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REVIEW

Current status and future prospects of PARP inhibitor clinical trials in ovarian cancer

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Abstract: Poly (ADP-ribose) polymerase (PARP) inhibitors are a class of targeted agents for the treatment of solid tumors. Concurrent PARP inhibition in Breast Cancer Susceptibility Gene (BRCA)-mutated or homologous recombination-deficient tumor cells can induce "synthetic lethality", which targets two DNA repair pathways and induces serious cytotoxicity to tumor cells without damaging normal cells. Currently, PARP inhibitors such as olaparib, rucaparib and niraparib, which improve progression-free survival, particularly in patients harboring BRCA mutations, are approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) for the treatment of ovarian cancers. Based on the results of different clinical trials, the indications for these drugs are slightly different. PARP inhibitors have been studied both as single agents and in combination with chemotherapy, antiangiogenic agents, and ionizing radiation. This review summarizes the critical clinical trials of PARP inhibitors that have been completed, provides an overview of the ongoing trials, presents the confirmed conclusions and notes the issues that need to be addressed in future studies.

Keywords: PARP inhibitor, BRCA mutation, olaparib, rucaparib, niraparib, ovarian cancer

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of gynecologic cancer-related deaths in women. Most patients present with advanced-stage disease.[1] Primary cytoreductive (debulking) surgery followed by platinum-based chemotherapy with or without concurrent and maintenance bevacizumab represents the currently recommended standard first-line systemic treatment for EOC, although most patients develop recurrence with a median progression-free survival (PFS) time of 12–18 months. Furthermore, the treatment efficacy diminishes over time and with chemotherapy cycles, and the toxicity of platinum drugs is cumulative. Moreover, the 5-year survival rate remains approximately 35%.[2–5] Thus, more efficient treatment methods are warranted to improve the survival of ovarian cancer patients.

PARP inhibitors are oral small molecule inhibitors of poly (ADP-ribose) polymerase (PARP) enzymes 1, 2 and 3 and have recently demonstrated great clinical efficacy among ovarian cancer patients. PARP inhibitors are the first FDA-approved biological agent for ovarian cancer based on the individualized features of cancer.[6] Patients with BRCA1/2-mutated or homologous recombination-deficient (HRD) ovarian tumors can benefit from PARP inhibitors. Currently, PARP inhibitors such as olaparib, rucaparib and niraparib have been approved by the FDA and EMA for the treatment of ovarian cancer.[7–9] The indications for PARP inhibitors approved in Europe (EU) and the United States (US), such as olaparib capsules,

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olaparib tablets, rucaparib, and niraparib, are listed in Table 1. Other PARP inhibitors, such as veliparib and talazoparib, are in various stages of clinical development.[6] A PubMed literature search was conducted using the search term "PARP inhibitors and ovarian cancer". The ClinicalTrials.gov website was searched to identify relevant clinical trials evaluating PARP inhibitors in ovarian cancer. An on-line search was conducted to identify all FDA approvals in the US and EMA approvals in EU of PARP inhibitors for ovarian cancer treatment. Proceedings from scientific meetings were searched to identify abstracts reporting unpublished data from clinical trials. This review summarizes the critical clinical trials on PARP inhibitors and augments our understanding of the past, present and future of PARP inhibitors.

Rationale for the mechanism of action of PARP inhibitors

The family of PARP enzymes (≥17 enzymes) is primarily involved in detecting single-strand breaks (SSBs) and triggering a cascade of events leading to the recruitment of DNA repair factors. PARP1, acting as a sensor and signal transducer for SSBs, binds DNA and catalyzes a series of PARylation events leading to PARP1 autoPARylation, which in turn induces the release of PARP1 from DNA. PARP inhibitors prevent the release of PARP1 from DNA by inhibiting autoPARylation, resulting in persistent SSBs, stalled replication forks and subsequently, double-strand breaks (DSBs).[8,10–12] The repair of DSBs relies on two pathways: homologous recombination (HR) and nonhomologous end-joining (NHEJ).[11,13] HR is a high-fidelity, while NHEJ is an error-prone, low-fidelity repair system, which directly ligates the ends of a DSB, resulting in the deletion or mutation of DNA sequences, genomic instability, cell cycle arrest, and cell apoptosis.[10,11,13] BRCA1 and BRCA2 are crucial proteins involved in mediating the HR repair pathway. Therefore, concurrent inhibition of PARP enzymes with BRCA1 or BRCA2 deficiency is synthetically lethal to tumor cells because the loss of function of either alone is compatible with cell viability, but the concurrent loss of both results in cell death.[14,15]

Of note, except for the catalytic inhibition of PARP1 autoPARylation, PARP inhibitors promote the trapping of PARP1-DNA complexes, and the cytotoxicity of the PARP inhibitors mainly depends on their trapping potential. All PARP inhibitors inhibit PARP1 and PARP2 in vitro at nanomolar concentrations but exhibit different levels of PARP-trapping ability on the DNA SSB sites. Talazoparib exhibits the highest potency in trapping PARPs and the highest single-agent cytotoxicity, 100-fold higher than that of olaparib and rucaparib; niraparib exhibits higher potency in trapping PARPs than olaparib and rucaparib, and the PARP-trapping ability of veliparib is the least potent. Therefore, the forming of PARP1-DNA complexes is crucial for the trapping ability of PARP inhibitors. PARP inhibition is not equivalent to PARP deletion. In vitro studies have demonstrated that PARP inhibitors have no effect on tumor cells with the complete absence of the PARP1 enzyme.[16] Table 1 shows the dissociation constant (Ki) reflecting the catalytic inhibition of PARP1 and the PARP-trapping capacity of PARP inhibitors (olaparib, rucaparib, niraparib, veliparib and talazoparib).

