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Latest clinical evidence and further development of PARP inhibitors in ovarian cancer

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Running head: PARP inhibitors in ovarian cancer: clinical evidence and further development
**Background:** For several decades, the systemic treatment of ovarian cancer has involved chemotherapy, with the relatively recent addition of anti-angiogenic strategies given with chemotherapy and in the maintenance setting. In the past decade, numerous poly(ADP-ribose) polymerase (PARP)-inhibiting agents have been assessed.

**Design:** We review key trials that have led to the approval of three PARP inhibitors – olaparib, niraparib and rucaparib – as maintenance therapy for platinum-sensitive recurrent ovarian cancer. We discuss the efficacy and safety of these agents in the populations studied in clinical trials. We then provide an overview of the numerous avenues of ongoing research for PARP inhibitors in different treatment settings: as treatment rather than maintenance strategies and in combination with other anti-cancer approaches, including anti-angiogenic and immunotherapeutic agents.

**Results:** Three phase III trials (NOVA, SOLO2 and ARIEL3) demonstrated remarkable improvement in progression-free survival (PFS) with PARP inhibitors given as maintenance therapy in patients with complete or partial response after platinum-based therapy for platinum-sensitive ovarian cancer. Differences in trial design and patient populations influence the conclusions that can be drawn from these trials. Overall survival data are pending and there is a limited experience regarding long-term safety.

**Conclusions:** PARP inhibitors have transformed the management of ovarian cancer and have changed the course of disease for many patients. Although recent approvals are irrespective of BRCA mutation or homologous repair deficiency status, genetic profiles, as well as dosing schedules, tolerability and affordability, may influence patient selection and the setting in which PARP inhibitors are used. The development and evolution of PARP inhibitors continue, with new agents, strategies, combinations and indications under intensive evaluation.

**Key words:** PARP inhibitor, ovarian cancer, olaparib, niraparib, rucaparib, phase III

**Key message:** PARP inhibitors have transformed the treatment of ovarian cancer. We review efficacy and safety demonstrated by three PARP inhibitors (olaparib, niraparib,
rucaparib), including results from three placebo-controlled randomised phase III trials, and discuss ongoing and future avenues of research with PARP inhibition.
**Introduction**

The management of ovarian cancer has improved incrementally for several decades. However, a transforming advance has been the introduction of agents targeting poly(ADP-ribose) polymerase (PARP). We review the latest clinical data supporting use of PARP inhibitors in ovarian cancer and summarise avenues of ongoing and future research.

**Mechanism of action and clinical rationale**

PARP is a key regulator of DNA damage repair. PARP enzymes play a critical role in the repair of single-strand breaks via base-excision repair [1]. In double-strand break repair, PARP contributes to homologous repair and inhibits less-conservative non-homologous and microhomology-mediated end-joining repair. Without PARP, homologous repair is dysfunctional, and less-conservative repair processes dominate.

*BRCA* encodes proteins involved in homologous recombination DNA repair [2]. Tumour cells with *BRCA1/2* mutations have impaired ability to repair double-strand breaks by homologous recombination [2–4], and show a high level of chromosomal instability. Germline or somatic mutations in *BRCA1* or *BRCA2* are present in approximately 20% of patients with newly diagnosed high-grade serous ovarian cancer (HGSOC) [5] and are associated with longer overall survival (OS) and sensitivity to platinum-based therapy [6, 7].

PARP inhibitors exploit synthetic lethality, a concept by which functional loss of two genes results in cell death, even though the cell remains viable with functional loss of either gene alone. Currently four mechanisms for PARP inhibition are proposed: inhibiting base-excision repair; trapping PARP on damaged DNA [8], thus interfering with the catalytic cycle of PARP, hindering DNA repair and promoting double-strand breaks; disrupting *BRCA1* recruitment to damaged DNA; and activating non-homologous end-joining, which is more prone to errors. These mechanisms are described in detail elsewhere [9].

In preclinical studies, *in vitro* sensitivity to PARP inhibitors was substantially increased in *BRCA1/2*-mutated models [2]. A subsequent phase I study of olaparib provided clinical proof of concept: PARP inhibitors exploited synthetic lethality in *BRCA1/2*-mutant
tumours [10]. Clinical benefit from PARP inhibitors is not limited to BRCA-mutated populations [11], with activity observed in the entire population of HGSOC; however, the greatest benefit is seen in BRCA-mutated populations. In BRCA-wildtype populations, the clinical efficacy of PARP inhibitors is more pronounced in patients with homologous recombination deficiency (HRD). HRD occurs in approximately half of all patients with newly diagnosed HGSOC [5], and correlates with sensitivity to platinum agents and DNA repair inhibitors [12].

