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Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial

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Summary

Background Poly(ADP-ribose) polymerase (PARP) inhibitors have activity in ovarian carcinomas with homologous recombination deficiency. Along with *BRCA1* and *BRCA2* (*BRCA*) mutations genomic loss of heterozygosity (LOH) might also represent homologous recombination deficiency. In ARIEL2, we assessed the ability of tumour genomic LOH, quantified with a next-generation sequencing assay, to predict response to rucaparib, an oral PARP inhibitor.

Methods ARIEL2 is an international, multicentre, two-part, phase 2, open-label study done at 49 hospitals and cancer centres in Australia, Canada, France, Spain, the UK, and the USA. In ARIEL2 Part 1, patients with recurrent, platinum-sensitive, high-grade ovarian carcinoma were classified into one of three predefined homologous recombination deficiency subgroups on the basis of tumour mutational analysis: *BRCA* mutant (deleterious germline or somatic), *BRCA* wild-type and LOH high (LOH high group), or *BRCA* wild-type and LOH low (LOH low group). We prespecified a cutoff of 14% or more genomic LOH for LOH high. Patients began treatment with oral rucaparib at 600 mg twice per day for continuous 28 day cycles until disease progression or any other reason for discontinuation. The primary endpoint was progression-free survival. All patients treated with at least one dose of rucaparib were included in the safety analyses and all treated patients who were classified were included in the primary endpoint analysis. This trial is registered with ClinicalTrials.gov, number NCT01891344. Enrolment into ARIEL2 Part 1 is complete, although an extension (Part 2) is ongoing.

Findings 256 patients were screened and 206 were enrolled between Oct 30, 2013, and Dec 19, 2014. At the data cutoff date (Jan 18, 2016), 204 patients had received rucaparib, with 28 patients remaining in the study. 192 patients could be classified into one of the three predefined homologous recombination deficiency subgroups: *BRCA* mutant (n=40), LOH high (n=82), or LOH low (n=70). Tumours from 12 patients were established as *BRCA* wild-type, but could not be classified for LOH, because of insufficient neoplastic nuclei in the sample. The median duration of treatment for the 204 patients was 5·7 months (IQR 2·8–10·1). 24 patients in the *BRCA* mutant subgroup, 56 patients in the LOH high subgroup, and 59 patients in the LOH low subgroup had disease progression or died. Median progression-free survival after rucaparib treatment was 12·8 months (95% CI 9·0–14·7) in the *BRCA* mutant subgroup, 5·7 months (5·3–7·6) in the LOH high subgroup, and 5·2 months (3·6–5·5) in the LOH low subgroup. Progression-free survival was significantly longer in the *BRCA* mutant (hazard ratio 0·27, 95% CI 0·16–0·44, p<0·0001) and LOH high (0·62, 0·42–0·90, p=0·011) subgroups compared with the LOH low subgroup. The most common grade 3 or worse treatment-emergent adverse events were anaemia or decreased haemoglobin (45 [22%] patients), and elevations in alanine aminotransferase or aspartate aminotransferase (25 [12%]). Common serious adverse events included small intestinal obstruction (10 [5%] of 204 patients), malignant neoplasm progression (10 [5%]), and anaemia (nine [4%]). Three patients died during the study (two because of disease progression and one because of sepsis and disease progression). No treatment-related deaths occurred.

Interpretation In patients with *BRCA* mutant or *BRCA* wild-type and LOH high platinum-sensitive ovarian carcinomas treated with rucaparib, progression-free survival was longer than in patients with BRCA wild-type LOH low carcinomas. Our results suggest that assessment of tumour LOH can be used to identify patients with *BRCA* wild-type platinum-sensitive ovarian cancers who might benefit from rucaparib. These results extend the potential usefulness of PARP inhibitors in the treatment setting beyond *BRCA* mutant tumours.

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Research in context

Evidence before this study

To identify other clinical trials of poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer, we searched PubMed for articles published up to July 28, 2016, using the following search terms: ("PARP inhibitor" OR rucaparib OR olaparib OR niraparib OR veliparib OR talazoparib) AND (ovarian AND [cancer OR carcinoma]). Our search identified several clinical trials with results reporting antitumour activity and progression-free survival with PARP inhibitor monotherapy in patients with ovarian carcinoma with or without a *BRCA* mutation. Although the findings of some of these clinical studies suggested activity in patients without a *BRCA* mutation, no specific biomarkers were tested in a trial of a PARP inhibitor in patients with ovarian carcinoma with measurable disease. There is currently no optimum method to identify which *BRCA* wild-type cancers are most likely to respond to a PARP inhibitor.

Added value of this study

Our results show that a tumour-based, next-generation sequencing homologous recombination deficiency assay combining *BRCA* mutation status and percentage of genome-wide loss of heterozygosity (LOH) in the tumour could identify which patients with platinum-sensitive carcinomas without a germline *BRCA* mutation are most likely to respond to rucaparib treatment. Using our novel algorithm, we found that patients with a germline or somatic *BRCA* mutation or wild-type *BRCA* with high LOH had longer progression-free survival and more objective responses with rucaparib treatment than did patients with wild-type *BRCA* and low LOH. The findings of ARIEL2 Part 1 also showed that the mutation and methylation status of other homologous recombination-related genes, such as *RAD51C*, can be associated with high genomic LOH in *BRCA* wild-type tumours and with rucaparib response.

Implications of all the available evidence

PARP inhibitors have been shown to have activity in patients with a germline or somatic *BRCA* mutation; however, there are no proven predictive biomarkers of response to PARP inhibition in patients with a *BRCA* wild-type tumour. The results of ARIEL2 greatly extend the usefulness of PARP inhibitors as a treatment for cancer. Additionally, our data provide evidence that our LOH analysis is more sensitive than either mutational or methylation analyses for the identification of responders in this setting and should be assessed in other tumour types in which homologous recombination deficiency might be common.

Introduction

Ovarian cancer is the fifth leading cause of death due to cancer in women in both the USA and European Union.[1,2] Mutations in one allele of *BRCA1* or *BRCA2* (*BRCA*) accompanied by loss of the wild-type allele hinders homologous recombination-mediated DNA damage repair,[3] leading to loss or duplication of chromosomal regions, also known as genomic loss of heterozygosity (LOH).[4–6] Half of all high-grade serous ovarian carcinomas are estimated to have homologous recombination deficiency, with about 15% of carcinomas harbouring a germline *BRCA* mutation, 6% a somatic *BRCA* mutation, and 20% a mutation in, or epigenetic silencing of, another homologous recombination gene.[7,8] Even without an identifiable mutation in *BRCA* or other known homologous recombination gene, many high-grade serous ovarian carcinomas show *BRCA* mutant-like genomic signatures,[6,9] which could serve as a downstream marker of homologous recombination deficiency.

Poly(ADP-ribose) polymerase (PARP) enzymes are involved in DNA repair through activation of the base excision repair and alternative end-joining pathways and inhibition of the non-homologous end-joining pathway.[10,11] PARP inhibition in cells with homologous recombination deficiency is postulated to cause accumulation of unrepaired DNA double-strand breaks, ultimately leading to cell death.[10–12] Consequently, PARP inhibitors are selectively lethal in cells with homologous recombination deficiency.[10,11,13–18] In clinical trials, PARP inhibitors have shown antitumour activity and extended progression-free survival compared with placebo in patients with or without a *BRCA* mutation;[19–22] however, the optimal method for the identification of which *BRCA* wild-type cancers are most likely to respond to a PARP inhibitor is unknown.[20–23]

Results from a phase 1/2 study[24] of rucaparib, an oral PARP inhibitor, have shown efficacy and safety in women with relapsed, platinum-sensitive, high-grade ovarian carcinoma harbouring a germline *BRCA* mutation, with 22 (67%) of 33 patients achieving an objective response. The aim of ARIEL2 Part 1 was to identify molecular predictors of rucaparib sensitivity in patients with platinum-sensitive recurrent high-grade ovarian carcinoma, including tumours without a germline or somatic *BRCA* mutation.