Approval indications of three PARP inhibitors in ovarian cancer

In December 2014, the olaparib capsule was approved in the EU as a maintenance monotherapy for adult patients with platinum-sensitive, recurrent BRCA1/2-mutated (germline and/or somatic, g/s) high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer (collectively termed ovarian cancer) (HGSOC) who have demonstrated complete or partial response (CR/PR) to platinum-based chemotherapy.[17] At the same time, the olaparib capsule was also approved in the US as monotherapy for patients with germline BRCA mutation (gBRCAm) and advanced ovarian cancer treated with three or more prior lines of chemotherapy.[18] In August 2017, an olaparib tablet was approved in the US as a maintenance monotherapy for adult patients with recurrent ovarian cancer who have demonstrated CR/PR to platinum-based chemotherapy and for the treatment of adult patients with gBRCAm and advanced ovarian cancer treated with three or more prior lines of chemotherapy.[19] In February 2018, the olaparib tablet was approved in the EU as a maintenance monotherapy for adult patients with platinum-sensitive recurrent high-grade ovarian carcinoma (HGOC) who have demonstrated CR/PR to platinum-based chemotherapy.[20] In December 2018, an olaparib tablet was approved in the US as a first-line maintenance treatment in BRCA1/2-mutated, advanced ovarian cancer after a CR/PR to first-line platinum-based chemotherapy.[21]

In December 2016, rucaparib was approved in the US for the treatment of adult patients with g/sBRCA mutation-associated ovarian cancer treated with two or more prior lines of chemotherapy and as a maintenance monotherapy for adult patients with recurrent

Table 1 Approval indications, dosing, dissociation constant (Ki), and relative trapping capacity of PARP inhibitors[17–25]

Drug	Time of approval	Agency	Population	BRCA status	Clinical Setting	Dosing	Ki	Relative trapping capacity
Olaparib capsule	December 2014	EMA	Platinum-sensitive relapsed HGSOC, post CR/PR	g/sBRCAm	Maintenance	400mg BID	PARP1:5nM PARP2:1nM	+++
	December 2014	FDA	Advanced OC	gBRCAm	Fourth line			
Olaparib tablet	August 2017	FDA	Recurrent OC, post CR/PR	—	Maintenance	300mg BID		
			Advanced OC	gBRCAm	Fourth line			
	February 2018	EMA	Platinum-sensitive relapsed HGOC, post CR/PR	—	Maintenance			
Rucaparib	December 2016	FDA	Advanced OC	g/sBRCAm	Third line	600mg BID	PARP1:1.4nM	+++
			Recurrent OC, post CR/PR	—	Maintenance			
	May 2018	EMA	Platinum-sensitive relapsed/progressive HGOC	g/sBRCAm	Third line			
Niraparib	March 2017	FDA	Recurrent OC, post CR/PR	—	Maintenance	300mg QD	PARP1:3.2nM PARP2:4.0nM	++++
	November 2017	EMA	Platinum-sensitive relapsed HGSOC, post CR/PR	—	Maintenance			
Veliparib	—	—	—	—	—	300mg BID	PARP1:5.2nM PARP2:2.9nM	+
Talazoparib	—	—	—	—	—	1.0mg QD	PARP1:1.2nM PARP2:0.9nM	+++++

Note: The relative trapping capacity of the PARP inhibitors is talazoparib (+++++) □niraparib (++++)□olaparib (+++) and rucaparib (+++)□veliparib (+).
Abbreviations: FDA, Food and Drug Administration; EMA, European Medicine Agency; BRCA, breast cancer susceptibility gene; PARP, poly (ADP-ribose) polymerase; CR/PR, complete response or partial response; g/sBRCAm, germline and/or somatic BRCA1/2 mutation; OC, epithelial ovarian, fallopian tube or primary peritoneal cancer; HGOC, High-grade epithelial ovarian, fallopian tube or primary peritoneal cancer; HGSOC, High-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer; QD, once daily; BID, twice daily.

ovarian cancer who have demonstrated CR/PR to platinum-based chemotherapy.[22] In May 2018, rucaparib was approved in the EU for the treatment of adult patients with platinum-sensitive, relapsed or progressive, g/sBRCA1/2-mutated HGOC treated with two or more prior lines of platinum-based chemotherapy.[23]

In March 2017, niraparib was approved in the US as a maintenance monotherapy for adult patients with recurrent ovarian cancer who have demonstrated CR/PR to platinum-based chemotherapy.[24] In November 2017, niraparib was also approved in the EU as a maintenance monotherapy for adult patients with platinum-sensitive, relapsed, HGSOC who have demonstrated CR/PR to platinum-based chemotherapy.[25]

To summarize, in the EU, the three PARP inhibitors can be administered only to patients with platinum-sensitive, relapsed HGSOC. Additionally, rucaparib is indicated as the third-line treatment in BRCA1/2 mutation-associated ovarian cancer; however, olaparib and niraparib are indicated only as maintenance treatment. In the US, olaparib is indicated as the fourth-line treatment for BRCA1/2-mutated advanced ovarian cancer, the maintenance treatment for recurrent ovarian cancer and the first-line maintenance treatment for newly-diagnosed, BRCA1/2-mutated, advanced ovarian cancer; rucaparib is indicated as both the third-line treatment for BRCA1/2 mutation-associated ovarian cancer and the maintenance treatment for recurrent ovarian cancer; and niraparib is indicated only as the maintenance treatment for recurrent ovarian cancer.