Clinical results

Olaparib

The first PARP inhibitor to become available in clinical practice was olaparib (Lynparza, AstraZeneca). In Europe, olaparib was initially approved as maintenance treatment for patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) HGSOC in complete or partial response (CR/PR) to platinum-based chemotherapy [13]. Approval was based on the results of Study 19 (NCT00753545) [14], a double-blind, placebo-controlled, randomised phase II trial in 265 patients with platinum-sensitive recurrent serous ovarian cancer who had received ≥2 platinum-based chemotherapy regimens and responded to their latest platinum regimen. Patients were randomised to maintenance olaparib capsules (400 mg twice daily [bid]) or placebo.

Progression-free survival (PFS; primary end point) was significantly improved with maintenance olaparib compared with placebo. The hazard ratio (HR) was 0.35 in unselected patients (Table 1) [14]. Preplanned retrospective analyses according to BRCA mutation status demonstrated that in 136 patients with germline or somatic BRCA mutation (representing approximately half of the intent-to-treat [ITT] population), the PFS HR was 0.18 (median PFS 11.2 versus 4.3 months with maintenance olaparib versus placebo, respectively) [18]. The protocol-specified final OS results after 78 months’ median follow-up showed a HR of 0.73 (95% confidence interval [CI] 0.55–0.95) in the ITT population (N = 265) and 0.62 (95% CI 0.42–0.93) in the BRCA-mutated subgroup [19]. As several interim
analyses of OS were performed during the conduct and follow-up of the study, the OS result was not considered to be statistically significant. Maintenance olaparib showed no adverse impact on health-related quality of life (QoL) [20].

In a second randomised phase II trial, Study 41 (NCT01081951), PFS was improved with olaparib given in combination with chemotherapy and then as maintenance therapy compared with chemotherapy alone [21]. However, this strategy was not pursued as the benefit appeared to be driven by the maintenance phase and doses of both carboplatin and olaparib were reduced in the concomitant phase because of overlapping toxicity.

In the US, olaparib initially gained accelerated approval from the Food and Drug Administration (FDA) as monotherapy for patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer (detected by BRACAnalysis, Myriad Genetics) treated with ≥3 prior lines of chemotherapy [22]. FDA approval was based on the 34% response rate and 7.9-month median duration of response observed in a subset of 137 heavily pretreated patients [23] treated in the single-arm phase II Study 42 (NCT01078662) in measurable germline BRCA-mutated ovarian cancer [24].

More recently, results of the confirmatory randomised phase III SOLO2 trial (NCT01874353) in BRCA-mutated platinum-sensitive recurrent ovarian cancer (PSROC) were published [15]. The study enrolled 295 patients who had received ≥2 lines of chemotherapy and had a continued CR/PR to the most recent platinum-based chemotherapy. Although patients with somatic BRCA mutations could be included, all had germline BRCA-mutated relapsed HGSOC or high-grade endometrioid cancer. Patients were randomised 2:1 to either olaparib 300 mg or placebo tablets bid as maintenance therapy. The primary end point was investigator-assessed PFS by Response Evaluation Criteria in Solid Tumours (RECIST).

Maintenance olaparib significantly improved investigator-assessed PFS compared with placebo in patients with BRCA-mutated ovarian cancer (HR 0.30) (Table 1). Median PFS was 19.1 months with olaparib versus 5.5 months with placebo. In a sensitivity analysis according to blinded independent central radiological (BICR) review, the PFS HR was 0.25
(95% CI 0.18–0.35); median PFS was 30.2 months with olaparib versus 5.5 months with placebo. However this analysis was biased because: (1) this was a sensitivity analysis; (2) nearly 25% (26 of 107) of the PFS events in the olaparib group captured in the primary analysis were excluded, without explanation; and (3) the impact of clinical progression was excluded.

The primary end point results were supported by significant improvements in the secondary end points of time to first subsequent therapy/death (TFST; HR 0.28, 95% CI 0.21–0.38; median 27.9 versus 7.1 months), time to second progression (PFS2; HR 0.50, 95% CI 0.34–0.72; median not reached versus 18.4 months) and time to second subsequent therapy/death (HR 0.37, 95% CI 0.26–0.53; median not reached versus 18.2 months).

Subgroup analyses according to the stratification factor response to previous platinum therapy (CR or PR) showed a similar magnitude of olaparib effect on PFS (HR 0.26 for patients in CR, HR 0.37 for patients in PR) [25]. The same pattern was observed for PFS2. Notably, some patients with residual disease at randomisation subsequently achieved a CR during maintenance therapy. Further subgroup analyses showed improved PFS irrespective of the number of lines of prior platinum-based chemotherapy [26].

