Rucaparib in ovarian cancer: an update on safety, efficacy and place in therapy

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Abstract: Rucaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor and potent inhibitor of PARP1, PARP2 and PARP3 enzymes. Phase II and III trials have documented that rucaparib has single-agent antitumor activity in patients with high-grade ovarian carcinoma, with both *BRCA*-mutated (germline and somatic) and with homologous recombination deficiency (HRD). Rucaparib as a maintenance treatment showed increased progression-free survival in patients with ovarian carcinoma who achieved a response to platinum-based chemotherapy, with an acceptable safety profile. The approval of this drug, along with the companion diagnostic FoundationFocus CDxBRCA test represents an important new therapeutic option in the treatment of ovarian cancer. This article reviews the mechanisms of action, safety, pharmacokinetics and pharmacodynamics and indications for use of rucaparib as well as future trials.

Keywords: BRCA, ovarian cancer, PARP, PARP inhibitors, platinum-sensitive ovarian cancer, rucaparib, Rubraca

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Introduction

Ovarian cancer is the eighth-leading cause of death from cancer in women worldwide.[1] This is in large part due to a lack of effective screening mechanisms leading to predominately advanced disease at diagnosis.[2] This also contributes to a worse prognosis.[3] Although patients often have a good response to taxane and platinum-based chemotherapy, most will unfortunately relapse.[4] Recurrent ovarian cancer remains a clinical challenge, owing to its relentless trajectory to eventual drug resistance. In the setting of recurrent disease, the outcome of patients is associated with different factors including volume of disease, response to platinum-based chemotherapy, histology, performance status and genotype, such as *BRCA* mutation status.[2] Targeted therapies, such as antiangiogenic agents (e.g. bevacizumab and cediranib) have proven useful in extending progression-free survival (PFS), and in one instance, overall survival, for patients in the setting of recurrent disease, although no biomarkers have been prospectively validated to identify individuals that will best respond to such treatment.[3,5,6]

While biomarkers do exist for the identification of patients most likely to respond to poly (ADP-ribose) polymerase (PARP) inhibitors (discussed below), this phenotype is somatically dynamic, eventually leading to drug resistance[7] and highlighting the unmet medical need for new treatment approaches and strategies.

Role of homologous recombination deficiency and PARP inhibitors in ovarian cancer

In epithelial ovarian cancer, homologous recombination (HR) is an important pathway that allows repair of double-stranded DNA breaks. Data from the Cancer Genome Atlas (TCGA) estimate that approximately 50% of high-grade serous ovarian cancers have genomic alterations that could impair homologous recombination response (HRR).[8] Both germline and *de novo* somatic mutations in HRR genes can result in ovarian cancer. *BRCA* germline mutations in the United States (US) population occur in about

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15% of women with high-grade epithelial ovarian cancer; *de novo* somatic *BRCA* mutations are found in another 5–7% in several cohorts of patients;[9–11] however, the true prevalence remains unknown. In some population clusters, more than 24% of ovarian cancers are associated with *BRCA* germline mutations.[12] Initially, the majority of homologous recombination deficiency (HRD) tumors were discovered in patients with germline *BRCA1* and *BRCA2* mutations.[13] Further studies showed that, in addition to these genes, there are many others involved in HR DNA repair, a phenotype called BRCA-like. The most common are the Fanconi anemia pathway genes (*RAD51C, RAD51D, RAD50, BRIP1, BARD1, CHEK2, MRE11A, NBN, PALB2*) and the mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*).[14,15]

Epithelial ovarian cancers with HRD have increased sensitivity to PARP inhibitors.[16] The PARP enzymes are involved in DNA repair through activation of the base excision repair. The 17-member PARP superfamily of nuclear enzymes includes PARP1, PARP2, and PARP3, which are activated by DNA damage.[17] There are many proposed mechanisms through which inhibition of PARP leads to cancer cell death;[18] however, a commonly referred to mechanism is the sequential inhibition of DNA single strand breaks that ultimately accumulate into DNA double-strand breaks (DSB), which in the absence of competent HRR leads to catastrophic cell damage. This process is frequently regarded as synthetic lethality.[19] Another DNA repair pathway is DSB recombination repair, which includes the nonhomologous end-joining (NHEJ).[20] It is also recognized that trapped PARP and DNA complexes can cause PARP inactivation.[21,22]

Rucaparib (formerly known as CO-338, AG-14699, and PF-01367338) is a potent PARP1, PARP2 and PARP3 inhibitor, and to a lesser extent PARP4, PARP10, PARP12, PARP15, and PARP16 and a mild inhibitor of PARP5a and PARP5b.[23] In 2011, *in vitro* studies have shown that rucaparib exhibits off-target effects with respect to PARP1 and PARP2.[22] Subsequently, preclinical studies revealed that tumors with mutated or epigenetically silenced *BRCA1/2* were sensitive to rucaparib.[24] Between 2013 and 2016, three clinical trials: Study 10 (a phase I/II treatment trial),[25] ARIEL 2 (a phase II treatment trial), and ARIEL 3 (a phase III

switch maintenance trial),[26,27] have documented that rucaparib has single-agent antitumor activity in patients with high-grade ovarian carcinoma.

