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 [≥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 ≥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 *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 [17, 25, 31], suggesting a role as definitive treatment as well as maintenance therapy.

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 ≥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 ≥6 years [19].

Class effects of the PARP inhibitors include grade ≥3 anaemia, grade ≥3 fatigue and all-grade nausea and vomiting [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 [14, 24]. The most common grade ≥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 ≥65 and <65 years [40]. Tolerability of the tablet formulation used in SOLO2 appears to be similar to that of the capsule formulation [15]. The most common AEs were anaemia, fatigue/asthenia, nausea and vomiting. Except for anaemia, most AEs were low grade. Grade ≥3 neutropenia occurred in 5% of patients and there was no grade ≥3 thrombocytopenia.

The most common grade 3/4 AEs with niraparib in NOVA were laboratory abnormalities (e.g. thrombocytopenia, anaemia, neutropenia), fatigue and hypertension [16]. Subgroup analyses in patients aged <70 versus ≥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 IIIB 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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Table 1. Summary of efficacy in randomised trials evaluating single-agent PARP inhibitors in platinum-sensitive ovarian cancer

PARP inhibitor	Trial	Analysis population	No. of patients		PFS HR (95% CI)	Median PFS, months	
			PARP inhibitor	Control		PARP inhibitor	Control
Olaparib	SOLO2 [15]	ITT (*BRCA1/2* mutated)	196	99	0.30 (0.22–0.41); *P* < 0.0001	19.1	5.5
Niraparib	NOVA [16]	Germline *BRCA* mutation	138	65	0.27 (0.17–0.41); *P* < 0.001	21.0	5.5
		HRD-positive non-germline *BRCA*-mutated	106	56	0.38 (0.24–0.59); *P* < 0.001	12.9	3.8
		All non-germline *BRCA*-mutated	234	116	0.45 (0.34–0.61); *P* < 0.001	9.3	3.9
Rucaparib	ARIEL3 [17]	*BRCA*-mutated	130	66	0.23 (0.16–0.34); *P* < 0.0001	16.6	5.4
		HRD-positive	236	118	0.32 (0.24–0.42); *P* < 0.0001	13.6	5.4

		ITT	375	189	0.36 (0.30–0.45); *P* < 0.0001	10.8	5.4
Randomised phase II trial							
Olaparib	Study 19 [14, 18]	ITT	136	129	0.35 (0.25–0.49); *P* < 0.001	8.4	4.8
		BRCA-mutated (germline or somatic, retrospective)			0.18 (0.10–0.31); *P* < 0.0001	11.2	4.3

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

Table 2. Randomised clinical trials evaluating PARP inhibitors

Treatment setting	Trial	PARP inhibitor	Combination partner	No. of patients	Primary end point	Trial design	Enrolment start/ estimated primary completion date
Maintenance after front-line therapy							
Newly diagnosed *BRCA*-mutated stage III/IV with CR/PR after front-line platinum	SOLO1 (NCT01844986)	Olaparib	–	450	PFS (investigator-assessed)	Double-blind placebo-controlled randomised phase III maintenance	Aug 2013/May 2018
Newly diagnosed stage IIIB/IV *BRCA*-mutated or high-grade serous/endometrioid, with CR/PR and ongoing bevacizumab	ENGOT-OV25/PAOLA-1 (NCT02477644)	Olaparib	Bevacizumab	612	PFS	Double-blind placebo-controlled randomised phase III maintenance	May 2015/Jun 2022
Newly diagnosed stage III/IV with	ENGOT-OV26/PRIMA	Niraparib	–	468	PFS	Double-blind placebo-controlled	April 2016/Aug 2019

CR/PR after front-line platinum	(NCT02655016)						randomised phase III maintenance	
Newly diagnosed stage III/IV HGSOC	GOG 3005 (NCT02470585)	Veliparib	Carboplatin/paclitaxel	1140	PFS		Placebo-controlled 3-arm randomised phase III concurrent + maintenance vs maintenance alone vs chemotherapy alone	Mar 2012/Jan 2019

Maintenance therapy in recurrent disease

BRCA-mutated high-grade serous/endometrioid, CR/PR to platinum, ≥2 prior lines of chemotherapy	ENGOT-OV21/SOLO2 (NCT01874353) [15]	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) [14]	Olaparib (capsules)	–	265	PFS		Double-blind placebo-controlled randomised phase II maintenance	Aug 2008/Jun 2010
Germline *BRCA*-mutated or high-	ENGOT-OV16/NOVA	Niraparib	–	597	PFS		Double-blind placebo-controlled	Jun 2013/Jun 2016