Methods

Study design and participants

ARIEL2 is an international, multicentre, two-part, phase 2, open-label study designed to assess rucaparib sensitivity in three prospectively defined subgroups (appendix pp 6). The study protocol is available in the appendix. Data are presented for ARIEL2 Part 1, which has completed enrolment; an extension (Part 2) of ARIEL2, added through a protocol amendment (May 11, 2015), is ongoing and will be published separately.

Investigators at each site identified eligible patients according to recruitment strategies approved by each centre and offered them the chance to enrol. Patients were eligible to enrol in ARIEL2 Part 1 if they had

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high-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal carcinoma and had received at least one previous platinum therapy. Eligible patients were at least 18 years old, had not previously received a PARP inhibitor, had progressed 6 months or more after their most recent platinum-based treatment, had an Eastern Cooperative Oncology Group Performance Status of 0 to 1, and had disease that was measurable with the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST) and amenable to biopsy at trial entry. Patients were ineligible if they had an active second malignancy, central nervous system metastases, or had received anticancer therapy 14 days or fewer before receiving their first dose of rucaparib. Formalin-fixed paraffin-embedded archival and pretreatment tumour biopsies of adequate quality were required for each patient. A complete list of inclusion and exclusion criteria is provided in the appendix (pp 16–17).

The study was done at 49 hospitals and cancer centres in Australia, Canada, France, Spain, the UK, and the USA. ARIEL2 was approved by the institutional review board at each study site and was done in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonisation. Patients provided written informed consent before participation.

Procedures

Patients were treated with oral rucaparib at 600 mg twice per day for continuous 28 day cycles until disease progression or any other reason for discontinuation. Supportive care (eg, antiemetics or analgesics for pain control) was permitted at the investigator's discretion. Dose reductions (in increments of 120 mg) were permitted if a patient had a grade 3 or worse adverse event. Treatment was discontinued if a dose interruption occurred for more than 14 consecutive days (longer dose interruptions were permitted with sponsor approval). Further details about dose modifications are shown in the appendix (p 2).

Tumour response was assessed by the investigators in line with RECIST, with CT scans at screening and every 8 weeks during treatment (and post-treatment for patients who discontinued for any reason other than disease progression). Assessments continued until confirmed disease progression, death, start of subsequent treatment, or loss to follow-up. Serum CA-125 measurements were taken at screening, day 1 of each cycle, the end of treatment, and when clinically indicated. Haematology, serum chemistry, and safety assessments were done at screening, day 1 and day 15 of cycle 1, and day 1 of any subsequent cycles. For pharmacokinetic analyses, a blood sample was taken on day 15 of cycle 1 and on day 1 of cycles 2, 3, and 4, before dosing with rucaparib and as close to 12 h after the last dose was taken as possible. Rucaparib pharmacokinetics were assessed with trough plasma concentrations (appendix pp 4–5). Adverse events were classified in accordance with the Medical Dictionary for Drug Regulatory Activities classification system version 18.1[25] and graded for severity in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[26]

At enrolment we used the Foundation Medicine T5 next-generation sequencing assay (Foundation Medicine, Cambridge, MA, USA)[27] to calculate the percentage of genomic LOH in archival and pretreatment biopsies.[27,28] We prespecified a cutoff of 14% or more to define LOH high, which was based on analysis of The Cancer Genome Atlas (TCGA) microarray and survival data for patients with ovarian carcinoma who had received platinum-based chemotherapy (appendix pp 2–5, 7, 18).[7] We classified patients into one of three predefined homologous recombination deficiency subgroups on the basis of this tumour analysis: *BRCA* mutant (deleterious germline or somatic), *BRCA* wild-type and LOH high (LOH high group), or *BRCA* wild-type and LOH low (LOH low group).

The tumour sequencing assay also identified mutations in homologous recombination genes other than *BRCA1* and *BRCA2* (appendix pp 3, 19). We assessed *BRCA1* and *RAD51C* promoter hypermethylation in tumours using a methylation-sensitive polymerase chain reaction (appendix p 4).[28,29] Mutations detected in tumour tissue were identified as germline or somatic by analysis of genomic DNA from blood by use of the BROCA-homologous recombination sequencing assay (University of Washington, Seattle, WA, USA).[30] For each patient, we used the most recently collected tumour specimen (ie, pretreatment biopsy if available or archival biopsy if not) to classify *BRCA* mutation, genomic LOH, and methylation status (appendix pp 4–5). Tumour tissue sequencing analyses were all done at the Foundation Medicine central laboratory (Cambridge, MA, USA).

Outcomes

In ARIEL2 Part 1, the primary endpoint was progression-free survival, defined as the time from the first dose of rucaparib to investigator-assessed disease progression or death from any cause. Secondary endpoints were the proportion of patients achieving an objective response (according to RECIST and Gynecological Cancer InterGroup [GCIG] CA-125 criteria),[31,32] duration of response (according to RECIST), safety, and pharmacokinetics. The proportion of patients achieving an objective response was defined as the proportion with a best response of complete or partial response. All RECIST and CA-125 responses were confirmed by a second assessment after at least 4 weeks. The combined proportion of patients achieving a RECIST or CA-125 objective response was assessed with GCIG combined RECIST and CA-125 criteria.[32] Duration of confirmed response (complete or partial response) was calculated from the initial date a response was detected to the first date of progressive disease. Tumour assessments were done by the investigators. Prior to study enrolment, each

patient's LOH status was unknown, and investigators were not provided the results of the LOH analysis during the study. Investigators were not blinded to *BRCA* mutation status because patients could enrol with a known germline *BRCA* mutation, and information about a *BRCA* mutation detected upon analysis of tumour tissue during the study was provided to consenting patients and investigators.

Exploratory endpoints included comparison of LOH classification in archival and pretreatment biopsies and RECIST and CA-125 response in patients with a mutation in a non-*BRCA* homologous recombination gene.

Statistical analysis

After reviewing data from the TCGA, we estimated that 30% of patients eligible for ARIEL2 Part 1 (ie, those with platinum-sensitive ovarian cancer) would be classified in the *BRCA* mutant subgroup, 30–50% in the LOH high subgroup, and 20–40% in the LOH low subgroup. Thus, ARIEL2 Part 1 was designed to enrol at least 180 patients such that any of the three possible pairwise comparisons of subgroups would contain at least 100 patients, with each of the three comparisons resulting in 80% power at a two-sided 10% significance level to detect a difference in progression-free survival distributions (assuming the hazard ratio [HR] between two subgroups was 0·50). Comparisons between the *BRCA* mutant and LOH high subgroups were outside the scope of this study. The number of patients with a known deleterious germline *BRCA* mutation was capped at 15 to ensure enough patients with *BRCA* wild-type tumours were enrolled to test the hypothesis that LOH status in patients with *BRCA* wild-type tumours would be correlated with progression-free survival and objective response. Patients who were in the screening process when the target enrolment of 180 patients was reached were allowed to complete screening and enrol into the study if eligible.