Clinical development of PARP inhibitor efficacy in ovarian cancer

The critical clinical trials of PARP inhibitors, including olaparib, rucaparib and niraparib, in ovarian cancer are summarized in Table 2.

Olaparib

Initially, the FDA approved olaparib as the fourth-line treatment for advanced ovarian cancer with gBRCAm, based on the results from Study 42, a phase II study demonstrating an objective response rate (ORR) of 31% and a median overall survival (OS) time of 16.6 months with olaparib treatment in 193 ovarian cancer patients (NCT01078662). Patients with platinum-resistant disease or those unsuited for further platinum therapy due to significant toxicity or hypersensitivity to platinum, were also included in this trial. This level of activity significantly exceeded that of conventional third-/fourth-line therapy; hence, the FDA approved olaparib for this indication.[26] A pooled analysis of 6 phase I/II trials [NCT00516373 (Study 2), NCT00777582 (Study 24), NCT00494442 (Study 9), NCT00628251 (Study 12), NCT00679783 (Study 20), and NCT01078662 (Study 42)] identified the ORR as 36% and the median duration of response as 7.4 months with olaparib treatment among patients with gBRCAm and advanced relapsed ovarian cancer. The ORR among patients who had received three or more lines of prior chemotherapy was 31%, with a duration of response of 7.8 months, indicating that a sustained response to olaparib could be achieved in heavily pretreated, relapsed, gBRCAm-associated ovarian cancers.[27]

The maximum tolerated dose (MTD) of olaparib was identified as 400 mg twice daily in a phase I trial (NCT00516373).[28] A dose-response relationship between different olaparib dose levels was studied in two phase II trials. In the first phase II study (NCT00628251), the ORR was observed to be higher in the 400 mg olaparib group (31%) than in the 200 mg olaparib group (25%).[29] In another phase II study (NCT00494442), a difference of 3.9 months in the median PFS was observed in the 400 mg olaparib group compared with the 100 mg olaparib group, in favor of the 400 mg olaparib group. And the ORRs were 33% and 13% in the 400 mg olaparib and 100 mg olaparib groups, respectively.[30] However, neither of these two trials had sufficient power to address the efficacy difference between the two olaparib dose levels. Therefore, whether olaparib exhibits a dose-response relationship requires additional evaluation.

Study 19, SOLO2 and SOLO1 are all randomized, double-blind, placebo-controlled phase II/III studies of olaparib monotherapy that are highly significant (Study 19: NCT00753545, SOLO2: NCT01874353, and SOLO1: NCT01844986). Study 19 showed that olaparib maintenance monotherapy significantly improved PFS [median, 8.4 vs 4.8 months; hazard ratio (HR) 0.35, 95% confidence interval (CI) 0.25–0.49; $p<0.001$] compared with placebo in patients with platinum-sensitive, recurrent HGSOC who had received 2 or more prior lines of platinum-based chemotherapy and demonstrated a CR/PR to the most recent platinum-based chemotherapy.[31] Retrospective germline and somatic BRCA mutation testing was performed on all patients with an additional 2 years of follow-up. A total of 51% of the HGSOC population had a germline or somatic BRCA mutation, and patients with or without g/sBRCA mutations both gained the PFS benefit from olaparib maintenance therapy versus placebo, with a greater PFS benefit in the g/sBRCA1/2-mutated group than in the wild-type BRCA group (g/sBRCA1/2-mutated: 11.2 vs 4.3 months; HR 0.18, 95% CI [0.10–0.31]; $p<0.0001$; wild-type BRCA: 7.4 vs 5.5 months; HR 0.54, 95% CI [0.34–0.85]; $p=0.0075$).[32] The first, second and third interim OS analyses from Study 19 were performed after 38%, 58% and 77% of patients had died, respectively. The final OS analysis was performed after 210 deaths (79% data maturity), after a median follow-up of 6.5 years.[31–34] Neither of the first or second interim OS analyses showed a benefit for olaparib versus placebo for either the BRCA1/2-mutated or BRCA wild-type groups in the overall population.[32] The third interim OS analysis and the final OS analysis both showed an OS advantage of olaparib versus placebo in all patients (median OS 29.8 vs 27.8 months, HR 0.73, 95% CI 0.55–0.95, $p=0.02$) and in patients with BRCA mutations (34.9 vs 30.2 months, HR 0.62, 95% CI 0.42–0.93, $p=0.02$).[33] However, the predefined threshold for statistical significance ($p=0.0095$) was not met.[33,34] In the final OS analysis, 32 patients (24%) had received olaparib maintenance for over 2 years, and 15 (11%) had received olaparib maintenance for over 6 years, which demonstrated the long-term safety and tolerability of olaparib maintenance therapy.[34]