Pharmacokinetics and pharmacodynamics of rucaparib

Rucaparib can be taken with or without food but has different pharmacokinetic parameters when taken with food (*versus* fasting) probably due to solubility in the small intestine. The mean fasting half-life is 17 h and the median time to maximal concentration is 1.9 h and can be delayed by 2.5 h after a high fat meal; however, the moderate food effect on pharmacokinetics was not considered to be clinically significant. The cytochrome P450 enzymatic pathway is responsible for rucaparib metabolism (primarily CYP2D6 and to a lesser extent by CYP1A2, and CYP3A4).[28,29] Dosing toxicity and pharmacokinetic assessments documented in the phase I part of the Study 10 concluded that rucaparib 600 mg twice daily was safe and manageable, and was the recommended dose for future studies.[25]

Clinical efficacy of rucaparib in ovarian cancer

Treatment

Study 10 was a phase I–II trial that evaluated rucaparib in patients with germline *BRCA1/2*-mutated ovarian carcinoma or other solid tumors. The phase II part enrolled 42 patients with platinum-sensitive, high-grade, predominately serous ovarian carcinoma associated with a germline *BRCA1/2* mutation who received two to four prior regimens and had a progression-free interval of 6 months or more following their most recent platinum therapy. The larger proportion of patients had a *BRCA1* mutation (71.4%), and *BRCA2* mutation was seen in 28.6% of patients. The investigator-assessed objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) was 59.5% and the median duration of response was 7.8 months [95% confidence interval (CI), 5.6–10.5].[25]

ARIEL 2, a two-part phase II trial[26] was conducted to assess the safety and efficacy of rucaparib in patients with platinum-sensitive, high-grade ovarian cancer patients with one or more chemotherapy regimen (part 1) or three or

four prior chemotherapy regimens (part 2; ClinicalTrials.gov identifier: NCT01891344).[30]

In part 1, a total of 204 patients were enrolled. The primary endpoint was PFS and secondary endpoints were ORR, duration of response, safety and pharmacokinetics. Rucaparib was given orally at 600 mg twice per day for continuous 28-day cycles until disease progression or any other reason for discontinuation. Tumor samples were analyzed to identify HRD. The biomarker chosen for HRD was the genomic loss of heterozygosity (LOH), and the prespecified (prospectively defined) cutoff to define LOH as high was ≥14%. Based on HRD, patients were classified in three subgroups: 'BRCA-mutant' [deleterious germline (capped at $N = 15$ patients) or somatic], 'BRCA-wildtype and LOH high' (LOH high group), or 'BRCA wildtype and LOH low' (LOH low group).

Of 204 patients, 192 were classified into three groups based on HRD status: BRCA-mutant ($n = 40/20.8\%$), LOH high group ($n = 82/42.8\%$) and LOH low group ($n = 70/36.4\%$). The median PFS (months; 95% CI) was: BRCA-mutant (12.8; 9.0–14.7), LOH high group (5.7; 5.3–7.6) and LOH low group (5.2; 3.6–5.5). PFS was significantly longer in the BRCA-mutant subgroup (hazard ratio 0.27, 95% CI 0.16–0.44, $p < 0.0001$) and LOH high subgroup (hazard ratio 0.62, 0.42–0.90, $p = 0.011$) than in the LOH low subgroup. The ORR by RECIST were: BRCA-mutant (80%), LOH high (29%) and LOH low (10%). 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. The median duration of response (months; 95% CI) was longer in the BRCA-mutant (9.2; 6.4–12.9) and LOH high (10.8; 5.7–NR) groups compared with the LOH low group (5.6; 4.6–8.5).