All efficacy and safety analyses were done with the safety population, which included all patients who were

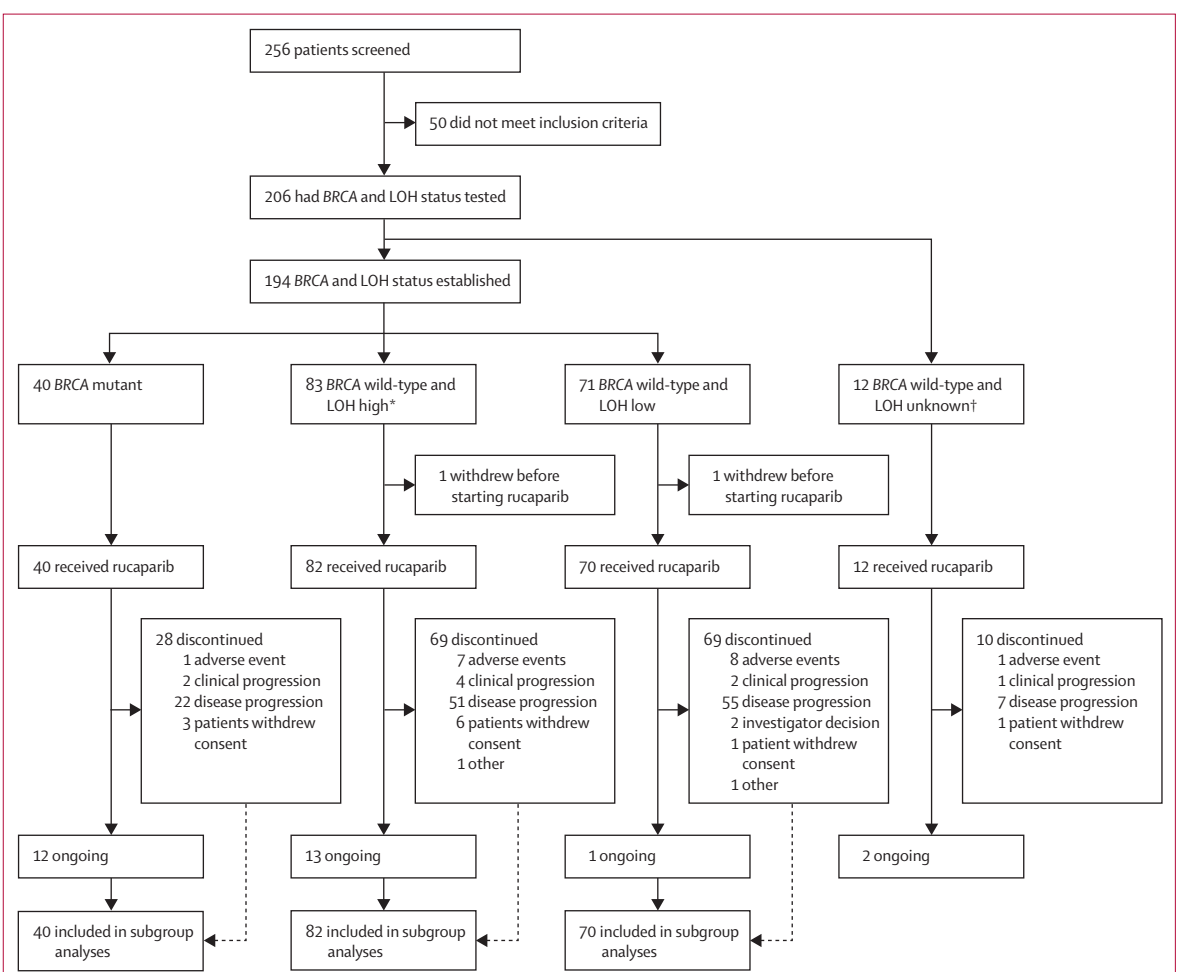


Figure 1: **Trial profile**

LOH=loss of heterozygosity. *Patients had genomic LOH ≥14%. †Sequencing of archival and pretreatment tumour samples from one patient did not pass quality check; therefore, the tumour cannot be definitively concluded to be *BRCA* wild-type.

treated with at least one dose of rucaparib. We analysed progression-free survival with Kaplan-Meier methods and a Cox proportional hazard model (two-sided test at the 5% significance level with 95% CI) to compare the *BRCA* mutant and LOH high subgroups with the LOH low subgroup. Patients without documented progression were censored as of their last tumour assessment. We analysed duration of response with Kaplan-Meier methods, with the log-rank test used to compare the distribution between subgroups. Patients with an ongoing response were censored as of their latest post-baseline scan. We used Clopper-Pearson methods to present proportions of patients achieving objective responses as percentages with 95% CIs and analysed differences between subgroups using a χ^2 test of proportions. We also did a post-hoc analysis of the best percentage change in the sum of all target lesions compared with baseline. We used SAS version 9.3 for the statistical analyses of progression-free survival, duration of response, objective response, and best percentage change in target lesions. We compared LOH classification in archival and pretreatment biopsies using Fisher's exact test. As an exploratory analysis, we also compared the sensitivity of different biomarkers (eg, genomic LOH, homologous recombination gene mutations, and methylation status) for the detection of RECIST response in patients with *BRCA* wild-type tumours using McNemar's test. We used R version 3.3.1 for the statistical analyses of comparison of LOH classification and sensitivity for the detection of response.

The principal investigators and sponsor personnel oversaw study conduct and reviewed risk–benefit every 6 months. ARIEL2 is registered with ClinicalTrials.gov, number NCT01891344.

Role of the funding source

The study was designed by the funder and a subgroup of investigators. Data presented herein were collected by the funder; the funder and all authors interpreted and analysed the data. Writing and editorial assistance were supported by the funder. EMS, KKL, HG, TCH, SG, LMal, JI, ARA, LR, MR, and IAM had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