Therefore, olaparib maintenance significantly improved PFS in patients with platinum-sensitive recurrent HGSOC treated with two or more previous lines of platinum-based chemotherapy, and patients with a g/sBRCA mutation had the greatest benefit from olaparib.[31,32] The analyses for time to first subsequent therapy or death, time to second progression, and time to second subsequent therapy or death showed that the PFS benefit was sustained until subsequent

Table 2 Clinical trials with PARP inhibitors (olaparib, rucaparib, niraparib) therapy in ovarian cancer

Drug	Clinical Trial Phase	Clinical setting	Population	Design	Results/Status
Olaparib	II Study 42 (NCT 01078662)	Platinum-resistant relapse	gBRCAm advanced OC or unsuitable for further platinum therapy	Non Randomized, Non Comparative Olaparib capsules 400mg po bid	ORR 31% Median PFS 7.0 ms Median OS 16.6 ms
	II Study19 (NCT00753545)	Platinum-sensitive relapse maintenance	HGSOC following ≥2 platinum-based chemo with CR/PR to last platinum	Randomized Olaparib capsules 400mg po bid vs placebo	Median PFS -Overall 8.4 vs 4.8 ms (p<0.001) -BRCAm 11.2vs 4.3 ms (p<0.0001) -BRCAwt 7.4vs 5.5 ms (p=0.0075) Median OS -Overall 29.8 vs 27.8 ms (N.S.) -BRCAm 34.9 vs 30.2 ms (N.S.) -BRCAwt 24.5 vs 26.6 ms (N.S.)
	III SOLO1 (NCT01844986)	First-line maintenance	Stage III/IV BRCAm HGS/EOC with CR/PR to initial first-line platinum-based chemo	Randomized Olaparib tablets 300mg po bid vs placebo	Median PFS BRCAm NR vs 13.8 ms (p<0.0001)
	III SOLO2 (NCT01874353)	Platinum-sensitive relapse maintenance	BRCAm HGS/EOC following ≥2 platinum-based chemo with CR/PR to last platinum	Randomized Olaparib tablets 300mg po bid vs placebo	Median PFS BRCAm 19.1vs 5.5 ms (p<0.0001)
	II (NCT01081951)	Platinum-sensitive relapse	HGSOC following≤3 platinum-based chemo with progression free for ≥6 months	Randomized [Paclitaxel (175mg/m^2) + carboplatin (AUC=4) iv + olaparib capsules 200mg bid po, 1–10 days/21 days, 4–6 cycles] + olaparib capsules 400 mg bid po vs Paclitaxel (175mg/m^2)+ carboplatin (AUC =6) iv/21 days, 4–6 cycles	Median PFS -Overall 12.2 vs 9.6 ms (p=0.0012) -BRCAm NR vs 9.7 ms (p=0.0015) Median OS -Overall 33.8 vs 37.6 ms (N.S.) -BRCAm NR vs 39.2 ms (N.S.)
	II (NCT00628251)	Platinum-sensitive and resistant relapse	gBRCAm OC Relapsed within 12 months of prior platinum	Randomized Olaparib capsules 200 mg/400 mg po bid vs PLD 50 mg/m^2 iv/4 weeks	Median PFS 6.5/8.8 vs 7.1 ms(N.S.) ORR 25%/31% vs18%(N.S.)
	II (NCT01116648)	Platinum-sensitive relapse	HGS/EOC or gBRCAm HGOC with any number of platinum-based chemo and ≤1 non-platinum therapy with response to last platinum	Randomized Olaparib capsules 200mg po bid + cediranib 30 mg po qd vs olaparib capsules 400 mg po bid	ORR -Overall 79.6% vs 47.8%(p=0.002) Median PFS -Overall 17.7 vs 9.0 ms (p=0.005) -gBRCAm 19.4 vs 16.5 ms (N.S.) -BRCAwt 16.5 vs 5.7 ms (p=0.008)

(*Continued*)

Table 2 (Continued).

Drug	Clinical Trial Phase	Clinical setting	Population	Design	Results/Status
Rucaparib	I/II Study 10 (NCT01482715)	-Part 2A Platinum-sensitive relapse -Part 2B Platinum-sensitive /resistant/refractory relapse	-Part 2A gBRCAm HGOC with 2–4 prior regimens, PFS ≥6 ms after last platinum -Part 2B g/sBRCAm HGOC with 3–4 prior regimens	Non Randomized, Non Comparative Rucaparib 600mg po bid	-Part 2A ORR 59.5% -Part 2B ongoing
	II ARIEL 2 (NCT 01891344)	-Part 1 Platinum-sensitive relapse -Part 2 Platinum-sensitive /resistant/refractory relapse	-Part 1 HGOC≥1 prior platinum-based chemo -Part 2 HGOC with 3–4 prior chemo, treatment-free>6 ms after first-line chemo	Non Randomized Rucaparib 600mg po bid	Part 1 Median PFS -BRCAm 12.8 ms (p<0.0001) -LOH high 5.7 ms (p=0.011) -LOH low 5.2 ms (reference) Part 2 Ongoing
	Study 10(Part 2A) +ARIEL 2(Parts 1 and 2)	Platinum-sensitive /resistant/refractory relapse	HGOC gBRCAm(Study 10) or g/sBRCAm(ARIEL2) with ≥2 prior platinum-based chemo	Non Randomized, Non Comparative Rucaparib 600mg po bid	ORR 53.8% Median DOR 9.2 ms
	III ARIEL 3 (NCT01968213)	Platinum-sensitive relapse maintenance	HGS/EOC ≥2 prior platinum-based chemo with CR/PR to last platinum, CA125<upper limit of normal, with ≥4 cycles last platinum-based doublet chemo	Randomized Rucaparib 600mg po bid vs placebo	Median PFS -BRCAm 16.6 vs 5.4 ms (p<0.0001) -HRD 13.6 vs 5.4 ms (p<0.0001) -Intention-to-treat population 10.8 vs 5.4 ms (p<0.0001)
Niraparib	III NOVA (NCT01847274)	Platinum-sensitive relapse maintenance	HGSOC following ≥2 platinum-based regimens with ≥4 cycles last platinum-based chemo and CR/PR to last platinum with residual disease<2cm	Randomized Niraparib 300mg po qd vs placebo	Median PFS -gBRCAm 21.0 vs 5.5 ms (p<0.001) -HRD 12.9 vs 3.8 ms (p<0.001) -BRCAwt 9.3 vs 3.9 ms (p<0.001)