In a maintenance setting, it is important that any efficacy gain is achieved without impairing QoL. In SOLO2, analyses showed no detrimental effect of olaparib on patient-reported outcomes over time as assessed by the Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O) Trial Outcome Index score [27]. Furthermore, quality-adjusted PFS was significantly longer with olaparib than placebo (14.0 versus 7.3 months, respectively; \( P < 0.0001 \)). Time without symptoms of disease or toxicity (TWiST) analysis showed a significant benefit from olaparib versus placebo (13.5 versus 7.2 months, respectively; \( P < 0.0001 \)).

In summary, the SOLO2 results (tablet formulation) provide confirmation of the Study 19 BRCA-mutated subset results. Surprisingly, US approval was expanded to include the tablet formulation as maintenance therapy for women with recurrent epithelial ovarian cancer in CR/PR to platinum-based chemotherapy irrespective of BRCA status [28]. Approval was
granted without further data on the BRCA-wildtype population. The accelerated approval of monotherapy beyond third line for BRCA-mutated ovarian cancer was converted to full approval at the same time. In Europe, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has given a similar positive opinion for the tablet preparation and the inclusion of patients with high-grade recurrent ovarian cancer responding to platinum-based chemotherapy, irrespective of BRCA status.

**Niraparib**

Niraparib (Zejula; Tesaro), an oral PARP1/2 inhibitor, was approved by both the FDA and the EMA as maintenance therapy for women with recurrent epithelial ovarian cancer in CR/PR to platinum-based chemotherapy [29, 30]. Approval was based on results of the randomised phase III ENGOT-OV16/NOVA trial (NCT01847274) [16], which included 553 patients with recurrent ovarian cancer with CR/PR to their most recent platinum-based chemotherapy. For inclusion, patients had to have: received ≥2 prior platinum-based regimens; achieved a CR/PR and PFS of ≥6 months after completing their penultimate platinum-based therapy before study therapy; achieved a CR/PR to their most recent chemotherapy, which must have included a platinum agent; and have no measurable disease >2 cm. The trial included two independent cohorts: a germline BRCA-mutated cohort (N=203) and a non-germline BRCA-mutated cohort (N=350) as determined by BRACAnalysis testing. Patients were randomised 2:1 to either niraparib 300 mg or placebo once daily until disease progression. Crossover was not permitted. There were three primary PFS end points: PFS in the germline BRCA-mutated cohort; PFS in the non-germline BRCA-mutated cohort; and PFS in the HRD-positive subgroup within the non-germline BRCA-mutated cohort. HRD status was determined using the myChoice HRD™ test (Myriad Genetics). The statistical design dictated hierarchical testing, whereby PFS was compared simultaneously in the germline BRCA-mutated cohort and the HRD-positive subgroup of the non-germline BRCA-mutated cohort. If results were significant in the HRD-positive
subgroup, PFS was to be compared between treatment arms in the entire non-germline 
BRCA-mutated cohort.

PFS was significantly improved with niraparib compared with placebo maintenance therapy. The magnitude of treatment effect appeared greater in patients with germline BRCA mutation or HRD-positive status: the PFS HR was 0.27 in the BRCA-mutant cohort, 0.38 in the HRD-positive subgroup of the non-germline BRCA-mutated cohort and 0.45 in the overall non-germline BRCA-mutated cohort (Table 1). Nevertheless, the ENGOT-OV16/NOVA trial demonstrated clinical benefit from niraparib in the whole population of patients with PSROC responding to platinum-based therapy, regardless of BRCA or HRD status.

Results for secondary end points (chemotherapy-free interval, TFST, PFS2) demonstrated significant improvements with niraparib versus placebo. Additional analyses showed that the magnitude of niraparib treatment effect in patients with a PR (rather than CR) to their most recent platinum regimen was at least as large as in the overall population (germline BRCA-mutated population: PFS HR 0.24 [95% CI 0.13–0.44] in patients with PR versus 0.27 [0.17–0.41] overall; non-germline BRCA-mutated population: 0.35 [0.23–0.53] in PR patients versus 0.45 [0.34–0.61] overall) [31]. Further subgroup analyses suggested similar efficacy in patients aged <70 versus ≥70 years in both the germline BRCA-mutated and the non-germline BRCA-mutated populations, although the small sample sizes limit interpretation [32].

QoL scores were similar between treatment arms, indicating that niraparib did not adversely affect patients’ QoL during treatment [33]. There was a trend towards less pain in niraparib-treated than placebo-treated patients. The increase in nausea was transient and abated over time. Other symptoms of the FACT-O Symptom Index (FOSI) scale showed similar scores between the two treatment groups. Haematological adverse events (AEs) had no detrimental effect on QoL.
In a recent update [34], the estimated probability of PFS at 2 years in niraparib-treated patients in the germline *BRCA*-mutated cohort was 42%. There was no difference in outcomes with subsequent therapy.