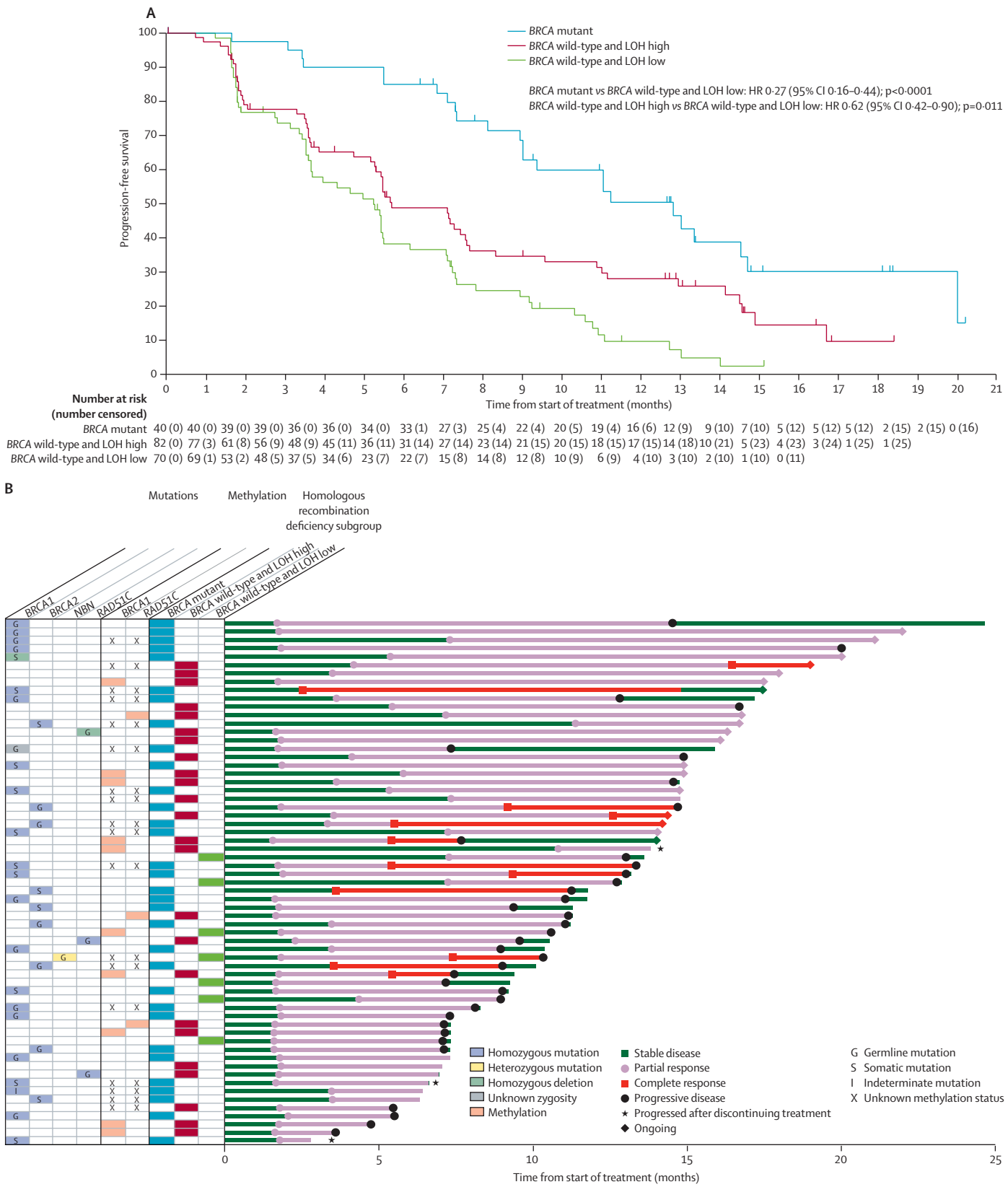
Results

Between Oct 30, 2013, and Dec 19, 2014, 256 patients were screened and 206 patients were enrolled into the trial (figure 1). At the data cutoff date (Jan 18, 2016), 204 patients had been treated with rucaparib, with 28 patients remaining on study medication. The median duration of treatment for the 204 patients was 5·7 months (IQR 2·8–10·1). 192 treated patients could be classified into one of the three predefined homologous recombination deficiency subgroups: *BRCA* mutant (n=40), LOH high (n=82), or LOH low (n=70). Tumours from 12 patients were established as *BRCA* wild-type, but could not be classified for LOH because of insufficient neoplastic nuclei (appendix p 8). Table 1 shows the demographic and disease characteristics of the enrolled patients. In view of the enrolment cap for known *BRCA* mutation carriers, only 20 (10%) of 204 patients were confirmed to have a germline *BRCA* mutation (14 had *BRCA1* mutations and six had *BRCA2* mutations) by use of the BROCA-homologous recombination assay. 19 (9%) other patients had a somatic *BRCA* mutation (14 had *BRCA1* mutations and five had *BRCA2* mutations) identified with tumour sequencing and the BROCA-homologous recombination assay. The germline or somatic status of one *BRCA1* mutation could not be established. 20 (10%) other patients had a somatic or germline mutation in another homologous recombination gene (appendix p 20). Of 165 tumours for which methylation analyses were completed, *BRCA1* promoter hypermethylation was detected in 21 (13%) tumours and *RAD51C* promoter hypermethylation was detected in four (2%) tumours. Methylation of *BRCA1* and *RAD51C* was only seen in tumours that did not harbour a germline or somatic mutation in *BRCA* or *RAD51C*.

	BRCA mutant (n=40)	*BRCA* wild-type and LOH high (n=82)	*BRCA* wild-type and LOH low (n=70)	*BRCA* wild-type and LOH unclassified (n=12)*
Age (years)	58·5 (53·5–67·5)	65·0 (58·0–71·0)	65·0 (55·0–72·0)	69·5 (63·0–77·0)
ECOG performance status				
0	26 (65%)	52 (63%)	47 (67%)	9 (75%)
1	14 (35%)	30 (37%)	23 (33%)	3 (25%)
Diagnosis†				
Epithelial ovarian cancer	38 (95%)	68 (83%)	49 (70%)	9 (75%)
Primary peritoneal cancer	1 (3%)	10 (12%)	12 (17%)	1 (8%)
Fallopian tube cancer	1 (3%)	4 (5%)	9 (13%)	2 (17%)
Histology				
Serous	39 (98%)	80 (98%)	66 (94%)	12 (100%)
Endometrioid	1 (3%)	1 (1%)	2 (3%)	0
Mixed	0	1 (1%)	2 (3%)	0
Previous treatment regimens				
Number of regimens	2 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)
1	17 (43%)	44 (54%)	47 (67%)	10 (83%)
≥2	23 (58%)	38 (46%)	23 (33%)	2 (17%)
Number of platinum-based regimens	2 (1–2)	1 (1–2)	1 (1–2)	1 (1–1)
1	17 (43%)	45 (55%)	49 (70%)	10 (83%)
≥2	23 (58%)	37 (45%)	21 (30%)	2 (17%)
Progression-free interval after completion of platinum-based chemotherapy				
6 to <12 months	23 (58%)	37 (45%)	31 (44%)	5 (42%)
≥12 months	17 (43%)	45 (55%)	39 (56%)	7 (58%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. LOH=loss of heterozygosity. *12 patients whose tumour specimens had sufficient nuclei to categorise as *BRCA* wild-type, but insufficient nuclei for genomic LOH analysis. †Diagnosis was unknown for one patient.

Table 1: **Demographic and disease characteristics by homologous recombination deficiency subgroup**


A
Progression-free survival
Time from start of treatment (months)
BRCA mutant
BRCA wild-type and LOH high
BRCA wild-type and LOH low
BRCA mutant vs BRCA wild-type and LOH low: HR 0·27 (95% CI 0·16–0·44); p<0·0001
BRCA wild-type and LOH high vs BRCA wild-type and LOH low: HR 0·62 (95% CI 0·42–0·90); p=0·011
Number at risk (number censored)
BRCA mutant 40 (0) 40 (0) 39 (0) 39 (0) 36 (0) 36 (0) 34 (0) 33 (1) 27 (3) 25 (4) 22 (4) 20 (5) 19 (4) 16 (6) 12 (9) 9 (10) 7 (10) 5 (12) 5 (12) 5 (12) 2 (15) 2 (15) 0 (16)
BRCA wild-type and LOH high 82 (0) 77 (3) 61 (8) 56 (9) 48 (9) 45 (11) 36 (11) 31 (14) 27 (14) 23 (14) 21 (15) 20 (15) 18 (15) 17 (15) 14 (18) 10 (21) 5 (23) 4 (23) 3 (24) 1 (25) 1 (25)
BRCA wild-type and LOH low 70 (0) 69 (1) 53 (2) 48 (5) 37 (5) 34 (6) 23 (7) 22 (7) 15 (8) 14 (8) 12 (8) 10 (9) 6 (9) 4 (10) 3 (10) 2 (10) 1 (10) 0 (11)
B
Mutations
Methylation
Homologous recombination deficiency subgroup
BRCA1
BRCA2
NBN
RAD51C
BRCA1
RAD51C
BRCA mutant
BRCA wild-type and LOH high
BRCA wild-type and LOH low
Time from start of treatment (months)
Homozygous mutation
Heterozygous mutation
Homozygous deletion
Unknown zygosity
Methylation
Stable disease
Partial response
Complete response
Progressive disease
Progressed after discontinuing treatment
Ongoing
G Germline mutation
S Somatic mutation
I Indeterminate mutation
X Unknown methylation status

