rucaparib group and none of the 116 patients in the chemotherapy group remained on their assigned study treatment; median follow-up was 41·2 months (IQR 37·8–44·6).

Five patients who crossed over from the chemotherapy group were still receiving rucaparib treatment at the

time of data cutoff. In the ITT population, the proportion of patients randomly assigned to rucaparib who did not receive subsequent therapy was higher than that of those randomly assigned to chemotherapy (98 [42%] of 233 patients *vs* 23 [20%] of 116 patients; table 1). The reasons for not receiving subsequent therapy included death (64 [65%] of 98 patients in the rucaparib group and 16 [70%] of 23 patients in the chemotherapy group), discontinuation or missing treatment (14 [14%] patients and five [22%] patients), ongoing on treatment (14 [14%] patients in the rucaparib group), withdrawal of consent (five [5%] patients and two [9%] patients), and other reasons (one [1%] patient in the rucaparib group). Among patients who did not receive subsequent therapy, the median time from end of therapy to death was 2·9 months (95% CI 2·1–3·6) in the rucaparib group and 3·1 months (95% CI 1·1–5·8) in the chemotherapy group.

Among patients randomly assigned to rucaparib who received one or more subsequent anticancer therapy, based on records of the patients' previous anticancer treatments submitted during screening, 29 (42%) of 69 patients in the platinum-resistant subgroup, 26 (65%) of 40 patients in the partially platinum-sensitive subgroup, and 20 (77%) of 26 patients in the fully platinum-sensitive subgroup received platinum-based chemotherapy as their first subsequent treatment (table 1). In the chemotherapy group, among patients who received one or more subsequent anticancer therapy, 41 (91%) of 45 patients in the platinum-resistant subgroup, 25 (96%) of 26 patients in the partially platinum-sensitive subgroup, and 14 (64%) of 22 patients in the fully platinum-sensitive subgroup received crossover rucaparib as their subsequent anticancer therapy. The duration of crossover rucaparib treatment was 6 months or longer in 27 (66%) of 41 patients with platinum-resistant disease, 18 (72%) of 25 patients with partially platinum-sensitive disease, and 12 (86%) of 14 patients with fully platinum-sensitive disease.

72 (31%) of 233 patients randomly assigned to rucaparib and 55 (47%) of 116 patients randomly assigned to chemotherapy received two or more subsequent anticancer therapies; 38 (16%) of 233 patients in the rucaparib group and 25 (22%) of 116 patients in the chemotherapy group received three or more subsequent anticancer therapies.

Median treatment duration in the randomised phase of the trial was 5·6 months (95% CI 4·8–6·4; range 0–44) with rucaparib and 4·4 months (3·5–5·3; 0–25) with chemotherapy in the platinum-resistant subgroup, 7·6 months (6·8–8·4; 0–60) with rucaparib and 4·5 months (3·3–5·7; 0–11) with chemotherapy in the partially platinum-sensitive subgroup, and 13·7 months (12·4–15·0; 0–53) with rucaparib and 3·4 months (2·6–4·2; 1–8) with chemotherapy in the fully platinum-sensitive subgroup. Patients who crossed over to rucaparib had a median treatment duration of 9·4 months (7·4–11·4; 2–39) in the platinum-resistant subgroup, 9·7 months (7·9–11·5; 0–36) in the partially platinum-sensitive subgroup, and 9·9 (7·9–11·9; 1–37) in the fully platinum-sensitive subgroup.

At data cutoff (April 10, 2022), 244 (70%) of 349 patients had died: 167 (72%) of 233 in the rucaparib group and 77 (66%) of 116 in the rucaparib group. In the ITT population, overall survival was longer in the chemotherapy group than the rucaparib group; median overall survival was 19·4 months (95% CI 15·2–23·6) in the rucaparib group versus 25·4 months (21·4–27·6) in the chemotherapy group (HR 1·3 [95% CI 1·0–1·7]; p=0·047; figure 1A). Overall survival in the efficacy population was similar to that in the ITT population (appendix 1 pp 148–50). Final overall survival was also analysed on the basis of platinum status subgroups. Among patients with platinum-resistant disease, median overall survival was 14·2 months (95% CI 11·8–17·4) in the rucaparib group (95 [57%] of 167 patients had died) versus 22·2 months (15·4–26·2) in the chemotherapy group (44 [57%] of 77 patients had died; HR 1·5 [95% CI 1·1–2·2]; p=0·022; figure 1B). Median overall survival for patients with partially platinum-sensitive disease was 21·1 months (13·9–30·4) in the rucaparib group (45 [27%] of 167 patients had died) and 23·2 months (15·6–27·6) in the chemotherapy group (22 [29%] of 77 patients had died; HR 0·97 [95% CI 0·58–1·60]; p=0·95; figure 1C). Median overall survival for patients with fully platinum-sensitive disease was 36·3 months (28·1–40·7) in the rucaparib group (27 [16%] of 167 patients had died) and 47·2 months (22·9–53·0) in the chemotherapy group (11 [14%] of 77 patients had died; HR 1·20 [95% CI 0·62–2·5]; p=0·49; figure 1D). Median overall survival for the combined platinum-sensitive and fully platinum-sensitive subgroups was 29·4 months (23·1–37·4) in the rucaparib group (72 [31%] of 233 patients had died) and 27·6 months (21·9–47·2) in the chemotherapy group (33 [28%] of 116 patients had died; HR 1·1 [95% CI 0·71–1·6]; p=0·72; figure 1E).