**Rucaparib**

A third PARP inhibitor, rucaparib (Rubraca; Clovis Oncology), gained accelerated FDA approval in December 2016 for the treatment of germline and/or somatic *BRCA*-mutated advanced ovarian cancer in women who have previously received ≥2 chemotherapy lines [35]. Approval was based on results of two single-arm studies: ARIEL2 (NCT01891344) and Study 10 (NCT01482715). Study 10 showed robust anti-tumour activity of rucaparib 600 mg bid in patients with germline *BRCA*-mutated PSROC [36]. Part 1 of the ARIEL2 study established a tumour-based next-generation sequencing (NGS) HRD assay to quantify loss of heterozygosity (LOH) and potentially identify patients more likely to respond to rucaparib [37]. However, in this single-arm study it was impossible to determine whether high LOH is predictive for rucaparib efficacy or simply a prognostic marker.

In an integrated analysis of patients receiving rucaparib 600 mg bid in Study 10 and ARIEL2, efficacy was evaluated in 106 patients with high-grade ovarian cancer with a deleterious germline or somatic *BRCA1/2* mutation previously treated with ≥2 chemotherapy lines including ≥2 platinum-based regimens [38]. The investigator-assessed confirmed objective response rate was 54%, median duration of response was 9.2 months and median PFS was 10.0 months. However, these are results from non-randomised trials; more robust efficacy evaluation was undertaken in the randomised phase III ARIEL3 trial in platinum-sensitive high-grade serous or endometrioid ovarian cancer [17]. Patients who had received ≥2 prior platinum regimens, were sensitive to their penultimate platinum regimen and had a CR/PR to their most recent platinum-based regimen were randomised 2:1 to receive either rucaparib or placebo maintenance therapy. Three populations were defined for step-down analysis of the primary end point, PFS: tumour *BRCA*-mutant (germline or somatic); HRD-
positive (including \(BRCA\) wildtype with high \([\geq 16\%]\) genomic LOH as defined by Foundation Medicine’s T5 NGS assay); and the ITT (all-comer) population.

PFS was significantly improved with rucaparib versus placebo in all three populations, although the most robust clinical outcomes were seen in the \(BRCA\)-mutated subgroup (Table 1) [17]. BICR results were supportive. ARIEL3 confirmed the findings of ENGOT-OV16/NOVA, showing clinical benefit from PARP inhibition in the entire population of PSROC responding to platinum-based therapy.

Exploratory analyses showed a PFS benefit in 161 patients with \(BRCA\)-wildtype LOH-low tumours (HR 0.58 [95% CI 0.40–0.85] by investigator assessment; 0.47 [95% CI 0.31–0.71] by BICR review). PFS improvement was seen in all subgroups according to clinical stratification factors (CR versus PR to last platinum agent, progression within 6–12 versus \(\geq 12\) months of penultimate platinum agent). Within the \(BRCA\)-mutated population, results were consistent for the germline and somatic populations. Among patients with measurable residual disease at baseline, many had further reduction in tumour burden with maintenance rucaparib. Confirmed RECIST responses were achieved in 38% of rucaparib-treated versus 9% of placebo-treated patients with measurable disease in the \(BRCA\)-mutated cohort (18% versus 0% CR, respectively), 27% versus 7%, respectively, in the HRD cohort (12% versus 0% CR) and 18% versus 8%, respectively, in the ITT population (7% versus 2% CR).

There was no significant difference between treatment arms in time to worsening of disease-related physical symptoms (disease-related symptoms–physical subscale of FOSI-18; secondary end point). Based on results from ARIEL3, the FDA approved rucaparib as maintenance therapy for women with recurrent epithelial ovarian cancer in CR/PR to platinum-based chemotherapy [39].

**Summary of efficacy**

The three randomised phase III trials (NOVA, SOLO2, ARIEL3) confirm that PARP inhibition is a highly effective maintenance strategy for PSROC, and suggest that the greatest benefit
is seen in \textit{BRCA}-mutated populations. Interestingly, exploratory analyses of all three trials suggested additional anti-tumour activity in patients with measurable disease at the start of maintenance therapy \cite{17, 25, 31}, suggesting a role as definitive treatment as well as maintenance therapy.

\textbf{Safety}

Safety data from all three randomised phase III trials indicate that these oral maintenance therapies are well tolerated but not without toxicity. In all three trials, grade $\geq 3$ AEs and AEs leading to treatment interruption, dose reduction or treatment discontinuation were substantially more common with maintenance PARP inhibitors than placebo (Supplementary Table S1). Many patients require dose tailoring to an individually tolerable dose, after which treatment can be continued for extended durations without dose-limiting toxicities. For example, in Study 19, 15 patients (11\%) continued on olaparib treatment for $\geq 6$ years \cite{19}.