The ARIEL2 part 2 included high grade serous ovarian cancer (HGSOC) platinum-sensitive, platinum-resistant and platinum-refractory patients. A secondary analysis of the population of ARIEL 2 part 2 with germline or somatic BRCA mutation was performed to assess ORR, disease control rate and PFS and to determine the effect of platinum sensitivity status and prior lines of chemotherapy on these endpoints. A total of 134 patients were stratified in four groups: platinum-sensitive with platinum as immediate prior treatment ($n = 57/42.5\%$), platinum-sensitive with nonplatinum therapy as an immediate prior treatment ($n = 14/10.4\%$), platinum-resistant ($n = 49/36.6\%$) and platinum-refractory ($n = 14/10.4\%$). There was no difference in PFS between germline and somatic BRCA mutations in the platinum-sensitive with platinum therapy as an immediate therapy: 12.8 and 12.7 months, respectively. The results are summarized in Table 1.[31] The genomic molecular signature established in part 1 will be prospectively applied to part 2. Completed part 2 data are not yet available.

In a review of the safety and efficacy of rucaparib, the US Food and Drug Administration (FDA) approved rucaparib to treat women with advanced

Table 1. Effect of platinum sensitivity status in efficacy and PFS in the ARIEL 2 population with germline or somatic *BRCA* mutation.

Platinum status	ORR % (95% CI)	Disease control rate % (95% CI)	PFS, months (95% CI)
Platinum sensitive ($n = 57$) (Immediate prior treatment = platinum therapy)	70 (57–82)	81 (68–90)	12.7 (9.0–14.7)
Platinum sensitive ($n = 14$) (Immediate prior treatment = nonplatinum-based therapy)	43 (18–71)	57 (29–82)	7.4 (3.7–11.4)
Platinum resistant ($n = 49$)	25 (13–39)	39 (25–54)	7.3 (5.5–7.7)
Platinum refractory ($n = 14$)	0	29 (8–58)	5.0 (1.9–5.7)

CI, confidence interval; ORR, objective response rate; PFS, progression-free survival.

ovarian cancer who have already been treated with at least two chemotherapies and have a *BRCA1* or *BRCA2* mutation identified by an approved companion diagnostic test. The agency also approved the FoundationFocus CDxBRCA (Cambridge, MA, USA) test to detect *BRCA* alterations on 19 December 2016 associated with the use of rucaparib.[32]

Maintenance

The findings of ARIEL 2 have been further expanded in the phase III ARIEL 3 trial. This was a randomized, double-blind, placebo-controlled trial that included patients with platinum-sensitive high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma. All patients received at least two previous platinum-based chemotherapy regimens and achieved complete or partial response to their last platinum-based regimen. This trial included 564 patients, who were randomized 2:1 to receive oral rucaparib 600 mg twice daily or placebo in 28-day cycles. Patients were stratified by LOH status, progression-free interval after the penultimate platinum-based regimen, and best response to the most recent platinum-based regimen. In this study, LOH $\geqslant 16\%$ was the discriminant for 'LOH high'. The statistical analytical plan evaluated three sequential cohorts of patients: *BRCA*-mutated (germline or somatic), *BRCA*-wild type with HRD (with LOH high) and intention to treat (ITT) population (*BRCA*-wild type and low LOH or *BRCA*-wild type and indeterminate LOH). The step-down procedure evaluated rucaparib (*versus* placebo) on PFS in the *BRCA*-mutated group first; if this analysis was statistically significant, the *BRCA*-wild type LOH high cohort was added and analyzed; if this analysis was significant, the remaining patient cohort was added and analyzed. This latter analysis, if reached, would assess the entire ITT population. A similar procedure was enacted for the patient-reported outcomes (PROs) as assessed by the FOSI-18.[27]

Of the 564 patients enrolled, 196 patients were *BRCA*-mutated (130 with germline mutation and 56 with somatic), 158 patients were *BRCA*-wild type with LOH high and 210 patients were included in the ITT population (161 patients were *BRCA*-wild type and low LOH and 49 with indeterminate LOH). The median PFS (months; 95% CI) in the *BRCA*-mutant group was 16.6 (13.4–22.9), compared with placebo with 5.4 months [3.4–6.7, (hazard ratio 0.23, 95% CI