24 patients in the *BRCA* mutant subgroup, 56 patients in the LOH high subgroup, and 59 patients in the LOH low subgroup had disease progression or died. Median progression-free survival after rucaparib treatment was 12·8 months (95% CI 9·0–14·7) in the *BRCA* mutant subgroup, 5·7 months (5·3–7·6) in the LOH high subgroup, and 5·2 months (3·6–5·5) in the LOH low subgroup (figure 2A). Progression-free survival was significantly longer in the *BRCA* mutant subgroup (HR 0·27, 95% CI 0·16–0·44, p<0·0001) and LOH high subgroup (HR 0·62, 0·42–0·90, p=0·011) than in the LOH low subgroup (figure 2A). 12 month progression-free survival was higher in the *BRCA* mutant subgroup (50%, 95% CI 33–65) and LOH high subgroup (28%, 18–39) than in the LOH low subgroup (10%, 4–19). The proportionality of hazards assumption was not violated (appendix pp 4–5, 15).

Confirmed objective RECIST responses are shown in table 2. The proportion of patients achieving RECIST responses was significantly higher in the *BRCA* mutant (p<0·0001) and LOH high (p=0·0033) subgroups than in the LOH low subgroup. The proportion of patients who achieved a response was similar irrespective of whether the *BRCA* mutation was germline or somatic or whether a patient had a *BRCA1* or *BRCA2* mutation (table 2). Confirmed combined RECIST and CA-125 responses were significantly more frequent in the *BRCA* mutant (p<0·0001) and LOH high (p=0·0018) subgroups than in the LOH low subgroup (table 2).

Median duration of response was longer in the *BRCA* mutant subgroup (9·2 months, 95% CI 6·4–12·9, p=0·013) and LOH high subgroup (10·8 months, 5·7–not reached, p=0·022) than in the LOH low subgroup (5·6 months, 4·6–8·5; appendix p 10). Pharmacokinetic data were obtained from 194 patients, including 40 from the *BRCA* mutant subgroup, 75 from the LOH high subgroup, 67 from the LOH low subgroup, and 12 with undetermined LOH status. Steady-state pharmacokinetics with rucaparib were achieved by cycle 1 day 15, with a mean trough plasma concentration of 2026 ng/mL (SD 1147; appendix pp 5, 9).

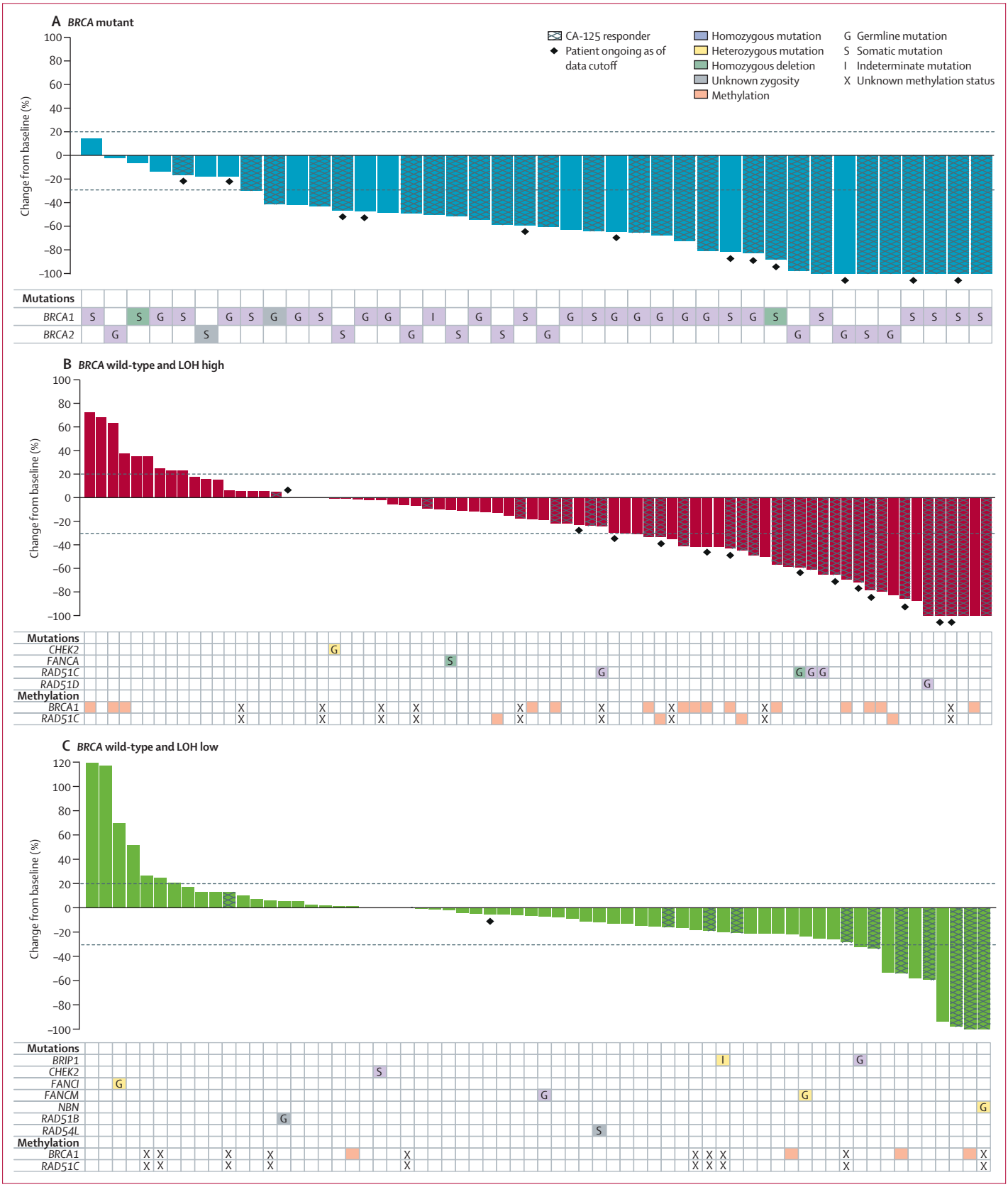
In an exploratory analysis, both RECIST and CA-125 responses were detected in patients with a mutation in a non-*BRCA* homologous recombination gene (eg, *ATM, NBN, RAD51C,* or *RAD51D*; appendix p 20). Confirmed RECIST responses were also detected in patients with tumours with *BRCA1* methylation and *RAD51C* methylation (figure 2B). Post-hoc analysis of the best percentage change in the sum of all target lesions by RECIST compared with baseline is shown for each patient according to molecular subgroup in figure 3.

In our exploratory analysis, among *BRCA* wild-type tumours (both LOH high and LOH low subgroups), genomic LOH was a more sensitive predictor of response (sensitivity 78%) than was mutation of other homologous recombination genes (sensitivity 11%; p<0·0001 by McNemar's test) and methylation of *BRCA1* or *RAD51C* (sensitivity 48%, p<0·021; appendix p 11). However, genomic LOH was not more sensitive than an analysis that combined both mutation in other homologous recombination genes and methylation (sensitivity 59%, p=0·13).