Additional analyses of overall survival were conducted to adjust for crossover. When patients who crossed over from chemotherapy to rucaparib were excluded, median overall survival was 19·4 months (95% CI 15·2–23·6) in the rucaparib group (167 [72%] of 233 patients had died) versus 9·1 months (7·0–18·1) in the chemotherapy group (26 [22%] of 116 patients had died; HR 0·42 [95% CI 0·28–0·65]; p<0·0001; figure 2A). When patients were censored at the time of crossover from chemotherapy to rucaparib, overall survival was similar between treatment groups; median overall survival was 19·4 months (15·2–23·6) in the rucaparib group versus 26·2 months (14·8–38·6) in the chemotherapy group (HR 1·1 [95% CI 0·69–1·6]; p=0·74; figure 2B).

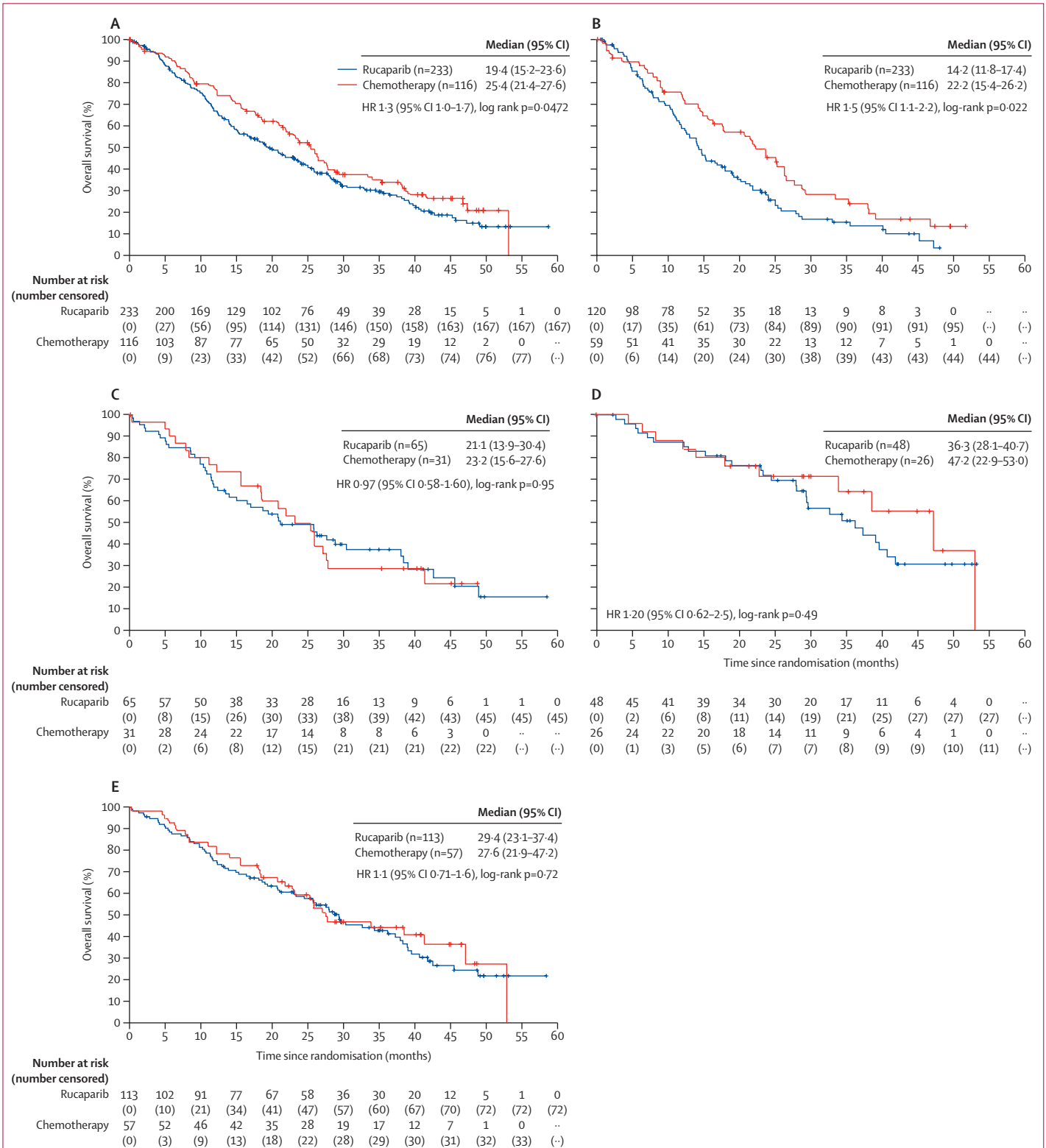

Figure 1: **Overall survival in the ITT population (A), and in the platinum-resistant (B), partially platinum-sensitive (C), fully platinum-sensitive (D), and combined platinum-sensitive (E) subgroups**

HRs were estimated using a Cox proportional hazards model. Crosses indicate censored patients. HR=hazard ratio. ITT=intention-to-treat.