0.16–0.34, $p < 0.0001$)]. The benefit of rucaparib in the HRD cohort was similar to the *BRCA*-mutant group, with a PFS of 13.6 (10.9–16.2) *versus* 5.4 months in the placebo [5.1–5.6; 0.32 (0.24–0.42); $p < 0.0001$]. In the ITT (*BRCA*-wild type and low LOH or *BRCA*-wild type and indeterminate LOH), the PFS was 10.8 (8.3–11.4) *versus* 5.4 in the placebo group [5.3–5.5; 0.36 (0.30–0.45); $p < 0.0001$]. All subgroups had a PFS benefit for rucaparib *versus* placebo, irrespective of volume of disease, response to chemotherapy, status of LOH or *BRCA* mutation. The overall survival data are not mature at this point. Most patients in ARIEL 3 ($n = 374/66\%$) had achieved an objective response by RECIST prior to enrolment, however 207 (37%) had measurable disease at the time of randomization and were assessable for objective response in a prespecified exploratory analysis. The ORR in the *BRCA*-mutant group with rucaparib was 38% (95% CI 23–54) *versus* 9% in the placebo group (95% CI 1–28). The ORR in the HRD cohort was also increased with rucaparib (27%; 95% CI 23–54) compared with the placebo group (7%, 95% CI 1–20). Even in the ITT population, there was a benefit in ORR with rucaparib (18%, 95% CI 12–16) *versus* placebo (8%, 95% CI 2–17); however, the majority of responses were accounted for in the previous two subsets. No differences in PROs were discovered between the treatment cohorts in the *BRCA*-mutant group so no further analysis was undertaken.

ARIEL 3 trial validated the next generation sequence HRD assay used in the previous trial. An additional exploratory endpoint was done to assess outcomes in women whose tumors had mutations in non-*BRCA* HRR genes. Overall, deleterious mutations were detected in 43/564 (7.6%) patients. In the rucaparib group with a non-*BRCA* HRD gene mutation ($n = 28$), the most common gene mutations were *RAD51C* ($n = 6$), *RAD51D* ($n = 4$), and *RAD54L* ($n = 3$). Patients with *RAD51C/D*-mutant were associated with rucaparib sensitivity, with only 2 of 10 patients having disease progression and 7 having a PFS duration of $\geqslant 1$ year (median PFS, 16.4 months; range, 5.4–30.4 months).[33]

Use of a HRD score to predict efficacy of PARP inhibitors

Clinical data with PARP inhibitors indicate that there is an ovarian cancer patient population

beyond those with germline *BRCA* mutations that may benefit from treatment with a PARP inhibitor.[34] Deficiency in HR DNA repair leads to loss or duplication of chromosomal regions. Next generation sequencing assays can quantify this genomic instability by measuring the percentage of genome-wide allelic imbalance or LOH, as a surrogate marker for HRD.[35,36] In the phase II and III trials of rucaparib in epithelial ovarian cancer, the HRD signature was chosen based on an association between the extent of LOH in tumor's samples and the clinical benefit from rucaparib treatment.[26,27] Tumor was evaluated for HRR mutation and LOH using the Foundation Medicine T5 next generation sequence assay (Cambridge). One of the main advantages of detecting tumor genomic LOH is that it can identify HRD-positive tumors regardless of the underlying mechanisms, which include both known (i.e. *BRCA* mutations) and unknown genetic and other mechanisms.[23] In the ARIEL2 part 1 trial [ClinicalTrials.gov identifier: NCT01891344], the prespecified cutoff to define LOH high was of 14% or higher.[26] Review of these data enabled optimization of the degree of LOH associated with clinical efficacy and were prospectively defined in ARIEL 3 [ClinicalTrials.gov identifier: NCT01968213] as ≥16%.[27]

However, even in the ITT population of ARIEL 3, a benefit with rucaparib in PFS was seen. The limitation of using a genomic scars it that past signatures may be present and confound the interpretation of clinical results if the tumor became resistant.[37]

Other measures of HRD have been evaluated in prospective trials, including that assessed in the phase III switch maintenance trial of niraparib in women with platinum-sensitive recurrent ovarian cancer response to induction platinum combination therapy (NOVA trial, ClinicalTrials.gov identifier: NCT01847274).[38] In that study, HRD was defined using a composite of factors associated with genomic instability, including LOH, telomeric allelic imbalance and large-scale state transitions (Myriad MyChoice, Salt Lake City, UT, USA).[38] Of note, in the NOVA trial, patients with nongermline *BRCA* mutation were randomized in a cohort that included HRD (defined as somatic *BRCA* mutation and nongermline *BRCA* mutation-associated HRD) and non-HRD genomic assessment. In this study niraparib demonstrated significant improvement over placebo among patients with HRD as assessed by this test.

However, a lesser but statistically significant benefit was seen in the HRD-negative cohort suggesting that these biomarkers may not be sufficiently precise to predict absence of benefit on an individual basis.[38]

The optimal method for the identification of which *BRCA* wildtype cancers are most likely to respond to a PARP inhibitor is still unknown. However, efforts to validate an HRD tool as a predictive biomarker with high sensitivity and specificity is a highly desired goal for future studies. Given the dynamic alterations that occur in the tumor microenvironment in response to intrinsic and extrinsic stress,[39] real-time surveillance tools are likely to be necessary to help clinicians in directing treatment decisions.