All 204 patients had at least one treatment-emergent adverse event (table 3). The most common grade 3 or worse treatment-emergent adverse events were anaemia or decreased haemoglobin (45 [22%] patients) and elevations in alanine aminotransferase or aspartate aminotransferase (25 [12%]); elevations in blood creatinine were only grade 1 or 2. One or more serious treatment-emergent adverse events were reported in 50 (25%) patients. Common serious adverse events included small intestinal obstruction (10 [5%] patients), malignant neoplasm progression (10 [5%] patients), and anaemia (nine [4%] patients; appendix p 21). 80 (39%) of all 204 treated patients needed a dose reduction, most commonly for anaemia (28 [14%] patients) and nausea (22 [11%] patients; appendix p 22). 19 (9%) patients discontinued treatment with an adverse event as the main reason; fatigue was the most common reason, occurring in six (3%) patients (appendix p 23). Three patients died during the study (two because of malignant neoplasm progression and one because of sepsis and malignant neoplasm progression). No treatment-related deaths were reported.

For 117 patients, LOH analyses were completed on paired archival and pretreatment tissue; our exploratory analysis showed that LOH classification was highly concordant between archival and pretreatment samples (r=0·86, p<0·0001; appendix p 12). Of 50 patients with an LOH low archival specimen, 17 (34%) had an LOH high pretreatment specimen. Of the 17 patients with a change in classification from LOH low to LOH high, five had a partial response. In contrast, we did not detect any cases in which the classification changed from LOH high to LOH low between the archival and the pretreatment tissue. Methylation of *BRCA1* was also highly concordant in 90 paired samples (p<0·0001; appendix p 12). Of 13 patients with *BRCA1* methylation in the archival specimen, four (31%) had an unmethylated pretreatment sample. Only one patient had methylation in the pretreatment biopsy but not in the archival biopsy.

Figure 2: **Progression-free survival and response duration**
(A) Kaplan-Meier estimates of progression-free survival in all patients who received at least one dose of rucaparib, stratified by homologous recombination deficiency subgroup. (B) Swimlane plot of duration of response in patients classified into the three predefined homologous recombination deficiency subgroups with confirmed partial or complete RECIST responses. Each bar represents an individual patient with the length corresponding to length of time on study drug. Tiles to the left of the plot show the homologous recombination deficiency subgroup of each patient and homologous recombination gene mutation type (colour coded by type) or methylation type identified in tumour or blood samples. Four patients (one with a complete response and three with a partial response) are not included in B because their archival or pretreatment biopsy could not be classified into a homologous recombination deficiency subgroup. HR=hazard ratio. LOH=loss of heterozygosity. RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.


A BRCA mutant
CA-125 responder
Patient ongoing as of data cutoff
Homozygous mutation
Heterozygous mutation
Homozygous deletion
Unknown zygosity
Methylation
G Germline mutation
S Somatic mutation
I Indeterminate mutation
X Unknown methylation status
Change from baseline (%)
Mutations
BRCA1
BRCA2
B BRCA wild-type and LOH high
Change from baseline (%)
Mutations
CHEK2
FANCA
RAD51C
RAD51D
Methylation
BRCA1
RAD51C
C BRCA wild-type and LOH low
Change from baseline (%)
Mutations
BRIP1
CHEK2
FANCI
FANCM
NBN
RAD51B
RAD54L
Methylation
BRCA1
RAD51C

Discussion

The results of ARIEL2 Part 1 show the activity of rucaparib in patients with relapsed platinum-sensitive, high-grade ovarian carcinoma. Our data also support the ability of a homologous recombination deficiency signature identified by an algorithm combining the percentage of tumour genomic LOH with *BRCA* mutation status to identify patients who may benefit from rucaparib treatment. To our knowledge, ARIEL2 is the first study to prospectively use a tumour-based, next-generation sequencing homologous recombination deficiency assay that combines *BRCA* mutation status and the percentage of genome-wide LOH in a novel algorithm to predict sensitivity to a PARP inhibitor in women with relapsed ovarian carcinoma. In ARIEL2 Part 1, the three groups defined by *BRCA* and LOH analysis had distinct outcomes. The *BRCA* mutant subgroup had a significantly longer progression-free survival and a higher proportion of patients achieving RECIST responses than did the LOH low subgroup. The proportions of rucaparib-treated patients who achieved responses were similar between patients with a somatic or germline *BRCA* mutation and with a *BRCA1* or *BRCA2* mutation.

For patients with a *BRCA* wild-type carcinoma, the benefit of rucaparib treatment was higher for those with an LOH high carcinoma than for those with an LOH low carcinoma. Although the two *BRCA* wild-type subgroups had similar median progression-free survival, the hazard ratio for disease progression or death was significant between the two subgroups. Additionally, more patients achieved confirmed RECIST responses, more patients achieved confirmed RECIST and CA-125 responses, and patients had longer response durations in the LOH high subgroup than did patients in the LOH low subgroup. The median duration of response for the LOH high subgroup was similar to that of the *BRCA* mutant subgroup, with 13 (16%) of 82 LOH high patients and 12 (30%) of 40 patients with *BRCA* mutations still on treatment at the cutoff date, supporting the ability of the homologous recombination deficiency assay to identify patients without a *BRCA* mutation who might achieve a durable response with rucaparib treatment. A retrospective analysis of these data suggested that a refined cutoff of 16% or greater in the LOH high subgroup provided the optimum discrimination of progression-free survival, objective response, and duration of response in patients with *BRCA* wild-type ovarian carcinoma.[33]

	Confirmed objective responses by RECIST	Objective responses by combined RECIST and CA-125
BRCA mutant (n=40)	32 (80%, 64–91)	34 (85%, 70–94)
Germline mutation (n=20)	17 (85%, 62–97)	17 (85%, 62–97)
Somatic mutation (n=19)	14 (74%, 49–91)	16 (84%, 60–97)
Indeterminate (n=1)	1 (100%, 3–100)	1 (100%, 3–100)
BRCA1 mutation (n=29)	23 (79%, 60–92)	25 (86%, 68–96)
BRCA2 mutation (n=11)	9 (82%, 48–98)	9 (82%, 48–98)
PFI ≥6 to <12 months (n=23)	20 (87%, 66–97)	20 (87%, 66–97)
PFI ≥12 months (n=17)	12 (71%, 44–90)	14 (82%, 57–96)
BRCA wild-type and LOH high (n=82)	24 (29%, 20–40)	36 (44%, 33–55)
BRCA wild-type and LOH low (n=70)	7 (10%, 4–20)	14 (20%, 11–31)
BRCA wild-type and LOH not classified (n=12)	4 (33%, 10–65)	7 (58%, 28–85)

Data are n (%, 95% CI). Confidence intervals calculated using Clopper-Pearson method. CA-125=cancer antigen 125. LOH=loss of heterozygosity. PFI=progression-free interval following completion of platinum-based chemotherapy. RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

Table 2: **Objective response rates by homologous recombination deficiency subgroup**

Comparison of the outcomes in ARIEL2 Part 1 with other studies investigating PARP inhibitors is difficult because of the ambiguity in how *BRCA* wild-type cancers have been defined historically. For example, in a previous study of patients with recurrent platinum-sensitive ovarian carcinoma,[34] median progression-free survival was 5·7 months and seven (32%) patients achieved objective responses following use of single-agent olaparib in a subgroup of 22 patients without a germline *BRCA* mutation. However, the *BRCA* mutation status of the tumour was unknown in half of the patients in that subgroup (11 of 22 patients).[34] Additionally, we are not aware of any studies that have prospectively investigated progression-free survival or objective responses following platinum therapy in patients with relapsed, *BRCA* wild-type ovarian carcinoma, which makes it difficult to compare the results from ARIEL2 Part 1 with an expected frequency of response to platinum therapy.