Abbreviations: BRCAwt, BRCA wild-type; N.S., no significance; ms, months; OC, epithelial ovarian, fallopian tube or primary peritoneal cancer; EOC, epithelial ovarian cancer; HGOC, High-grade epithelial ovarian, fallopian tube or primary peritoneal cancer; HGSOC, High-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer; HGS/EOC, High-grade serous or endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer; CR/PR, complete response or partial response; g/sBRCAm, germline or somatic BRCA1/2 mutation; PLD, Pegylated liposomal doxorubicin. PFS, Progression-free survival; OS, overall survival; HRD, homologous recombination deficiency; ORR, objective response rate; NR, not reached; AUC, area under curve; LOH, loss of heterozygosity; DOR, duration of response; po, orally; iv, intravenous; vs, versus; qd, once daily; bid, twice daily.

treatment and that a long-term benefit was achieved irrespective of BRCA1/2 mutation status.[32,33] The long follow-up time required to obtain sufficient OS data increases the chance that post-progression PARP inhibitor therapy and patient crossover will effect the OS data. When excluding the patients from places where placebo patients were treated with post-progression PARP inhibitors, the OS hazard ratio was significantly improved, indicating that in Study 19, post-progression PARP inhibitor therapy had a confounding effect on the interim OS analysis for patients with BRCA mutations.[35]

SOLO2 (NCT01874353) aimed to investigate the efficacy and safety of olaparib in platinum-sensitive, recurrent ovarian cancer patients with a g/sBRCA1/2 mutation who had received two or more lines of previous chemotherapy and demonstrated a CR/PR to the most recent platinum-based chemotherapy. The median PFS was significantly longer with olaparib (19.1 months) than with placebo (5.5 months; HR 0.30 [95% CI 0.22–0.41], $p<0.0001$). The PFS benefit from olaparib maintenance compared with that from placebo in SOLO2 substantially exceeded that observed in Study 19, which is not surprising because SOLO2 included only patients with g/sBRCA1/2-mutated tumors.[36] Furthermore, heavily pretreated patients with BRCA1/2-mutated ovarian cancer whose disease progressed following PARP inhibitor therapy retain the potential to respond to subsequent chemotherapy, including platinum-based chemotherapy. The ORR to subsequent chemotherapy and platinum-based chemotherapy was reported to be as high as 36% and 40%, respectively.[37,38]

SOLO 1 (NCT01844986) aimed to evaluate the efficacy and safety of olaparib versus placebo in patients with BRCA1/2-mutated advanced (FIGO stage III-IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian tube cancer (HGS/EOC) following CR/PR to initial first-line platinum-based chemotherapy. SOLO 1 was the first trial to investigate the efficacy of olaparib as a first-line maintenance therapy for primary advanced ovarian cancers. Patients who had no evidence of disease at 2 years stopped receiving the trial intervention. Maintenance olaparib led to a substantial improvement in the PFS of patients with newly diagnosed advanced ovarian cancer and BRCA mutation, with a difference of approximately 3 years in the median PFS for olaparib compared with that of placebo (the median PFS in the placebo group was 13.8 months, and up to 53% of patients in the olaparib group had no recurrence after 48 months of follow-up). The Kaplan-Meier curves for the olaparib group did not appreciably change after 2 years, suggesting an enduring treatment benefit after treatment cessation. The second PFS showed a statistically significant improvement, suggesting that olaparib did not diminish patients' ability to benefit from subsequent therapy.[39] Considering the significant PFS advantage in favor of first-line maintenance treatment with PARP inhibitors, patients would have to undergo g/sBRCA testing immediately after ovarian cancer diagnosis and adopt the PARP inhibitor first-line maintenance treatment if they were positive for g/sBRCA mutation. Moreover, the PFS benefit from maintenance olaparib compared with that from placebo in SOLO1 also substantially exceeded that in SOLO2, indicating that olaparib is more beneficial to BRCA mutation carriers as a first-line maintenance treatment than as a third-line treatment.