In addition to the previously reported progression-free survival in the platinum status subgroups in the efficacy population,[10] progression-free survival was assessed in the ITT population according to platinum status. The median progression-free survival in the platinum-resistant subgroup was 5·6 months (95% CI 4·3–7·3) with rucaparib and 5·6 months (3·7–6·3) with chemotherapy (HR 0·82 [95% CI 0·58–1·20]; p=0·26); median progression-free survival in the partially platinum-sensitive subgroup was 7·5 months (6·7–9·4) with rucaparib and 5·5 months (3·5–5·6) with chemotherapy (0·41 [0·26–0·66]; p=0·0002); in the fully platinum-sensitive subgroup, median progression-free survival was 12·9 months (9·2–14·8) with rucaparib and 9·6 months (7·5–15·4) with chemotherapy (0·69 [0·37–1·30]; p=0·25; appendix 1 pp 146–47). In the subgroup of patients with combined partial and fully platinum-sensitive disease, median progression-free survival was 9·3 months (7·5–12·8) with rucaparib and 6·5 months (5·5–7·9) with chemotherapy (0·50 [0·34–0·73]; p=0·0004).

Median progression-free survival on first subsequent line of treatment in the ITT population was similar between the rucaparib group and the chemotherapy group (figure 3A). Subgroup analyses of disease progression on first subsequent line of therapy based on platinum sensitivity status are shown in figures 3B–E.

Median progression-free survival on first subsequent treatment after randomisation to rucaparib was 4·2 months (95% CI 3·5–4·9) in the subgroup of patients with platinum-resistant disease, 5·5 months (4·8–6·2) in those with partially platinum-sensitive disease, and 7·0 months (6·2–7·8) in those with fully platinum-sensitive disease (appendix 1 p 151). In patients who were randomly assigned to chemotherapy who crossed over to rucaparib, median progression-free survival from beginning crossover rucaparib was 7·3 months (6·5-8·1) in the platinum-resistant subgroup, 7·5 months (6·7–8·3) in the partially platinum-sensitive subgroup, and 8·7 months (7·9–9·5) in the fully platinum-sensitive subgroup (appendix 1 p 151). To study the dynamics of *BRCA* reversion mutations under different treatments, their prevalence in plasma cfDNA at baseline (before receiving rucaparib or paclitaxel) and at end of treatment (after randomised treatment) was examined. 13 of 19 patients with baseline *BRCA* reversion mutations had an end of treatment sample collected, and the baseline reversion mutation was detected in the end of treatment sample in nine of those patients (five patients in the rucaparib group and four patients in the paclitaxel group). The normalised variant allele frequency of the most prevalent reversion mutation decreased by at least 20% in three of the four patients who received paclitaxel (appendix 1 p 154). By contrast, among patients administered rucaparib the reversion variant allele frequency increased or remained unchanged in four of five patients (appendix 1 p 154).

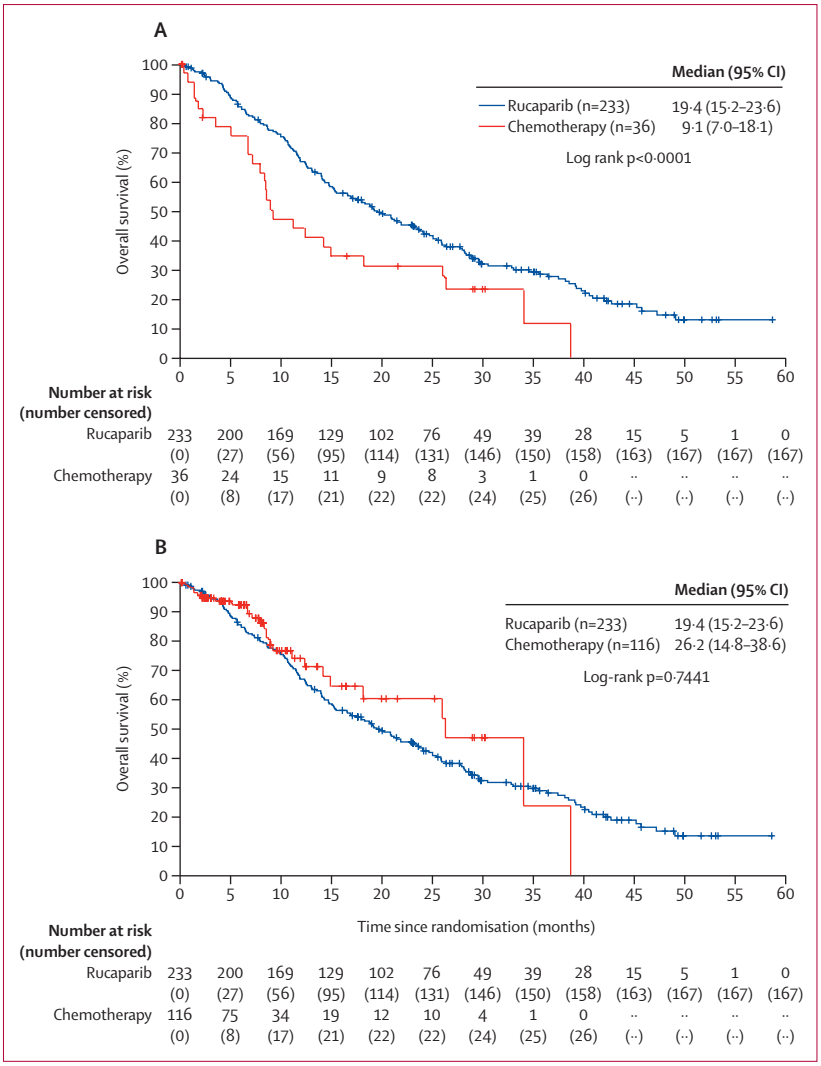

Figure 2: **Supportive overall survival analyses adjusting for crossover**
(A) Overall survival analysis in which patients who crossed over from chemotherapy to rucaparib were excluded. (B) Overall survival analysis in which patients were censored at crossover (B). HRs were estimated with a Cox proportional hazards model. Crosses indicate censored patients. HR=hazard ratio. OS=overall survival.