Class effects of the PARP inhibitors include grade $\geq 3$ anaemia, grade $\geq 3$ fatigue and all-grade nausea and vomiting \cite{15–17}. However, safety profiles also show some differences between agents (Supplementary Table S2). The safety profile of the approved olaparib capsule formation was well characterised in Studies 19 and 42: the most common AEs were fatigue/asthenia, nausea, vomiting, diarrhoea and anaemia, typically occurring at grade 1 or 2 intensity \cite{14, 24}. The most common grade $\geq 3$ AEs were fatigue/asthenia, anaemia and abdominal pain. An analysis of 398 patients treated in eight prospective trials suggested that the tolerability of olaparib capsules was similar in patients aged $\geq 65$ and $< 65$ years \cite{40}. Tolerability of the tablet formulation used in SOLO2 appears to be similar to that of the capsule formulation \cite{15}. The most common AEs were anaemia, fatigue/asthenia, nausea and vomiting. Except for anaemia, most AEs were low grade. Grade $\geq 3$ neutropenia occurred in 5\% of patients and there was no grade $\geq 3$ thrombocytopenia.

The most common grade 3/4 AEs with niraparib in NOVA were laboratory abnormalities (e.g. thrombocytopenia, anaemia, neutropenia), fatigue and hypertension \cite{16}. Subgroup analyses in patients aged $<70$ versus $\geq 70$ years raised no specific safety
concerns for older niraparib-treated patients, with no major differences in the proportions of patients requiring dose reduction, interruption or discontinuation [32]. All-grade dyspnoea and decreased appetite were more common in older patients, whereas grade ≥3 anaemia was less common. However, whether these results from a highly selected clinical trial population apply to patients in broader everyday clinical practice or the real-world setting remains to be seen. Additional exploratory analyses suggest an increased risk of grade 3/4 thrombocytopenia in women weighing <77 kg or with baseline platelet count <150 000/µL [41].

Results from the ARIEL3 trial suggest a safety profile for rucaparib consistent with that reported in the integrated analysis of Study 10 and ARIEL2 [38]. In addition to the class effects of PARP inhibitors, grade 3 liver enzyme elevations were reported in 10% of patients. However, there were no grade 4 episodes and liver enzyme elevations were generally transient, self-limiting and not associated with other signs of liver toxicity [17].

Observations from early olaparib studies raised some concerns about a potentially increased incidence of myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML), leading to a specific warning about these events [13]. However, in SOLO2, MDS and AML occurred in 2% of olaparib-treated versus 4% of placebo-treated patients [15]. Likewise, in NOVA, MDS was reported in five (1.4%) niraparib-treated patients versus one (0.6%) placebo-treated patient [16]. There was only one case of AML (placebo-treated patient). In ARIEL3, MDS/AML occurred in three (1%) rucaparib-treated patients and no patients in the placebo arm [17]. The initial concerns about these effects may simply reflect high prior exposure to carboplatin, which is associated with increased risk of leukaemia.

In summary, as a class, the PARP inhibitors are tolerable for long periods in many patients. In all three phase III trials, only 10–15% of patients discontinued therapy because of AEs. However, it has been suggested that peak toxicity may not be the most appropriate way to describe safety, and the duration of toxicity and manageability of AEs (i.e. the pattern after individual dose adjustment) may be more important.
Other PARP inhibitors

Other PARP inhibitors in clinical development include veliparib [42], currently undergoing phase III evaluation combined with carboplatin and paclitaxel and continued as a single agent in 1100 patients (NCT02470585) and the new-generation PARP inhibitor talazoparib [43], which appears to be far more potent than either rucaparib or olaparib in preclinical studies [44].

Patient selection for PARP inhibition

Germline BRCA status testing rapidly became standard of care in Europe with the introduction of olaparib in a population defined by its BRCA mutation status. However, results from the NOVA and ARIEL3 trials, and a broader indication for all three agents irrespective of BRCA or HRD status, suggest diminishing importance of BRCA mutation as a predictive marker for deciding on PARP therapy, although BRCA mutation remains the most important biomarker predicting response to treatment. Furthermore, the reversion of BRCA mutations after resistance may make HRD testing of genomic instability less reliable [45]. Consequently there may be a shift in the role of testing: rather than determining eligibility for PARP inhibitors, BRCA testing may provide an indication of the likely magnitude of benefit from treatment and perhaps influence the sequence of PARP inhibition versus other strategies.

Future directions for PARP inhibition

Results are pending from two placebo-controlled randomised phase III trials evaluating single-agent maintenance PARP inhibitors in patients with a CR/PR to front-line platinum-based therapy: the PRIMA trial (NCT02655016; niraparib) and the SOLO1 trial (NCT01844986; olaparib in patients with deleterious BRCA mutations). Two additional randomised phase III trials are comparing PARP inhibitors with chemotherapy in the ‘treatment’ rather than maintenance setting: ARIEL4 (NCT02855944; rucaparib) and SOLO3
(NCT02282020; olaparib). These trials are summarised in Table 2 together with other randomised trials of PARP inhibitors.