Safety and tolerability of rucaparib

Several different PARP inhibitors have been approved in the last few years and although long-term follow up is required for a precise assessment of safety, rucaparib appears to have a manageable toxicity profile. In the phase II part of Study 10, the most common treatment-emergent adverse events (AEs) of grades 3 or 4 were anemia (38.1%), asthenia/fatigue (26.2%) and alanine aminotransferase or aspartate transferase elevations (14.3%). The grade 3 or 4 AEs were managed with treatment modification or supportive care. In the phase 2 ARIEL2 trial, rucaparib displayed a satisfactory safety profile and toxicity similar to Study 10.[26] All patients had at least one treatment-emergent AE and the most frequent grade 3 or greater AEs were anemia or decreased hemoglobin in 22% of patients and elevations in alanine aminotransferase or aspartate aminotransferase in 12% of patients. An integrated analysis of the antitumor activity and safety of Study 10 and ARIEL2 trials revealed that rucaparib has a manageable safety profile.[40]

No new safety signals appeared in the much larger ARIEL 3 trial.[27] Aligned with previous experience and noted as probable class effects, the most common AEs were: nausea (75%), asthenia/fatigue (69%), constipation (37%) and vomiting (37%). Grade 3 or 4 AEs were seen in 56% of patients in the rucaparib group. AEs leading to dose reduction were observed in 55% and 4% of patients in the rucaparib and placebo group, respectively. Treatment interruption due to a treatment-emergent AE was common and occurred in 64% of patients in the rucaparib group and 10% in the

placebo group. However, treatment discontinuation due to a treatment-emergent AE was far lower (13%) and compared with 2% in the placebo group. The most common serious AEs were anemia (4% of patients), pyrexia (2%), vomiting (2%) and small intestinal obstruction (1%).

Considering laboratory abnormalities, decreased hemoglobin concentration (anemia) was the most common AE, occurring in any grade in 37% of patients and in 19% grade 3 or greater. A decline in hemoglobin concentration occurred generally in the first few cycles. Compared with other PARP inhibitors, anemia is a common side effect for this class of drug and it was noticed as grade 3 or greater in 19% of patient using olaparib[41] and in 25.3% of patients using niraparib.[38] Another AE noticed in ARIEL 3 that was seen less frequently with other PARP inhibitors was an increase in alanine aminotransferase or aspartate aminotransferase concentration (grade 3–4: 34% of rucaparib-treated patients *versus* 10% with placebo). These transaminase alterations were transient, self-limiting, and not associated with any parameters of hepatic dysfunction. Grade 1 or 2 creatinine increases were observed within the first few weeks of rucaparib treatment and then stabilized with continued rucaparib treatment.

Rucaparib and others PARP inhibitors

Others PARP inhibitors have also been approved for the treatment of ovarian cancer. Olaparib was the first PARP inhibitor approved by the US FDA. In the US, olaparib was first approved as monotherapy with the capsule formulation for patients with high-grade ovarian carcinoma and germline *BRCA1* or 2 mutation who have received three or more prior chemotherapies on 19 December 2014.[16] The SOLO-2 trial was a phase III study that evaluated olaparib as a maintenance treatment of patients with high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with platinum-sensitive, relapsed, *BRCA*-mutated who had received at least two lines of previous chemotherapy and had an objective response to platinum-based chemotherapy. In this study, the investigator-assessed median PFS was significantly longer in the olaparib arm [19.1 months (95% CI 16.3–25.7)] than with placebo [5.5 months (5.2–5.8); hazard ratio 0.30 (95% CI 0.22–0.41), $p < 0.0001$].[41] The results allowed the approval of olaparib as maintenance therapy on 17 August 2017 in the US and on 16 December 2014 in the European Union. The first

agent to receive US FDA approval as a maintenance therapy in platinum-sensitive recurrent ovarian cancer patients was niraparib (27 March 2017) based on results from the NOVA trial. This phase III, double-blinded, placebo-controlled randomized trial of niraparib monotherapy maintenance showed an increase in PFS in the germline *BRCA* mutation group of 21 months with niraparib *versus* 5.5 months in the placebo group (hazard ratio 0.27, 95% CI 0.17–0.41). The non-*gBRCA* cohort with HRD had also a benefit in PFS of 12.9 months *versus* 3.8 (hazard ratio 0.38, 95% CI 0.24–0.59) as the overall non-*gBRCA* cohort of 9.3 months *versus* 3.9 months (hazard ratio 0.45, 95% CI, 0.34–0.61).[38]

Veliparib is a PARP inhibitor that is not approved but has been evaluated in a phase II trial for the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline *BRCA1* or *BRCA2* mutation. The ORR in platinum-resistant and platinum-sensitive patients was 20% and 35%, respectively.[42] An ongoing placebo-controlled phase III trial in newly diagnosed ovarian cancer patients, which is combining veliparib/placebo and chemotherapy, followed by veliparib/placebo maintenance has recently completed enrolment [ClinicalTrials.gov identifier: NCT 02470585].