The safety population included 232 of 233 patients who received rucaparib and 113 of 116 patients who received chemotherapy. Any-grade treatment-emergent adverse events were reported in 229 (99%) of 232 patients in the rucaparib group, and 109 (96%) of 113 patients in the chemotherapy group (table 2). The most common any-grade treatment-emergent adverse events were anaemia or decreased haemoglobin (132 [57%] of 232 patients in the rucaparib group *vs* 38 [34%] of 113 patients in the chemotherapy group), nausea (128 [55%] *vs* 39 [35%]), and asthenia or fatigue (129 [57%] *vs* 57 [50%]; table 2). In the safety population, grade 3 or worse treatment-emergent adverse events were more common in the rucaparib group than the

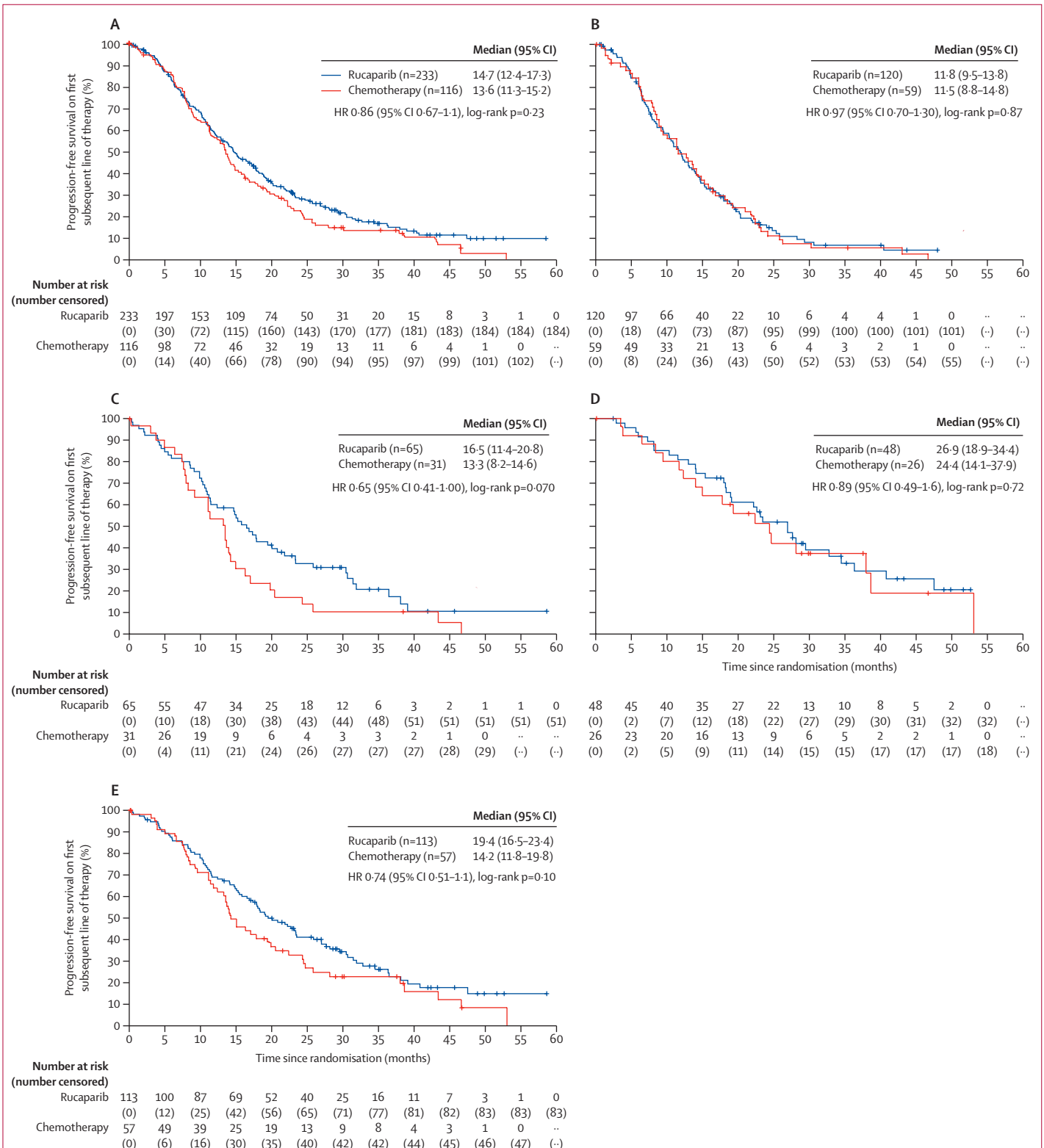

Figure 3: **Time to disease progression on first subsequent line of therapy in the ITT population (A) and in the platinum-resistant (B), partially platinum-sensitive (C), fully platinum-sensitive (D), and combined platinum-sensitive (E) subgroups**

HRs were estimated with a Cox proportional hazards model. Crosses indicate censored patients. HR=hazard ratio. ITT=intention-to-treat.