Our results add to the increasing body of evidence showing the potential of homologous recombination deficiency analysis to identify patients who will benefit from PARP inhibitor treatment. Other biomarkers for homologous recombination deficiency have been assessed in previous studies,[4,35,36] for example, through retrospective analysis of *BRCA* mutations in ovarian carcinoma[21] or prospective identification of homozygous deletions or mutations through next-generation sequencing in prostate cancer.[22] Additionally, the NOVA

Figure 3: **Best response in size of target lesions**

Best percentage change from baseline in sum of longest diameter of target lesions according to RECIST for patients with both baseline and postbaseline measurements in the (A) *BRCA* mutant subgroup, (B) *BRCA* wild-type and LOH high subgroup, and (C) *BRCA* wild-type and LOH low subgroup. Each bar represents percentage change from baseline in sum of the longest diameter of target lesions for an individual patient according to RECIST. Upper dotted lines represent the threshold for progressive disease (20% increase in the sum of the longest diameter of the target lesions) and lower dotted lines show the threshold for partial response (30% decrease in the sum of the longest diameter of the target lesions). Tables below plots show homologous recombination gene mutations (colour coded by type) and methylation identified in the tumour samples. CA-125=cancer antigen 125. LOH=loss of heterozygosity. RECIST=Response Evaluation Criteria In Solid Tumors version 1.1.

	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	154 (75%)	9 (4%)	0	0
Asthenia or fatigue	141 (69%)	18 (9%)	0	0
Constipation	91 (45%)	3 (1%)	0	0
Vomiting	85 (42%)	4 (2%)	0	0
Dysgeusia	87 (43%)	0	0	0
Alanine aminotransferase or aspartate aminotransferase increased*	61 (30%)	24 (12%)	1 (<1%)	0
Decreased appetite	80 (39%)	4 (2%)	0	0
Anaemia; decreased haemoglobin	29 (14%)	43 (21%)	2 (1%)	0
Diarrhoea	61 (30%)	7 (3%)	0	0
Abdominal pain	56 (27%)	5 (2%)	0	0
Dyspnoea	46 (23%)	1 (<1%)	0	0
Abdominal distension	43 (21%)	0	0	0
Dizziness	37 (18%)	1 (<1%)	0	0
Urinary tract infection	33 (16%)	4 (2%)	0	0
Blood creatinine increased	34 (17%)	0	0	0
Headache	34 (17%)	0	0	0
Cough	33 (16%)	0	0	0
Back pain	30 (15%)	2 (1%)	0	0
Thrombocytopenia; platelet count decreased	25 (12%)	5 (2%)	0	0
Photosensitivity reaction	27 (13%)	0	0	0
Neutropenia; neutrophil count decreased	10 (5%)	9 (4%)	7 (3%)	0
Insomnia	25 (12%)	0	0	0
Pyrexia	24 (12%)	1 (<1%)	0	0
Abdominal pain (upper)	22 (11%)	0	0	0
Oedema peripheral	22 (11%)	0	0	0
Alopecia	21 (10%)	0	0	0
Stomatitis	20 (10%)	1 (<1%)	0	0
Upper respiratory tract infection	21 (10%)	0	0	0
Blood alkaline phosphatase increased	16 (8%)	3 (1%)	0	0
Dyspepsia	18 (9%)	1 (<1%)	0	0
Pain in extremity	17 (8%)	1 (<1%)	0	0
Weight decreased	16 (8%)	1 (<1%)	0	0
Dehydration	10 (5%)	6 (3%)	0	0
Myalgia	15 (7%)	1 (<1%)	0	0
Ascites	7 (3%)	7 (3%)	0	0
Blood cholesterol increased	11 (5%)	2 (1%)	0	0
Hypokalaemia	7 (3%)	5 (2%)	0	0
White blood cell count decreased	11 (5%)	1 (<1%)	0	0
Small intestinal obstruction	1 (<1%)	10 (5%)	0	0
Hydronephrosis	8 (4%)	2 (1%)	0	0
Malignant neoplasm progression	0	8 (4%)	1 (<1%)	3 (1%)
Blood bilirubin increased	7 (3%)	1 (<1%)	1 (<1%)	0
Mucosal inflammation	7 (3%)	1 (<1%)	0	0
Hypotension	5 (2%)	2 (1%)	0	0
Acute kidney injury	1 (<1%)	5 (2%)	0	0
Bronchitis	5 (2%)	1 (<1%)	0	0
Gamma-glutamyltransferase increased	1 (<1%)	4 (2%)	1 (<1%)	0
Hypercholesterolaemia	5 (2%)	1 (<1%)	0	0
Hyperglycaemia	4 (2%)	2 (1%)	0	0
Hypophosphataemia	1 (<1%)	5 (2%)	0	0
Rectal haemorrhage	5 (2%)	1 (<1%)	0	0
Fall	4 (2%)	1 (<1%)	0	0
Hyponatraemia	1 (<1%)	4 (2%)	0	0
Transaminases increased	2 (1%)	3 (1%)	0	0
Malaise	3 (1%)	1 (<1%)	0	0
Sepsis	0	1 (<1%)	2 (1%)	1 (<1%)
Leucopenia	2 (1%)	1 (<1%)	0	0
Presyncope	2 (1%)	1 (<1%)	0	0
Pulmonary embolism	1 (<1%)	2 (1%)	0	0
Syncope	0	3 (1%)	0	0
Food poisoning	1 (<1%)	1 (<1%)	0	0
Hyperbilirubinaemia	1 (<1%)	1 (<1%)	0	0
Lymphocyte count decreased	1 (<1%)	0	1 (1%)	0
Lymphoedema	1 (<1%)	1 (<1%)	0	0
Tachycardia	1 (<1%)	1 (<1%)	0	0
Pneumonia	0	2 (1%)	0	0
Agitation	0	1 (<1%)	0	0
Bile duct obstruction	0	1 (<1%)	0	0
Cataract	0	1 (<1%)	0	0
Dyspareunia	0	1 (<1%)	0	0
Empyema	0	1 (<1%)	0	0
Granulocytopenia	0	1 (<1%)	0	0
Hypermagnesaemia	0	1 (<1%)	0	0
Intestinal obstruction	0	1 (<1%)	0	0
Liver function test abnormal	0	1 (<1%)	0	0
Lymphangitis	0	1 (<1%)	0	0
Mental status changes	0	1 (<1%)	0	0
Peritonitis	0	1 (<1%)	0	0
Febrile neutropenia	0	0	1 (<1%)	0
Granulocyte count decreased	0	0	1 (<1%)	0
Intestinal perforation	0	0	1 (<1%)	0
Large intestinal obstruction	0	0	1 (<1%)	0
Long QT syndrome congenital	0	0	1 (<1%)	0
Acute myeloid leukaemia or myelodysplastic syndrome	0	0	0	0

(Table 3 continues in next column)

(Continued from previous column)

Data are n (%) in the safety population (n=204). *Elevations were transient, self-limiting, and not associated with other signs of liver toxicity.