Currently, there are no head-to-head trials of PARP inhibitors in the setting of high-grade recurrent platinum-sensitive ovarian cancer. However, it is important to recognize that despite the fairly homogeneous outcomes across these three phase III trials, several design, population, and assessment differences exist. These are summarized in Table 2.

There are still many unanswered questions regarding the use of PARP inhibitors in ovarian cancer, such as the optimal timing and duration of administration of these drugs, the long-term effects of PARP inhibition, how PARP inhibitor resistance develops, whether PARP inhibitors can be used again if previously administered, whether there are combinations that can overcome HR resistance (innate or induced), whether PARP inhibitor response can be augmented in cohorts where they are already known to be clinically active, and how somatic events can be evaluated and addressed in 'real-time'. The answers to these questions will have a profound impact on the broader clinical utility of this class of agent in

Table 2. Differences in methodology in single-agent PARP inhibitors phase III trials in ovarian cancer.

Drug	Clinical trial	Inclusion criteria	Exclusion criteria	Definition of HRD	Assessment of PFS	Schedule of assessment for response
Olaparib	SOLO 2	*gBRCA* 1/2mut	No restriction to tumor size	None	Investigator-assessed	Every 12 w until w 72, then every 24 w until PD
Niraparib	NOVA	*gBRCA* 1/2mut Non-*gBRCA* HRD+/ HRD–	Individual tumor nodule >2 cm or failure of CA125 to drop >90%	Composite of LOH, telomeric allelic imbalance and large-scale state transitions	Blinded independent central review	Every 8 w through cycle 14, then every 12 w until TD
Rucaparib	ARIEL 3	*gBRCA* 1/2mut *sBRCA* 1/2mut *BRCAwt* LOH high/ LOH low/LOH indeterminate	No restriction to tumor size	LOH >16%	Investigator assessed	Every 12 w during treatment (and after TD for any reason other than PD), following clinical symptoms

BRCAwt, wildtype; *gBRCAmut*, germline mutation; HRD, homologous recombination deficiency; HRD+, presence of HRD; HRD–, absence of HRD; LOH, loss of heterozygosity; PD, progressive disease; PFS, progression-free survival; *sBRCAmut*, somatic mutation; TD, treatment discontinuation; w, weeks.

patients with solid tumors. A summary of the results of single-agent trials of PARP inhibitors in ovarian cancer is presented in Table 3.

Future directions and conclusions

To further investigate the activity of rucaparib, additional studies have been designed with the aim to assess the role of rucaparib in different clinical settings. The ARIEL4 is an ongoing phase III trial that will compare the efficacy and safety of rucaparib with chemotherapy (monotherapy platinum or platinum doublet; investigator's choice: carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine) as a treatment for relapsed ovarian, fallopian tube, or primary peritoneal cancer with *BRCA* germline or somatic mutations who have received two or more prior lines of chemotherapy. The physician's choice option allows for platinum-based chemotherapy. The primary outcome is PFS and secondary outcomes are overall survival, safety and tolerability of rucaparib as compared with chemotherapy [ClinicalTrials.gov identifier: NCT02855944].[49] The results of ARIEL 3 and ARIEL 4 will help to further understand the ideal timing of use of rucaparib, as a maintenance or treatment for patients with relapsed disease. Another trial that is expected to begin soon is the ATHENA study, a first-line maintenance treatment trial with four arms (rucaparib in combination with nivolumab, rucaparib,

nivolumab and placebo) in newly diagnosed patients with stage III/IV high-grade ovarian, fallopian tube or primary peritoneal cancer who have completed platinum-based chemotherapy.[50]