grade serous PSROC	(NCT01847274) [16]						randomised phase III maintenance trial
High-grade serous/endometrioid PSROC, ≥2 prior platinum regimens	ARIEL3 (NCT01968213) [17]	Rucaparib	–	540	PFS (investigator assessed)	Double-blind placebo-controlled phase III trial as switch maintenance after platinum	Jan 2014/Apr 2017
PSROC with CR/PR to second-line platinum-based chemotherapy	ICON9 (NCT03278717)	Olaparib	Cediranib	618	PFS and OS	Open-label randomised phase III maintenance trial	Dec 2017/Dec 2023
Definitive treatment setting							
Germline *BRCA1/2*-mutated PSROC, ≥2 prior lines of platinum-based chemotherapy	SOLO3 (NCT02282020)	Olaparib	–	411	PFS (blinded independent central review)	Open-label randomised phase III trial of olaparib vs physician's chosen single-agent non-platinum chemotherapy	Feb 2015/Jan 2019
Recurrent ovarian cancer, ≥1 prior line of chemotherapy	CLIO (NCT02822157)	Olaparib	–	160	ORR	Open-label randomised 2-arm trial of olaparib vs	Aug 2016/Sep 2018

						chemotherapy, with crossover	
BRCA1/2-mutated recurrent ovarian cancer after platinum-based chemotherapy	ICEBERG3 (NCT00628251)	Olaparib	–	97	PFS	Open-label 3-arm randomised phase II comparing two doses of olaparib vs liposomal doxorubicin	Jul 2008/Sep 2009
BRCA1/2-mutated high-grade recurrent eOC and ≥2 prior chemotherapy regimens	ARIEL4 (NCT02855944)	Rucaparib		345	PFS (investigator assessed)	Open-label randomised phase III trial of rucaparib vs chemotherapy	Sep 2016/Jun 2022
High-grade serous/ endometrioid PSROC	ENGOT-OV24-NSGO/AVANOVA (NCT02354131)	Niraparib	Bevacizumab	108 (94 part 2)	PFS (part 2)	2-part (phase Ia dose escalation to determine regimen for part 2) open-label randomised phase II trial of niraparib $\pm$ bevacizumab	Feb 2015/Nov 2018
Recurrent platinum-resistant or -refractory HGSOC or germline	NRG GY005 (NCT02502266)	Olaparib	Cediranib	680	OS (phase III) and PFS (phase II and III)	Open-label 4-arm randomised phase II/III of olaparib and/or cediranib vs	Feb 2016/Jun 2023

BRCA-mutant ovarian cancer						chemotherapy	
High-grade serous/endometrioid or germline *BRCA*-mutated PSROC	NRG GY004 (NCT02446600)	Olaparib	Cediranib	549 (trial suspended)	PFS	Open-label randomised 3-arm phase III of olaparib ± cediranib vs platinum-based chemotherapy	Feb 2016/Dec 2019
Platinum-sensitive recurrent HGSOC	NEO (NCT02489006)	Olaparib	–	71	Translational	Open-label randomised phase II trial of neoadjuvant and adjuvant olaparib ± adjuvant chemotherapy	Jul 2016/Dec 2018

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

BRCA1/2-mutated PROC	OCTOVA (NCT03117933)	Olaparib	Cediranib	132	PFS	Open-label 3-arm randomised phase II trial comparing olaparib vs olaparib + cediranib vs paclitaxel	Mar 2017/Mar 2021
High-grade PROC	BAROCCO	Olaparib	Cediranib	100	PFS/GI toxicity	3-arm open-label	Jun 2017/Nov

	(NCT03314740)					randomised phase II of olaparib + cediranib (intermittent vs continuous schedules) vs paclitaxel	2019
Recurrent ovarian cancer or TNBC	(NCT01116648) [46]	Olaparib	Cediranib	90 in phase II	DLT/MTD (phase I)/PFS (phase II)	Open-label randomised phase II	Mar 2010/Oct 2018

Concomitant with chemotherapy

Platinum-sensitive advanced serous OC	Study 41 (NCT01081951) [21]	Olaparib (capsule)	Carboplatin + paclitaxel	162	PFS	Open-label randomised phase II, chemotherapy ± olaparib	Feb 2010/Oct 2011
Recurrent HGSOC	(NCT01113957)	Veliparib	Temozolomide	168	ORR	Open-label randomised phase II vs pegylated liposomal doxorubicin	Mar 2010/Jun 2013
Refractory *BRCA*-mutated ovarian cancer or HGSOC	(NCT01306032) [47]	Veliparib	Cyclophosphamide	75	ORR	Open-label randomised cyclophosphamide ± veliparib	Jan 2011/Dec 2016

PARP inhibitor re-treatment

Non-mucinous eOC with progression on previous maintenance PARP inhibitor and CR/PR to subsequent platinum-based chemotherapy	OReO/ENGOT (NCT03106987)	Olaparib	–		416	PFS	Double-blind placebo-controlled randomised phase IIIb maintenance re-treatment	Jun 2017/Nov 2020

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.