An important unanswered question is whether the effect of PARP inhibitors differs between the maintenance and treatment settings. As described above, in SOLO2, NOVA and ARIEL3, there was no evidence of reduced PFS benefit in patients in PR (versus CR) at the start of study therapy. To date, there has been no comparison of chemotherapy followed by maintenance PARP inhibitor versus initial PARP inhibitor therapy followed by chemotherapy. Furthermore, there is little information on the effect of PARP inhibitor re-treatment with, although the phase IIIIB OrEO/ENGOT Ov-38 trial (NCT03106987) aims to address this question.

Generally, combining established PARP inhibitors with chemotherapy resulted in increased toxicity in early studies. However, several ongoing studies are evaluating PARP inhibitors combined with other anti-cancer strategies. Increased DNA damage induced by PARP inhibitors may increase genomic instability and enhance the efficacy of radiation therapy. Trials are underway to test this hypothesis in head and neck and cervical cancers. Another approach is to combine PARP inhibitors with anti-angiogenic agents. Hypoxia induced by anti-angiogenic agents may (re)create homologous recombination repair deficiency, thus enhancing the effect of PARP inhibition. A proof-of-concept trial combining olaparib with cediranib showed promise [46] and several randomised trials are ongoing, including PAOLA-1, ICON9 and AVANOVA (Table 2). There is also a rationale for combining PARP inhibitors with cancer immunotherapy. Ovarian cancer is strongly immunogenic and BRCA1/2-mutated and HRD tumours may have more neoantigens than homologous recombination-proficient tumours [48]. Data for single-agent immunotherapy are quite limited [49–51], but preclinical data suggest crosstalk between PARP inhibitors and tumour-associated immunosuppression, and upregulation of programmed cell death 1 ligand 1 (PD-L1) expression by PARP inhibitors [52], supporting evaluation of combination strategies. Phase I results have led to further evaluation of olaparib combined with durvalumab [53].
However, identifying the optimal stage of disease in which to test these combinations is not without challenges.

**Conclusions**

Maintenance therapy with a PARP inhibitor in the recurrent setting provides the longest period without disease symptoms compared with no maintenance, with manageable treatment-related toxicities. PARP inhibitors are changing the course of disease in ovarian cancer, as illustrated by treatment for ≥6 years in 11% of olaparib-treated patients in study 19 [19]. Delaying the need to initiate further chemotherapy (TFST) may be clinically valuable, perhaps indicating that PARP inhibitors modify the rate of disease progression. Given the wealth of available data supporting the use of PARP inhibitors in PSROC, a major question facing oncologists is which agent to use in which clinical situation? An important factor when considering the evidence is trial design. For all three agents, the magnitude of benefit in *BRCA*-mutated populations seems similar. However, there are currently no phase III data supporting the use of olaparib in patients with *BRCA*-wildtype tumours, despite FDA approval irrespective of *BRCA* mutation status. Convenience of the dosing schedule may be important for patients: once-daily dosing with niraparib is likely to be preferable to twice-daily dosing with olaparib. With all three agents, side effects are generally manageable with dose titration and do not seem to have a negative impact on patients.

If all PARP inhibitors are equally efficacious, cost is likely to be among the most important considerations for healthcare providers, particularly if patients continue therapy for prolonged periods. Treatment duration provides an indication of the long-term tolerability of therapy. Currently, only olaparib has extensive data supporting long-term safety. Overall, the incidences of grade 3/4 AEs and AEs leading to treatment discontinuation are low with all three agents.

The successful development of PARP inhibitors in ovarian cancer is being followed in other tumour types, particularly those in which *BRCA* mutations and HRD appear to play an important role, such as breast and prostate cancer. In the recently published randomised
phase III OlympiAD trial in germline BRCA-mutated HER2-negative metastatic breast cancer, olaparib tablets as first-, second- or third-line therapy demonstrated significantly superior PFS to chemotherapy [54]. These results led to an expansion of the FDA approval of olaparib to include BRCA-mutated metastatic breast cancer. Even more recently, results from the EMBRACA phase III trial in pretreated germline BRCA1/2-positive locally advanced or metastatic breast cancer demonstrated significantly improved PFS with talazoparib compared with the physician’s choice of chemotherapy, accompanied by significantly improved objective response rate and significantly delayed time to deterioration of global health status/QoL [55]. The major contribution of PARP inhibition to ovarian cancer may be only the first chapter of this exciting story.