Table 3: **Treatment-emergent adverse events**

trial (NCT01847274) prospectively tested a homologous recombination deficiency-based assay in a trial of niraparib as maintenance therapy in patients with platinum-sensitive ovarian cancer.[37] However, to our knowledge, ARIEL2 is the only study to prospectively assess a homologous recombination deficiency assay in patients with ovarian cancer who have measurable disease treated with a PARP inhibitor, thereby testing the assay as a biomarker for PARP inhibitor response. Other prospective trials in ovarian cancer are assessing homologous recombination deficiency assays in the maintenance setting following platinum therapy (eg, NOVA and ARIEL3 [NCT01968213]).

Our results also suggest that, in platinum-sensitive ovarian carcinomas, a mutation in a homologous recombination gene other than *BRCA1* or *BRCA2* (eg, *RAD51C*) or promoter hypermethylation of *BRCA1* or *RAD51C* can be associated with high genomic LOH and rucaparib response. However, not all homologous recombination gene mutations were associated with an LOH high genotype. Although the LOH analysis was more sensitive in the identification of responders in *BRCA* wild-type ovarian carcinomas than were either mutational or methylation analyses, LOH analysis was not more sensitive than mutation and methylation analyses combined. The high correlation of genomic LOH in archival and pretreatment biopsies suggests that either source can be used to predict response to rucaparib in this population of patients. However, a subset of patients whose archival tumour samples were defined as having low genomic LOH had increased genomic LOH in matched pretreatment tumour biopsies. This observation meant that recent biopsies had higher predictive sensitivity than did archival biopsies. Even in this platinum-sensitive population, loss of *BRCA1* methylation between the archival and pretreatment biopsy was detected in 31% of tumours. Data from patients with ovarian cancer with acquired chemotherapy resistance have shown that loss of *BRCA1* methylation could serve as a mechanism of therapeutic resistance.[38] Given that the homologous recombination deficiency status within a tumour might change over time, we recommend testing of the most recently collected tumour biopsy.

In ARIEL2, treatment-emergent adverse events were frequent and led to dose reductions in 39% of patients; however, only 9% of patients withdrew from the study as a result of a treatment-emergent adverse events. As with studies of other PARP inhibitors, treatment-emergent anaemia or decreased haemoglobin was the most common grade 3 adverse event. Anaemia was managed through transfusions and dose reductions. Alanine and aspartate aminotransferase levels increased after use of rucaparib; however, these increases were asymptomatic, reversible, and rarely associated with increased bilirubin levels. Patients with elevated alanine and aspartate aminotransferase levels were able to continue rucaparib treatment without dose reduction, and these elevations normalised over time.

Mild-to-moderate elevations in creatinine were also reported within the first few weeks following initiation of rucaparib treatment. Veliparib, another PARP inhibitor, has been reported to inhibit drug transporters expressed in the liver (MATE1) and kidneys (OCT2, MATE1, and MATE2-K).[39] Similarly, results from in-vitro studies have shown that rucaparib inhibits MATE1 and MATE2-K transporters, which have a role in the renal secretion of creatinine. Thus, inhibition of these transporters might be responsible for the increases in blood creatinine noted following rucaparib treatment. On the basis of this mechanism, elevations in serum creatinine should be assessed in conjunction with other laboratory parameters to assess renal function.

Our study had several limitations. Although ARIEL2 Part 1 identified a biomarker that seems to be predictive, it is possible that the homologous recombination deficiency assay is only prognostic; therefore, the predictive ability of the biomarker will need to be confirmed in the setting of a larger randomised study. Indeed, the refined LOH high cutoff of 16% or higher that was identified retrospectively in ARIEL2 Part 1[33] is being prospectively applied in the randomised, phase 3 ARIEL3 trial, which aims to assess progression-free survival and overall survival with rucaparib as maintenance therapy following platinum-based chemotherapy for patients with platinum-sensitive, recurrent ovarian carcinoma. The randomised design of ARIEL3 will enable confirmation of genomic LOH as a predictive biomarker. Additionally, it is not known whether the findings in ARIEL2 Part 1 will extend to patients whose disease is resistant or refractory to platinum therapy. Hence, the homologous recombination deficiency assay is also being prospectively tested in an extension (Part 2) of ARIEL2, which is investigating rucaparib in patients with carcinomas that are platinum-sensitive, platinum-resistant, or platinum-refractory; who have received at least three but not more than four prior chemotherapies; and have had a treatment-free interval of more than 6 months following first-line chemotherapy. The primary endpoint of ARIEL2 Part 2 is the proportion of patients achieving objective responses; progression-free survival and overall survival are key secondary endpoints. Additional studies should assess whether the homologous recombination deficiency assay developed in ARIEL2 predicts sensitivity to rucaparib and other PARP inhibitors in patients with other cancer types, including non-serous ovarian cancer, and gastric, pancreatic, prostate, or breast cancers.[9,22,40–42]

Contributors

EMS, CLS, HG, SHK, ARA, LR, MR, and IAM were involved in the study conception. EMS, KKL, HG, TCH, LMal, JI, ARA, LR, MR, and IAM were involved in the study design. EMS, RLC, RSK, JDB, SHK, and IAM acquired funding. EMS, KKL, and IAM were involved in the protocol development and co-wrote the first draft of the manuscript.

EMS, AMO, CLS, GEK, RLC, AVT, DMO, RSK, LMa, KMB-M, JDB, JMC, AO, IR-C, AF, AL, and IAM treated patients. EMS, KKL, AMO, CLS, GEK, RLC, AVT, DMO, RSK, LMal, KMB-M, JDB, JMC, AO, IR-C, MIH, SHK, AF, AL, and IAM acquired data. EMS, KKL, CLS, HG, JS, SHK, TCH, SG, LMal, JI, ARA, LR, RY, MR, and IAM interpreted the data. EM contributed to sample acquisition and management. MIH analysed data. All authors contributed to manuscript revisions and approved the final draft for submission.

Declaration of interests

KKL, HG, EM, TCH, SG, LMal, JI, LR, and MR are employees of Clovis Oncology; ARA was employed at Clovis Oncology at the time of the study and owns stock in the company. CLS's institution received in kind research support for parallel laboratory work using rucaparib. JS is a current employee and RY was an employee of Foundation Medicine, the developer of the homologous recombination deficiency assay used in ARIEL2. RLC reports grants from AstraZeneca, Genentech (Roche), Janssen, OncoMed, Millennium, Esperance, and AbbVie. AVT has served on an advisory board for and received grants from AstraZeneca. DMO has received research funding from Clovis Oncology; institutional research support from Amgen, VentiRx, Regeneron, Immunogen, Array Biopharma, Janssen R&D, Clovis Oncology, EMD Serono, Ergomed, Ajinomoto, and Genentech (Roche); and has served on a steering committee or advisory boards for Amgen, AstraZeneca, Janssen, Clovis Oncology, Genentech (Roche), and Eisai. During the conduct of the study, RSK served on an advisory board for Clovis Oncology. KMB-M served on advisory boards for Clovis Oncology and AstraZeneca. JDB has been advisor for and owns stock in Inivata, has served on a speakers' bureau for AstraZeneca, has received non-financial support from Clovis Oncology and Aprea AB, and has a pending patent for a diagnostic method of relevance to the current work. AO has served on advisory boards for Roche, AstraZeneca, Pharmamar, and Clovis. IR-C has served on an advisory board for AstraZeneca, Pharmamar, and Roche. SHK has a patent for a diagnostic method of relevance to the current work. AL has served on an advisory board for Clovis, Pfizer, and Pharmamar, and reports institutional research grant support from Gamamabs and Merus. IAM has served on advisory boards for Clovis Oncology and AstraZeneca. All other authors declare no competing interests.

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