Rucaparib

An integrated analysis of two single-arm clinical trials (Study 10, NCT01482715; ARIEL2, NCT01891344)

Table 3 The safety profiles of PARP inhibitors (olaparib, rucaparib and niraparib) in clinical trials[27,31,36,39–43,45]

Drugs	Study	Grade 3/4 AEs	Dose interruption	Dose reduction	Dose discontinuation	MDS/AML	Treatment related deaths
Olaparib	Study2/24/9/ 12/20/42(n=223)	54%	40%	4%	7%	2%	3.6%
	Study19(n=136)	35.3%	27.9%	22.8%	2.2%	2%	0%
	SOLO2(n=195)	36%	45%	25%	11%	2%	1%
	SOLO1(n=260)	39%	52%	28%	12%	1%	0%
Rucaparib	ARIEL2 + Study10 (n=377)	60.7%	58.6%	45.9%	10%	0.5%	0%
	ARIEL3(n=372)	56%	64%	55%	13%	1%	1%
Niraparib	NOVA(n=367)	64.6%	68.9%	66.5%	14.7%	1.4%	0.3%

Abbreviations: AEs, Adverse Events; MDS/AML, myelodysplastic syndrome/acute myeloid leukemia; PARP, poly (ADP-ribose) polymerase.

Table 4 The adverse events rates of PARP inhibitors (olaparib, rucaparib and niraparib) in clinical trials[27,31,36,39–43,45]

Grade 3/4 AEs	Olaparib				Rucaparib		Nirparib
	Study2/24/9/12/20/42 (n=223)	Study 19 (n=136)	SOLO2 (n=195)	SOLO1 (n=260)	ARIEL2 + Study10 (n=377)	ARIEL3 (n=372)	NOVA (n=367)
Anemia	15%	5.1%	19%	22%	24.9%	19%	25.3%
Neutropenia	-	-	5%	9%	9.8%	7%	19.6%
Thrombocytopenia	-	-	1%	1%	4.5%	5%	33.8%
Fatigue/asthenia	7%	7.3%	4%	4%	10.9%	7%	8.2%
Nausea	3%	2.2%	3%	1%	5.0%	4%	3.0%
Vomiting	4%	2.2%	3%	□1%	4.0%	4%	1.9%

Abbreviations: AEs, Adverse Events; PARP, poly (ADP-ribose) polymerase.

evaluated the efficacy and safety of rucaparib in 106 advanced ovarian cancer patients who had progressed after two or more prior lines of chemotherapy.[40,41] The ORR was 54% in all patients and 66%, 25%, and 0% in platinum-sensitive, platinum-resistant and platinum-refractory patients, respectively.[42] The recommended dose of rucaparib was identified as 600 mg twice daily in the phase I part of Study 10.[40] The first part of ARIEL2 aimed to assess the ability of tumor genomic loss of heterozygosity (LOH) as a biomarker, beyond the g/sBRCA1/2 mutation, to predict the response to rucaparib. Patients with platinum-sensitive recurrent HGS/EOC who had received one or more prior lines of platinum-based chemotherapy and had progressed 6 months or more after the most recent platinum-based chemotherapy were classified into one of three predefined HRD subgroups: g/sBRCA mutant, BRCA wild-type and LOH high, and BRCA wild-type and LOH low. Compared with that of the LOH low subgroup (median 5.2 months), the PFS was significantly longer in the BRCA mutant (median 12.8 months, HR 0.27, 95% CI 0.16–0.44, $p<0.0001$) and LOH high (5.7 months, 0.62, 0.42–0.90, $p=0.011$) subgroups. These results indicate that tumor genomic LOH can be used as a biomarker, beyond the g/sBRCA1/2 mutation, to identify patients with BRCA wild-type platinum-sensitive ovarian cancers who might benefit from rucaparib.[41] In a phase III trial (ARIEL3, NCT01968213), compared to placebo, rucaparib maintenance significantly improved PFS in patients with platinum-sensitive recurrent HGS/EOC treated with two or more prior lines of platinum-based chemotherapy and following CR/PR to platinum-based chemotherapy, which included the BRCA1/2-mutated (16.6 vs 5.4 months, $p<0.0001$), HRD (13.6 vs 5.4 months, $p<0.0001$), and intention-to-treat populations (10.8 vs 5.4 months, $p<0.0001$).[43]

Niraparib

The MTD of niraparib was identified in a phase I dose escalation study as 300 mg daily.[44] The approval of niraparib was based on a randomized phase III trial (ENGOT-OV16/NOVA, NCT01847274), in which patients with platinum-sensitive, recurrent ovarian cancer and a CR/PR after two or more prior lines of platinum-based chemotherapy were treated with niraparib or placebo maintenance. Niraparib maintenance significantly improved the PFS, compared to placebo, irrespective of the gBRCAm or HRD status (21.0 vs 5.5 months in the gBRCAm group, 12.9 vs 3.8 months in the HRD plus BRCA wild-type group, and 9.3 vs 3.9 months in the overall BRCA wild-type group [$p<0.001$]). Compared to placebo, niraparib also significantly improved the time to second progression and chemotherapy-free interval in the gBRCAm, BRCA wild-type, and HRD subgroups. Similar to tumor genomic LOH, HRD status as a biomarker might indicate the potential usefulness of PARP inhibitors; however, the absence of either does not preclude benefit from niraparib maintenance therapy.[45]