	Rucaparib group (n=232)				Chemotherapy group (n=113)				Crossover rucaparib group (n=80)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Anaemia or decreased haemoglobin	73 (31%)	53 (23%)	6 (3%)	0	31 (27%)	7 (6%)	0	0	13 (16%)	14 (18%)	1 (1%)	0
Nausea	121 (52%)	7 (3%)	0	0	39 (35%)	0	0	0	24 (30%)	1 (1%)	0	0
Asthenia or fatigue	109 (47%)	20 (9%)	0	0	52 (46%)	5 (4%)	0	0	18 (23%)	6 (8%)	0	0
ALT or AST increased	132 (57%)	22 (9%)	0	0	21 (19%)	0	0	0	48 (60%)	11 (14%)	0	0
Vomiting	72 (31%)	10 (4%)	0	0	21 (19%)	0	0	0	12 (15%)	3 (4%)	0	0
Thrombocytopenia or decreased platelets	40 (17%)	14 (6%)	6 (3%)	0	17 (15%)	0	0	0	9 (11%)	5 (6%)	0	0
Abdominal pain	81 (35%)	12 (5%)	0	0	21 (19%)	0	0	0	20 (25%)	5 (6%)	0	0
Neutropenia or decreased absolute neutrophil count	28 (12%)	17 (7%)	8 (3%)	1 (<1%)	18 (16%)	16 (14%)	0	0	9 (11%)	5 (6%)	1 (1%)	0
Diarrhoea	46 (20%)	5 (2%)	0	0	24 (21%)	1 (1%)	0	0	8 (10%)	1 (1%)	0	0
Decreased appetite	45 (19%)	3 (1%)	0	0	20 (18%)	0	0	0	16 (20%)	2 (3%)	0	0
Blood creatinine increased	34 (15%)	6 (3%)	0	0	10 (9%)	0	0	0	13 (16%)	0	0	0
Constipation	39 (17%)	1 (<1%)	0	0	21 (19%)	0	0	0	12 (15%)	0	0	0
Dysgeusia	39 (17%)	0	0	0	8 (7)	0	0	0	9 (11%)	0	0	0
Weight decreased	30 (13%)	2 (1%)	0	0	4 (4%)	0	0	0	7 (9%)	0	0	0
Dyspnea	25 (11%)	3 (1%)	0	0	7 (6%)	2 (2%)	0	0	8 (10%)	0	0	0
Pyrexia	24 (10%)	1 (<1%)	0	0	7 (6%)	0	0	0	3 (4%)	0	0	0
Leukopenia	19 (8%)	6 (3%)	1 (<1%)	0	16 (14%)	4 (4%)	0	0	7 (9%)	1 (1%)	0	0
Hyperglycaemia	16 (7%)	3 (1%)	0	0	12 (11%)	3 (3%)	0	0	6 (8%)	0	0	0
Ascites	8 (3%)	6 (3%)	0	0	1 (1%)	1 (1%)	0	0	2 (3%)	0	0	0
Alopecia	12 (5%)	0	0	0	40 (35%)	0	0	0	2 (3%)	0	0	0
Intestinal obstruction	4 (2%)	10 (4%)	0	0	0	1 (1%)	0	0	1 (1%)	4 (5%)	1 (1%)	0
Neuropathy*	6 (3%)	0	0	0	27 (24%)	0	0	0	3 (4%)	0	0	0

Data are n (%) and presented in order of decreasing incidence of any-grade treatment-emergent adverse event in the rucaparib group, including any treatment-emergent adverse events occurring in at least one patient. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *Neuropathy includes neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral neuropathy, peripheral sensory neuropathy, polyneuropathy, and toxic neuropathy.

Table 2: **Treatment-emergent adverse events in the safety population**

chemotherapy group. Specifically, 147 (63%) of 232 patients in the rucaparib group had grade 3 or worse treatment-emergent adverse events, with the most common being anaemia or decreased haemoglobin (59 [25%] patients) and neutropenia or decreased neutrophil count (26 [11%] patients). 45 (40%) of 113 patients in the chemotherapy group reported grade 3 or worse treatment-emergent adverse events, predominantly neutropenia or decreased neutrophil count (16 [14%] patients) and anaemia or decreased haemoglobin (seven [6%] patients). These findings underscore the clinical significance of anaemia as a concern in the rucaparib group, and neutropenia emerged as a notable issue in both groups. Additionally, serious treatment-emergent adverse events, defined as events leading to hospital admission or those deemed life-threatening, were reported more frequently in the rucaparib group, affecting 66 (28%) of 232 patients in the rucaparib group compared with 14 (12%) of 113 patients in the chemotherapy group (appendix 2). Deaths attributed to treatment-emergent adverse events (excluding those related to disease progression) were observed in both groups: ten (5%) of 232 patients in the rucaparib group, with two deaths considered rucaparib-related, attributed to a cardiac disorder in one patient and myelodysplastic syndrome in another patient. In the chemotherapy group, one patient died due to a treatment-emergent adverse event (sepsis), but the death was not deemed related to chemotherapy. Furthermore, seven (3%) of 232 patients initially assigned to rucaparib reported myelodysplastic syndrome or acute myeloid leukaemia, with three cases identified during long-term follow-up, whereas no such cases were reported in the chemotherapy group.