Rucaparib has also been evaluated as monotherapy in other solid tumors in different ongoing trials: metastatic castration-resistant prostate cancer (mCRPC) and HRD (TRITON 2, ClinicalTrials.gov identifier: NCT 02952534 and TRITON 3, ClinicalTrials.gov identifier: NCT02975934), metastatic urothelial carcinoma (ATLAS, ClinicalTrials.gov identifier: NCT03397394), pancreatic cancer and a *BRCA* mutation [ClinicalTrials.gov identifier: NCT 02042378], metastatic breast cancer with a *BRCAness* genomic signature (RUBY, ClinicalTrials.gov identifier: NCT 02505048) or with *BRCA* mutation [ClinicalTrials.gov identifier: NCT 00664781], phase I trial with advanced solid tumors with *BRCA* mutation [ClinicalTrials.gov identifier: NCT 01482715]. Furthermore, combination with other drugs are being evaluated. Table 4 shows the ongoing clinical trials of rucaparib in monotherapy in different solid tumors. Rucaparib and temozolomide were studied in a phase II trial for patients with melanoma, where 36 % of patients were progression-free at 6 months.[51] The CheckMate 9KD [ClinicalTrials.gov identifier: NCT03338790] will evaluate the combination of nivolumab and rucaparib in mCRPC. A trial is

Table 3. Clinical trial results for PARP inhibitors in ovarian cancer.

Drug	Clinical trial (NCT)	Phase	Population	Treatment arms	Primary endpoint	Results
Olaparib	SOLO2[41] (NCT 01874353)	III	Platinum-sensitive recurrent HGSOC (*gBRCAmut*)	1. Olaparib 300 mg BID (t) 2. Placebo	PFS	Median PFS 19.1 m (olap) *versus* 5.5 (placebo)
	Study 19[16] (NCT00753545)	II	Platinum-sensitive recurrent HGSOC (*gBRCAmut* and *sBRCAmut*)	1. Olaparib 400 mg BID (c) 2. Placebo	PFS	Median PFS 11.2 m (olap in *gBRCAmut*) *versus* 7.4 m (olap in *BRCAwt*) *versus* 5.5 m (placebo)
	Kaye and colleagues[43] (NCT00628251)	II	Platinum-sensitive recurrent HGSOC (*gBRCAmut* and *sBRCAmut*)	1. Olaparib 400 mg BID (c). 2. Olaparib 200 mg BID (c) 3. PLD 50 mg/m²	PFS	Median PFS: 6.5 m (200), 8.8 m (400), 7.1 m (PLD) $p = 0.66$
	Oza and colleagues[44] (NCT01081951)	II	Platinum-sensitive recurrent HGSOC (*gBRCAmut* and *sBRCAmut*)	1. Olaparib (200 mg BID, d1–10/21) (c). paclitaxel (175 mg/m² iv, d1) Carboplatin (AUC4 iv, d1), olaparib 400 BID maintenance (c) 2. Carboplatin AUC6, Pac 175 mg/m²	PFS	Median PFS: 12.2 (olap), 9.6 m (no olap) $p = 0.0012$
	Liu and colleagues[45] (NCT01116648)	II	Platinum-sensitive recurrent HGSOC (*gBRCAmut* and sBRCAmut)	1. Cediranib 30 mg daily and olaparib 200 mg BID (c). (ced/olap) 2. Olaparib 400 mg BID (olap) (c).	PFS	Median PFS 17.7 m (ced/olap) *versus* 9 m (olap). For *BRCAmut* pts 19.4 *versus* 16.5 m. For *BRCAwt*/ unknown 16.5 *versus* 5.7 m
	Kaufman and colleagues[46] (NCT01078662)	II	Advanced tumors with *gBRCAmut*	1. Olaparib 400 mg BID (c).	ORR	Median ORR: 26.2%, ovarian cancer: 31%.
	Gelmon and colleagues[47] (NCT00679783)	II	Recurrent HGSOC and triple negative breast cancer	1. Olaparib 400 mg BID (c).	ORR	Ovarian cancer cohort: ORR 41% *gBRCAmut*, 24% *BRCAwt*
Niraparib	NOVA[38] (NCT01847274)	III	Platinum-sensitive recurrent HGSOC *gBRCAmut, BRCA* HRD+ (includes *sBRCAmut* and LOH high, ITT)	1. Niraparib 300 mg 2. Placebo	PFS	Median PFS: 21 m (*gBRCAmut*) *versus* 12.9 m (*BRCAwt* HRD+) *versus* 9.3 m (overall non-*gBRCA*)

Table 3. (Continued)