Veliparib

The MTD of veliparib was identified in a phase I/II study (NCT01472783) as 300 mg twice daily. In this study, the ORR of veliparib monotherapy in patients with gBRCA1/2-mutated, platinum-resistant or intermediate-sensitive (disease relapse within 6 to 12 months of previous platinum-based therapy) relapsed ovarian cancer was 65% (6% CR and 59% PR). The PFS and OS of the intention-to-treat population were 5.6 months and 13.7 months, respectively. Treatment with veliparib in heavily pretreated, recurrent ovarian cancer

patients demonstrates considerable efficacy with an acceptable toxicity profile.[46] A phase II trial (NCT01540565) studied the efficacy and tolerability of veliparib monotherapy (400 mg twice daily) in persistent or recurrent EOC patients with gBRCAm after three or fewer prior chemotherapy regimens. The ORRs were 26%, 20% and 35% for the overall, platinum-resistant and platinum-sensitive patient populations, respectively.[47]

Talazoparib

In a phase I dose-escalation study (NCT01286987), talazoparib demonstrated single-agent antitumor activity and was well tolerated at an MTD of 1.0 mg/day. At 1.0 mg/day, clinical responses were observed in 5 of 12 (42%) patients with BRCA1/2-mutated ovarian cancers.[48]

Safety profiles of PARP inhibitors in ovarian cancer

The safety data for olaparib treatment in a pooled analysis of 6 phase I/II trials (Study 2, Study 24, Study 9, Study 12, Study 20, and Study 42), in Study 19, in SOLO2 and in SOLO1; for rucaparib treatment in ARIEL3 and in an integrated analysis of Study 10 and ARIEL2; and for niraparib treatment in NOVA are shown in Tables 3 and 4. The occurrence of treatment-related deaths was the highest (up to 3.6%) in the pooled analysis of 6 phase I/II trials; these deaths were attributed to acute leukemia, chronic obstructive pulmonary disease, pulmonary embolism, cerebrovascular accident, intestinal perforation, sepsis, and suture rupture. However, none of the adverse events (AEs) leading to death was considered causally related to olaparib.[27] The secondary malignancies myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) seemed to be prominent problems associated with PARP inhibitor treatment. The incidence of MDS/AML was approximately 2% in 298 patients with advanced cancer and a deleterious gBRCAm treated with olaparib in Study 42;[26] in 136 patients with advanced relapsed ovarian cancer treated with olaparib in Study 19;[31] and in 195 patients with advanced g/sBRCA1/2-mutated, relapsed ovarian cancer treated with olaparib in SOLO2.[36] However, confirming whether the secondary MDS/AML was causally related to PARP inhibitor treatment was difficult because the patients had undergone multiple lines of chemotherapy before they were enrolled in the trial, as proven by the high rate of secondary AML/MDS in patients in the placebo group, up to 4% in 99 patients with advanced ovarian cancer and a BRCA1/2 mutation, in SOLO2.[36] In addition, MDS/AML occurred in 5 of 367 (1.4%) patients receiving niraparib and in 2 of 179 (1.1%) patients receiving placebo in NOVA;[45] MDS/AML were reported in three (1%) patients in the rucaparib group but in no patients in the placebo group in ARIEL3.[43] MDS/AML occurred in 3 of 260 (1%) patients in the olaparib group but in none of the 130 patients in the placebo group in SOLO1, in which the patients had undergone only first-line platinum-based chemotherapy and olaparib maintenance therapy.[39]

The incidence of MDS/AML in a large case-control study of 28,971 ovarian cancer patients who had received prior platinum therapy between 1980 and 1993 was 0.33%.[49] An epidemiological analysis identified 109 (0.17%) therapy-related myeloid leukemia cases in 63,359 patients after treatment for EOC from 1973–2006. The development of secondary leukemia with EOC diagnosis was significantly decreased following a shift from a melphalan and platinum regimen to a paclitaxel and platinum regimen.[50] The incidence of MDS/AML in a large cohort study of 23,862 ovarian cancer patients who had received DNA-damaging therapy between 2000 and 2014 was 0.8%, and the duration of exposure to DNA-damaging therapy was demonstrated to be a significant risk factor for developing MDS/AML during follow-up.[51] The incidence of MDS/AML in a population of patients carrying a gBRCAm is unknown. Therefore, whether the high incidences of secondary MDS/AML in Study 42, Study 19 and SOLO2 were correlated with the high rates of BRCA mutation among these patients is also unknown. Based on these figures, secondary MDS/AML cannot be definitively regarded as causally related to PARP inhibitor treatment. However, patients should be warned of the risks and be monitored for hematologic toxicity. Further investigations are warranted.

The predominant AE with PARP inhibitor treatment is anemia. The incidence of grade 3/4 anemia was reported to be as high as 22% in SOLO1[39] and 25% in ARIEL2 +Study10[42] and NOVA,[45] far higher than the incidence of other AEs such as fatigue/asthenia, nausea, and vomiting. Hematologic toxicity was more serious with niraparib treatment than with olaparib or rucaparib treatment. Both thrombocytopenia (33.8%) and neutropenia (19.6%) were prominent AEs with niraparib treatment,[45] compared with their incidence with olaparib treatment [thrombocytopenia (1%) and neutropenia (9%)] in SOLO1[39] or rucaparib treatment [thrombocytopenia (4.5%) and neutropenia (9.8%)] in ARIEL2+Study10.[42] In NOVA, thrombocytopenia was