Safety was also separately evaluated in 80 (34%) of 232 patients who crossed over to receive rucaparib. Any-grade treatment-emergent adverse events were reported in 76 (95%) of 80 crossover patients. Grade 3 or worse treatment-emergent adverse events were reported in 43 (54%) of 80 patients receiving crossover rucaparib, and the most common grade 3 or worse treatment-emergent adverse events were anaemia or decreased haemoglobin (15 [19%] patients) and increased alanine aminotransferase or aspartate aminotransferase (11 [14%] patients). Of the 80 patients who crossed over to receive rucaparib, 69 (86%) patients had treatment-related adverse events (appendix 2). Serious treatment-emergent

See Online for appendix 2

adverse events were reported in 24 (30%) of 80 crossover patients (appendix 2), and treatment-emergent adverse events (excluding disease progression) leading to treatment discontinuation occurred in three (4%) crossover patients (grade 4 anaemia or decreased haemoglobin, neutropenia, or decreased absolute neutrophil count and intestinal obstruction). Death due to treatment-emergent adverse events (excluding disease progression) was reported in two (3%) of 80 patients during crossover due to acute respiratory failure and sepsis (n=1 each), but neither death was considered related to chemotherapy or rucaparib from crossover. Myelodysplastic syndrome or acute myeloid leukaemia were reported by seven (3%) of 233 patients initially randomised to rucaparib, three (43%) of whom reported it during the long-term follow-up; no cases were reported among patients initially randomly assigned to chemotherapy. Treatment interruption, dose reduction, or both due to treatment-emergent adverse events occurred in 115 (50%) of 232 patients in the rucaparib group and 50 (44%) of 113 patients in the chemotherapy group. Excluding disease progression, treatment-emergent adverse events leading to discontinuation occurred in 19 (8%) of 232 patients in the rucaparib group and 14 (12%) of 113 patients in the chemotherapy group. Additional safety data are provided in the appendix 1 (pp 20–21).

Discussion

In the phase 3 ARIEL4 study comparing rucaparib with chemotherapy in patients with relapsed ovarian cancer and a deleterious *BRCA* mutation, progression-free survival was significantly longer with rucaparib than chemotherapy in the ITT population. Although the study was not powered to identify differences between subgroups, patients in the rucaparib group had similar or longer progression-free survival versus patients in the chemotherapy group across all platinum status subgroups.

Overall survival data were evaluated when the study reached 70% maturity (ie, the point at which 70% of the total events [eg, deaths] required for the final overall survival analysis had occurred). Overall survival was longer in patients who were randomly assigned to chemotherapy than those randomly assigned to rucaparib in the ITT population. Among the platinum status subgroups, patients with platinum-sensitive disease had similar overall survival regardless of their randomly assigned treatment, but overall survival was longer in the chemotherapy group than in the rucaparib group in patients with platinum-resistant disease, suggesting that the longer overall survival with chemotherapy in the ITT population was driven by the platinum-resistant subgroup. Nevertheless, it should be noted that the median overall survival in patients with platinum-resistant disease treated with paclitaxel (22·2–23·2 months) was considerably longer than outcomes reported for paclitaxel in other trials of platinum-resistant ovarian cancer (13·2–15·5 months), whereas the outcome in patients randomly assigned to rucaparib were within the range expected with standard of care, albeit with differing genomic populations.[13–16]

Crossover and other post-progression therapies are important confounders in trial design, and serve as determinants of overall survival. In ARIEL4, crossover was allowed for patient benefit, but this introduced imbalance between the rucaparib and chemotherapy groups, consequently leading to an imbalance in post-progression therapies. Simple methods of adjusting overall survival for crossover yielded trends inconsistent with unadjusted overall survival; overall survival was longer in the rucaparib group than in the chemotherapy group when crossover patients were excluded, whereas overall survival was similar between treatment groups when patients were censored at the time of crossover. However, this is a smaller group of patients and risks excluding patients who are unfit for therapy or have a poor prognosis.

Patients with platinum-resistant disease at baseline who crossed over to rucaparib after being randomly assigned to paclitaxel had longer median progression-free survival than those randomly assigned to rucaparib (5·6 months *vs* 7·3 months). One possible reason for this phenomenon might be due to the behaviour of platinum-resistant subclones when exposed to paclitaxel, which has a different mechanism of action from PARP inhibitors and platinum. It was hypothesised that tumour subclones harbouring cross-resistance mechanisms to PARP inhibitors and platinum (eg, *BRCA* reversion mutations);[17] present in tumours of platinum-resistant patients might be selected against during paclitaxel treatment (versus expanded during rucaparib treatment), thus forming a smaller fraction of the tumour burden by the end of paclitaxel treatment. This decrease of cross-resistant subclones with paclitaxel treatment might sensitise tumours to subsequent rucaparib treatment in the crossover period.

Time to disease progression on first subsequent line of therapy was similar between treatment groups in the ITT population and in the platinum-resistant subgroup. However, time to disease progression on first subsequent line of therapy was longer in the rucaparib group than chemotherapy group in the subgroup of patients comprising all those with platinum-sensitive disease. This finding highlights that there was no detrimental effect on the progression-free survival benefit of the first subsequent treatment in patients who were initially randomly assigned to the rucaparib group.

An important factor to consider is that approximately twice as many patients in the rucaparib group compared with those in the chemotherapy group did not receive

any subsequent anticancer treatment. The reasons for these differences remain unclear but the lack of or inability to receive subsequent therapy could have a substantial impact on overall survival.

More patients in the rucaparib group were continuing to receive their randomly assigned treatment than in the chemotherapy group at study end; but there was no noticeable imbalance between treatment groups in terms of deaths, withdrawal of consent, or discontinuation or missing subsequent data for patients who had not received subsequent ovarian cancer treatment (appendix 1 p 145).