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<td>Rucaparib</td>
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<td>BRCA-mutated</td>
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<td>0.23 (0.16–0.34); P &lt; 0.0001</td>
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<td></td>
<td>HRD-positive</td>
<td>236</td>
<td>0.32 (0.24–0.42); P &lt; 0.0001</td>
<td>13.6 5.4</td>
</tr>
<tr>
<td></td>
<td>ITT</td>
<td>189</td>
<td>0.36 (0.30–0.45)</td>
<td>10.8</td>
<td>5.4</td>
</tr>
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</tbody>
</table>

**Randomised phase II trial**

<table>
<thead>
<tr>
<th>Olaparib</th>
<th>Study 19 [14, 18]</th>
<th>ITT</th>
<th>136</th>
<th>129</th>
<th>0.35 (0.25–0.49)</th>
<th>8.4</th>
<th>4.8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

BRCA-mutated (germline or somatic, retrospective)

<table>
<thead>
<tr>
<th></th>
<th>0.18 (0.10–0.31)</th>
<th>11.2</th>
<th>4.3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.
<table>
<thead>
<tr>
<th>Treatment setting</th>
<th>Trial</th>
<th>PARP inhibitor</th>
<th>Combination partner</th>
<th>No. of patients</th>
<th>Primary end point</th>
<th>Trial design</th>
<th>Enrolment start/estimated primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance after front-line therapy</td>
<td></td>
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</tr>
<tr>
<td>Newly diagnosed BRCA-mutated stage III/IV with CR/PR after front-line platinum</td>
<td>SOLO1 (NCT01844986)</td>
<td>Olaparib</td>
<td>–</td>
<td>450</td>
<td>PFS (investigator-assessed)</td>
<td>Double-blind placebo-controlled randomised phase III maintenance</td>
<td>Aug 2013/May 2018</td>
</tr>
<tr>
<td>Newly diagnosed stage III/IV with</td>
<td>ENGOT-OV26/PRIMA</td>
<td>Niraparib</td>
<td>–</td>
<td>468</td>
<td>PFS</td>
<td>Double-blind placebo-controlled</td>
<td>April 2016/Aug 2019</td>
</tr>
</tbody>
</table>
## Maintenance therapy in recurrent disease

<p>| BRCA-mutated high-grade serous/endometrioid, CR/PR to platinum, ≥2 prior lines of chemotherapy | ENGOT-OV21/SOLO2 (NCT01874353) | Olaparib (tablets) | 295 | PFS (investigator assessed) | Double-blind placebo-controlled randomised phase III maintenance trial | Sep 2013/Sep 2016 |
| PSROC, ≥2 prior platinum-containing regimens | Study 19 (NCT00753545) | Olaparib (capsules) | 265 | PFS | Double-blind placebo-controlled randomised phase II maintenance | Aug 2008/Jun 2010 |
| Germline BRCA-mutated or high-grade | ENGOT-OV16/NOVA | Niraparib | 597 | PFS | Double-blind placebo-controlled | Jun 2013/Jun 2016 |</p>
<table>
<thead>
<tr>
<th>Grade and PSROC</th>
<th>Trial Name</th>
<th>Drug combo</th>
<th>Patients</th>
<th>End Point</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade serous/endometrioid PSROC, ≥2 prior platinum regimens</td>
<td>ARIEL3</td>
<td>Rucaparib –</td>
<td>540</td>
<td>PFS (investigator assessed)</td>
<td>Double-blind placebo-controlled phase III trial as switch maintenance after platinum</td>
</tr>
<tr>
<td>PSROC with CR/PR to second-line platinum-based chemotherapy</td>
<td>ICON9</td>
<td>Olaparib Cediranib</td>
<td>618</td>
<td>PFS and OS</td>
<td>Open-label randomised phase III maintenance trial</td>
</tr>
<tr>
<td>Definitive treatment setting</td>
<td>SOLO3</td>
<td>Olaparib –</td>
<td>411</td>
<td>PFS (blinded independent central review)</td>
<td>Open-label randomised phase III trial of olaparib vs physician’s chosen single-agent non-platinum chemotherapy</td>
</tr>
<tr>
<td>Recurrent ovarian cancer, ≥1 prior line of chemotherapy</td>
<td>CLIO</td>
<td>Olaparib –</td>
<td>160</td>
<td>ORR</td>
<td>Open-label randomised 2-arm trial of olaparib vs</td>
</tr>
<tr>
<td>Study</td>
<td>BRCA1/2-mutated</td>
<td>ICEBERG3 (NCT00628251)</td>
<td>Olaparib –</td>
<td>97</td>
<td>PFS</td>
</tr>
<tr>
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</tr>
<tr>
<td>Study</td>
<td>BRCA1/2-mutated</td>
<td>ARIEL4 (NCT02855944)</td>
<td>Rucaparib</td>
<td>345</td>
<td>PFS (investigator assessed)</td>
</tr>
<tr>
<td>Study</td>
<td>High-grade serous/ endometrioid PSROC</td>
<td>ENGOT-OV24-NSGO/AVANOVA (NCT02354131)</td>
<td>Niraparib Bevacizumab</td>
<td>108 (94 part 2)</td>
<td>PFS (part 2)</td>
</tr>
<tr>
<td>Study</td>
<td>Recurrent platinum-resistant or -refractory HGSOC or germline</td>
<td>NRG GY005 (NCT02502266)</td>
<td>Olaparib Cediranib</td>
<td>680</td>
<td>OS (phase III) and PFS (phase II and III)</td>
</tr>
</tbody>
</table>
### BRCA-mutant ovarian cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Design</th>
<th>Treatment</th>
<th>Duration</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRG GY004 (NCT02446600)</td>
<td>High-grade serous/endometrioid or germline BRCA-mutated PSROC</td>
<td>Open-label randomised 3-arm phase III trial of olaparib ± cediranib vs platinum-based chemotherapy</td>
<td>Olaparib, Cediranib</td>
<td>Feb 2016/Dec 2019</td>
<td>549 (trial suspended)</td>
<td>PFS</td>
</tr>
<tr>
<td>NEO (NCT02489006)</td>
<td>Platinum-sensitive recurrent HGSOC</td>
<td>Open-label randomised phase II trial of neoadjuvant and adjuvant olaparib ± adjuvant chemotherapy</td>
<td>Olaparib</td>
<td>Jul 2016/Dec 2018</td>
<td>71</td>
<td>Translational</td>
</tr>
</tbody>
</table>