Drug	Clinical trial (NCT)	Phase	Population	Treatment arms	Primary endpoint	Results
Rucaparib	Study 10[25]	I/II	Platinum-sensitive recurrent HGSOC *gBRCAmut* (phase II part)	1. Rucaparib 600 mg BID (phase II dose)	ORR	Median ORR: 59.5%
	ARIEL 2 part 1[26] (NCT01891344)	II	Platinum-sensitive recurrent HGSOC (*BRCAmut, BRCAwt* LOH high, *BRCAwt* LOH low, ITT)	1. Rucaparib 600 mg BID	PFS	Median PFS 12.8 m (*BRCAmut*) *versus* 5.7 m (*BRCAwt* LOH high) *versus* 5.2 m (*BRCAwt* LOH low)
	ARIEL 3[27] (NCT01968213)	III	Platinum-sensitive recurrent HGSOC (*BRCAmut, wBRCA* HRD+, *BRCA* ITT)	1. Rucaparib 600 mg BID 2. Placebo	PFS	Median PFS 16.6 m (*BRCAmut*) *versus* 13.6 m (*BRCA* HRD+) *versus* 10.8 m (*BRCA* ITT)
Veliparib	Coleman and colleagues[42] (NCT 02470585)	II	Recurrent HGSOC (*gBRCA*)	1. Veliparib 400 mg BID	PFS	Median PFS 8.18
	Kummar and colleagues[48] (NCT01306032)	II	Recurrent HGSOC (*gBRCA* and *sBRCA*)	1. Oral cyclophosphamide 50 mg daily and veliparib 60 mg daily 2. Oral cyclophosphamide	ORR	No improvement in ORR (3 PR combination arm, 6 PR in cyclophosphamide arm)

BID, twice daily; *BRCAwt, BRCA*-wild type; c, capsules; ced, cediranib; *gBRCA*mut, germline *BRCA* mutation; HGSOC, high grade serous ovarian cancer; HRD, homologous recombination deficiency; HRD+, presence of HRD; HRD–, absence of HRD; iv, intravenous; ITT, intention to treat population; LOH, loss of heterozygosity; m, months; NCT, National Clinical Trials; olap, olaparib; ORR, objective response rate; PFS, progression-free survival; PLD, liposomal doxorubicin; PR, partial response; *sBRCA*, somatic *BRCA* mutation; t, tablets.

Table 4. Ongoing clinical trials of rucaparib in monotherapy in different solid tumors.

Study	Setting	Phase	Primary endpoints
TRITON 2 (NCT 02952534)	Metastatic castration-resistant prostate cancer and HRD	II	ORR, PSA response
TRITON 3 (NCT 02975934)	Metastatic castration-resistant prostate cancer and HRD	III	Radiographic PFS
ATLAS (NCT03397394)	Metastatic urothelial carcinoma	II	ORR
NCT 02042378	pancreatic cancer and a *BRCA* mutation	II	ORR
RUBY 2 (NCT 02505048)	Metastatic breast cancer with a *BRCA*ness genomic signature	II	Clinical benefit rate
NCT 01482715	Advanced solid tumors with *BRCA* mutation	I	Incidence of grade 3 or 4 AEs and clinical laboratorial abnormalities defined as DLT, PK profile for single dose and at steady state
NCT 03101280	Advanced gynecologic cancers and triple negative breast cancer	Ib	Incidence of AEs, incidence of DLT, recommended phase II dose, number of dose modifications due to AEs

AE, adverse event; DLT, dose-limiting toxicity; HRD, homologous recombination deficiency, NCT, National Clinical Trials; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics parameters; PSA, prostate-specific antigen.

ongoing for rucaparib in combination with atezolizumab for advanced gynecologic cancers and triple negative breast cancer [ClinicalTrials.gov identifier: NCT 03101280]. Future areas of investigation include combination of rucaparib and other targeted therapies, like PI3K inhibitors, Wee1 kinase inhibitors, DNA topoisomerase I inhibitors, and DNA methyltransferase inhibitors, immune checkpoint inhibitors and anti-angiogenics agents.[23,52]

In summary, the use of rucaparib showed an increase in PFS compared with placebo in all patients with ovarian carcinoma who achieved response to platinum-based chemotherapy, with an acceptable safety profile. The approval of this drug in the third-line of platinum-sensitive disease, as also with the companion diagnostic test, represents an important new therapeutic option in the treatment of ovarian cancer. Based on these findings, a new drug application of rucaparib is under review by the US FDA, as a maintenance treatment for women with platinum-sensitive recurrent ovarian cancer following response to induction platinum-based therapy (Prescription Drug User Fee Act date: 6 April 2018). Further evaluation of rucaparib in other disease cohorts and in combination with other agents is warranted. Intensive efforts in the characterization of tumor biomarkers are ongoing, and a systematic approach will likely be necessary to better identify the patients that will better respond to therapy.

Conflict of interest statement
RLC has clinical research funding from Merck, AstraZeneca/Medimmune, Genentech/Roche, Novartis, Clovis Oncology, Abbvie, and Janssen

pharmaceuticals. AKS has research funding from M-Trap, is on SAB for Kiyatec, and holds stock in BioPath. All other authors have no conflicts of interests to declare.

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