The difference between treatment groups might also have been affected by the study design. Patients assigned to the chemotherapy group had the option to cross over and receive subsequent treatment with rucaparib, whereas patients assigned to rucaparib received subsequent anticancer treatment, if administered, outside of the study at the investigator's discretion. The increased use of subsequent treatments in the chemotherapy group was heavily influenced by the high degree of investigator interest in selecting treatment with rucaparib as the next subsequent treatment in this *BRCA*-mutant population via the crossover option built into the protocol. The decreased rate of subsequent therapy in patients assigned to rucaparib could also reflect the paucity of treatment options demonstrating clinical benefit in a heavily pretreated population of patients with ovarian cancer, particularly in the platinum-resistant group. 85 (73%) of 116 patients from the chemotherapy group received a PARP inhibitor as subsequent therapy, including 80 patients who crossed over to rucaparib and five who received another PARP inhibitor or rucaparib outside of the trial. Regional limitations might have prevented patients who received rucaparib as part of the study (and thus ineligible for crossover treatment) from accessing further effective treatment.[18] The lack of therapy after progression in patients initially randomly assigned to rucaparib and provides an example of imbalanced crossover in trials, albeit after the primary progression-free survival endpoint. Analysis of time to disease progression on first subsequent line of therapy did not demonstrate a negative impact of initial rucaparib, but there are no data to suggest patients who progressed on initial rucaparib had disease aggressive enough to not even warrant therapy. Future trials with post-progression crossover and overall survival endpoints should ensure equitable access to standard-of-care therapy.

The poor post-progression outcomes among patients randomly assigned to rucaparib with platinum-resistant disease might have been associated with the absence of appropriate subsequent therapies after the discontinuation of rucaparib treatment. Despite the possible need for subsequent therapies, 43% of patients in the platinum-resistant subgroup assigned to receive rucaparib did not receive any subsequent therapy. Among the 69 patients randomly assigned to rucaparib who received subsequent anticancer treatments, 31 (54%) received platinum-based chemotherapy at least once as either first, second, or third subsequent treatment, despite the fact that it is known to be ineffective in patients with platinum-resistant disease.[19] The longer progression-free survival and overall survival in patients with platinum-resistant disease who crossed over to rucaparib than those randomly assigned to rucaparib was notable.

In the phase 3 SOLO3 study (NCT00628251) the clinical effectiveness of the PARP inhibitor olaparib was compared with non-platinum chemotherapy in patients with relapsed ovarian cancer who had received two or more lines of platinum-based therapy.[6] The study population in the SOLO3 trial differed from that in ARIEL4 because it only included patients with partially and fully platinum-sensitive disease with a germline *BRCA* mutation but did not utilise a platinum-based chemotherapy in the control group. The study used single-agent non-platinum chemotherapy as a comparator, and there was no formal crossover part of the study. The proportion of patients from the chemotherapy group who received a PARP inhibitor as subsequent therapy was much lower than in ARIEL4 (11% *vs* 73%). In SOLO3, investigator-assessed median progression-free survival was longer in the olaparib group than the non-platinum chemotherapy group (13·2 *vs* 8·5 months; HR 0·49 [95% CI, 0·35–0·70]; p<0·0001). Median overall survival was longer for patients who received olaparib than patients who received chemotherapy (34·9 *vs* 32·9 months; 1·1 [0·76–1·50]; p=0·71), but the differences were not statistically significant.[20] In the subgroup of patients who had received three or more previous lines of chemotherapy, the median overall survival was 29·9 months in the olaparib group versus 39·4 months in the chemotherapy group (HR 1·3 [95% CI 0·84–2·20]),[21] suggesting that early use of PARP inhibitors might be less susceptible to resistance mechanisms.[5] Similar to the improvements observed in the platinum-sensitive subgroup in ARIEL4, time to disease progression on first subsequent line of therapy was longer in the olaparib group than the chemotherapy group (23·6 *vs* 19·6 months; HR 0·80 [95% CI 0·56–1·20]; p=0·23).[20]

Although a significant overall survival benefit was not observed in the treatment setting for recurrent ovarian cancer, PARP inhibitors, including rucaparib, have demonstrated efficacy and benefit in other settings. In the phase 3 ARIEL3 study, rucaparib in maintenance setting significantly improved progression-free survival and showed no apparent decrement in overall survival versus placebo after response to second-line or later platinum-based chemotherapy in patients with platinum-sensitive ovarian cancer.[4,22] Although the

phase 3 NOVA trial was not powered to detect differences in overall survival, restricted mean survival time analyses for overall survival up to 72 months in patients with platinum-sensitive recurrent ovarian cancer with a germline *BRCA* mutation was 45·9 months with maintenance niraparib versus 43·2 months with placebo;[23] updated final overall survival data have been published by the US Food and Drug Administration.[24] In the phase 3 SOLO2 trial, median overall survival was 51·7 months with maintenance olaparib versus 38·8 months with placebo (HR 0·74 [95% CI 0·54–1·0]; p=0·054) in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation.[25]

The updated safety data were consistent with what was reported in the primary analysis of ARIEL4[10] and no new safety signals were observed in the safety population, including during crossover. No additional deaths due to treatment-emergent adverse events related to rucaparib were reported since the last data cutoff (Sept 30, 2020).[10] In patients who crossed over to receive rucaparib, the reported treatment-emergent adverse events and incidences were generally similar to those recorded the rucaparib group.