### PARP inhibitor + anti-angiogenic therapy (trials not mentioned elsewhere)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Design</th>
<th>Treatment</th>
<th>Duration</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTOVA (NCT03117933)</td>
<td>BRCA1/2-mutated PROC</td>
<td>Open-label 3-arm phase II trial comparing olaparib vs olaparib + cediranib vs paclitaxel</td>
<td>Olaparib, Cediranib</td>
<td>Mar 2017/Mar 2021</td>
<td>132</td>
<td>PFS</td>
</tr>
<tr>
<td>BAROCCO</td>
<td>High-grade PROC</td>
<td>3-arm open-label</td>
<td>Olaparib, Cediranib</td>
<td>Jun 2017/Nov</td>
<td>100</td>
<td>PFS/GI toxicity</td>
</tr>
<tr>
<td>Study</td>
<td>Disease</td>
<td>Drugs</td>
<td>Doses</td>
<td>Endpoint</td>
<td>Type</td>
<td>Phase</td>
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<tr>
<td>(NCT03314740)</td>
<td>Recurrent ovarian cancer or TNBC</td>
<td>Olaparib, Cediranib</td>
<td>90 in phase II</td>
<td>DLT/MTD (phase I)/PFS (phase II)</td>
<td>Open-label</td>
<td>Randomised phase II</td>
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<tr>
<td>(NCT01116648)</td>
<td>Recurrent ovarian cancer or TNBC</td>
<td>Olaparib, Cediranib</td>
<td>162</td>
<td>PFS</td>
<td>Open-label</td>
<td>Randomised phase II</td>
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</tbody>
</table>

**Concomitant with chemotherapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Drugs</th>
<th>Doses</th>
<th>Endpoint</th>
<th>Type</th>
<th>Phase</th>
<th>Start Date</th>
<th>End Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>(NCT01113957)</td>
<td>Recurrent HGSOC</td>
<td>Veliparib, Temozolomide</td>
<td>168</td>
<td>ORR</td>
<td>Open-label</td>
<td>Randomised phase II</td>
<td>Mar 2010/Nov 2013</td>
<td>2013</td>
</tr>
<tr>
<td>(NCT01306032)</td>
<td>Refractory BRCA-mutated ovarian cancer or HGSOC</td>
<td>Veliparib, Cyclophosphamide</td>
<td>75</td>
<td>ORR</td>
<td>Open-label</td>
<td>Randomised</td>
<td>Jan 2011/Dec 2016</td>
<td>2016</td>
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<tr>
<td>PARP inhibitor re-treatment</td>
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</tr>
<tr>
<td>Non-mucinous eOC with progression on previous maintenance PARP inhibitor and CR/PR to subsequent platinum-based chemotherapy</td>
<td>OReO/ENGOT (NCT03106987)</td>
<td>Olaparib</td>
<td>–</td>
<td>416</td>
<td>PFS</td>
<td>Double-blind placebo-controlled randomised phase IIIb maintenance re-treatment</td>
<td>Jun 2017/Nov 2020</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; DLT, dose-limiting toxicity; eOC, epithelial ovarian cancer; GI, gastrointestinal; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PR, partial response; PROC, platinum-resistant ovarian cancer; PSROC, platinum-sensitive recurrent ovarian cancer; TNBC, triple-negative breast cancer.