In addition to the limitations discussed in the initial report of this trial,[10] this study had high rate of crossover, with 90% of patients in the study receiving rucaparib. In an independent analysis of clinical trials with crossovers, demonstrating an overall survival benefit of an experimental treatment becomes more difficult and the comparison of overall survival between randomised treatment groups becomes more limited in the case of a high crossover rate, particularly considering heterogeneity and lack of randomisation after progression during a clinical study.[26] Moreover, commercial availability of PARP inhibitors for patients to use after they completed the study, use of platinum-based subsequent therapy in patients with platinum-resistant disease, and the high proportion of patients initially treated with rucaparib who did not receive subsequent treatment might have further impacted the overall survival benefit. Therefore, for clinical trials with crossovers or multiple rounds of subsequent therapies, an endpoint of time to progression after first subsequent line of therapy might be a more valid measure than overall survival for evaluating long-term benefit of investigational treatments.[27]

Efficacy data from ARIEL4 reaffirmed that patients with platinum-sensitive disease are also sensitive to PARP inhibitors. Future studies are required to investigate optimal sequencing of chemotherapy and PARP inhibitors in advanced disease and identify the most appropriate treatment options in this setting. The hypothesis-generating pattern of selection against platinum-resistant subclones during paclitaxel treatment and expansion during rucaparib treatment highlights the need for further analyses into mechanisms of PARP inhibitor resistance.

In conclusion, among patients with advanced, relapsed *BRCA*-mutated ovarian cancer, those treated with rucaparib had longer progression-free survival than those treated with chemotherapy. Overall survival favoured those randomly assigned to chemotherapy versus rucaparib in the ITT population but was similar between treatment groups among patients with platinum-sensitive disease. The difference in overall survival in the ITT population was driven by the platinum-resistant subgroup, but the result was confounded by the high rate of crossover from chemotherapy to rucaparib, with 90% of patients receiving rucaparib after either randomisation or crossover. In 2022, PARP inhibitor indications in ovarian cancer were restricted to the maintenance setting, removing the monotherapy treatment indication for relapsed *BRCA*-mutated disease,[28,29] further highlighting the need for better understanding of the most appropriate treatment for patients with ovarian cancer who have progressed on a PARP inhibitor.

Contributors

AMO, KKL, SG, and RK designed the study. AMO, AL, AF, ACdM, YS, IR, IB, NC, VS, LB, MN, DL, GS, DC, RP, AO, TS, BM-M, LM, and RK treated patients. AMO, AL, AF, ACdM, YS, IR, IB, NC, VS, LB, MN, DL, GS, DC, RP, AO, TS, BM-M, LM, DT, KKL, KM, SG, and RK acquired data. AMO, KKL, KM, SG, and RK analysed, verified, or interpreted data. All authors had access to all the data and 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.

Declaration of interests

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. AL is currently affiliated with the Department of Oncology, Almazov National Medical Research Center (Saint Petersburg, Russia). ACdM has received institutional funding from Clovis Oncology for this clinical 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; and 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 travelling 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 is currently affiliated with the Gynecologic Oncology Unit, Fondazione Policlinico Universitario A Gemelli IRCCS and Catholic University of Sacred Heart (Rome, Italy); has received honoraria from Clovis Oncology, AstraZeneca, GlaxoSmithKline, Merck Sharp & Dohme, Immunogen, Genmab, Amgen, Seagen, and PharmaMar; has served as an invited member on

advisory boards for Corcept, Genmab, Immunogen, Merck Serono, Oncoinvest, Seagen, and Sutro; has served as an invited speaker and member of advisory boards from AstraZeneca; has served as an invited speaker and member of advisory boards and reports receiving direct research institutional funding from Clovis Oncology, GlaxoSmithKline, Merck Sharp & Dohme, and PharmaMar; and reports travel expenses from Clovis Oncology, AstraZeneca, GlaxoSmithKline, PharmaMar, and Roche; and has served as a principal investigator without compensation for Clovis Oncology, AstraZeneca, Genmab, GlaxoSmithKline, Immunogen, Incyte, Merck Sharp & Dohme, Novartis Roche, and Seagen; and serves as a member of the board of directors of Gynecological Cancer InterGroup. 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. BM-M has received honoraria from AstraZeneca, GlaxoSmithKline, and Roche; has served on advisory boards for GlaxoSmithKline and Seagen; and participated in clinical trials for Clovis Oncology, AstraZeneca, AstraZeneca Pharma Poland sp zoo, Merck Sharp & Dohme, Merck Sharp & Dohme Polska sp zoo; Mersana Therapeutics, Quintiles Eastern Holdings, Parexel, Regeneron Pharmaceuticals Roche Polska sp zoo, Seagen, Tesaro, and Tesaro Bio Netherlands BV. DT, KKL, KM, and SG are or were employees of Clovis Oncology and have stock and stock options. RK is currently affiliated with Department of Oncology, Guy's and St Thomas' NHS Foundation Trust (London, UK); 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; and 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 affiliated with P A Herzen Cancer Research Institute (Moscow, Russia). IR, IB, VS, LB, MN, RP, AO, TS, and LM declare no competing interests.

Data sharing

Requests for deidentified datasets for the results reported in this publication will be made available to qualified researchers following submission of a methodologically sound proposal to medinfo@pharmaand.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 anonymization. Data will be provided by Pharma and GmbH. Pharma and GmbH does not share identified participant data or a data dictionary.

Acknowledgments

This study was funded by Clovis Oncology. The authors received writing support from Clovis Oncology during the conduct of the study. Clovis Oncology assets are now owned by Pharma and GmBH. The authors thank Andrew Croskery for his help with obtaining and organising the data, Lisa Wang and Wei Xu for their help with statistical analysis, and Paula Sliwo for her help with editing the final manuscript. Medical writing support was provided by Shelly Lim (Ashfield MedComms, Dublin, Ireland) and editorial support, funded by Clovis Oncology, was provided by Kathleen Blake (Ashfield MedComms).

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