transient, platelet levels stabilized after cycle 3, and treatment discontinuations were not attributed to these hematologic events.[45] A prominent AE with rucaparib treatment was grade 3/4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation in ARIEL2+Study 10 (17%) or ARIEL3 (10%); this elevation was transient, self-limiting and not associated with other signs of liver toxicity.[42,43] Grade 3/4 hypertension occurred in 9% of niraparib-treated patients and 2% of patients assigned to placebo.[45] The most common AEs with veliparib treatment included fatigue, nausea, and vomiting,[46,47] and AEs with talazoparib treatment included fatigue, anemia and thrombocytopenia.[48] Other common AEs of any grade observed in PARP inhibitor clinical trials included nausea, vomiting, diarrhea, constipation, fatigue/asthenia, dysgeusia, dyspepsia, decreased appetite, cough, headache, abdominal pain, dyspnea, leukopenia, palpitations, mucositis/stomatitis, dry mouth, nasopharyngitis, urinary tract infection, myalgia, back pain, arthralgia, dizziness, insomnia, anxiety and rash. Overall, the AEs with PARP inhibitors were managed with appropriate dose reductions and delays. Few patients required dose discontinuation due to serious fatigue or nausea or to other rare treatment-unrelated complications.[27,31,42,43,45]

Combination of PARP inhibitors with chemotherapy or ionizing radiation

Combination of olaparib with chemotherapy

Up to 50% of patients with HGSOC are deficient in the HR pathway for the repair of DNA damage—as a result of germline or somatic BRCA1/2 mutations, epigenetic inactivation of BRCA1, or BRCA-independent defects in the HR pathway.[52,53] The frequent impairment of HR repair in HGSOC potentially explains the response to DNA-damaging agents such as platinum compounds. The rationale for combining PARP inhibitors with cytotoxic chemotherapy is the common mechanism of DNA repair and synthetic lethal DNA damage.[54,55] Carboplatin combined with paclitaxel is the most commonly used chemotherapy regimen to treat patients with platinum-sensitive, recurrent HGSOC.[56] In a randomized open-label phase II study (NCT01081951), compared with carboplatin and paclitaxel chemotherapy alone, concurrent olaparib with carboplatin and paclitaxel followed by olaparib maintenance significantly improved the PFS of patients with platinum-sensitive, recurrent HGSOC, and the greatest PFS benefit was achieved in patients with BRCA mutations. With regard to OS, the combination schedule did not confer a survival advantage to these patients compared with that of chemotherapy alone. In the combination group, the dose of carboplatin was lower (area under the curve [AUC] 4 mg/mL per min) than that in the chemotherapy group (AUC 6 mg/mL per min). The dosage of concurrent olaparib was 200 mg twice daily for 10 days; that of sequential olaparib was 400 mg twice daily continuously. The late separation of the PFS curves suggested that the therapeutic benefit was derived mostly from the olaparib maintenance phase.[57] Increased marrow suppression limits the concurrent use of PARP inhibitors with chemotherapy, and the appropriate dosage of PARP inhibitors to achieve chemopotentiation requires further assessment. Studies will be required to assess the appropriate combination schedules and an effective yet tolerable dosing strategy. Whether the modified concurrent combined with maintenance dosing strategy is more superior than the maintenance alone strategy is still unknown.

Comparison of olaparib with chemotherapy

The question of whether PARP inhibitors are more effective than cytotoxic chemotherapy for patients with recurrent EOC and BRCA1/2 mutations is intriguing. In a randomized open-label phase II study (NCT00628251), the efficacy of olaparib (200 mg or 400 mg twice daily) was compared with that of pegylated liposomal doxorubicin (PLD), which is a DNA-intercalating agent that inhibits topoisomerase II and induces DNA DSBs, in patients with BRCA1/2-mutated recurrent EOC with a less than 12 months platinum-free interval. The PFS time was not significantly different between the 200 mg or 400 mg olaparib and PLD groups, and also between the combined olaparib doses and PLD groups. The median PFS was 6.5, 8.8, and 7.1 months for the 200 mg olaparib, 400 mg olaparib, and PLD groups, respectively.[29] In this trial, the median PFS of 7.1 months with PLD therapy was higher than that observed in another phase III randomized trial of patients treated with PLD (PFS of 4 months) with unknown BRCA1/2 status and consistent proportions of platinum-resistant and platinum-sensitive relapsed disease.[58] A retrospective analysis suggested that there might be a potential link between BRCA1/2 mutations and improved clinical benefit with PLD treatment.[59] Therefore, patients with HRD tumors, including those with BRCA mutations, may derive more benefit from

chemotherapeutics, including PLD, than unselected patients.

Combination of veliparib with chemotherapy

Veliparib has been predominantly studied in clinical trials in combination with cytotoxic chemotherapy, probably due to its relatively weak cytotoxicity as a single agent. Currently, trials of veliparib combination strategies are in phase I; the aims of these phase I trials are to investigate the safety, tolerability and preliminary efficacy of veliparib combined with different chemotherapy regimens. Researchers are aiming to investigate the best combination approach to sensitize and potentiate the efficacy of chemotherapy without the cumulative toxicity of chemotherapeutics. In a phase I study (NCT01063816), 54 patients with metastatic or unresectable ovarian cancer treated with ≤2 prior chemotherapy regimens received veliparib combined with carboplatin and gemcitabine, followed by optional veliparib maintenance therapy. Responses were observed in 69% of patients with BRCA1/2-mutated ovarian cancer (45% PR, 24% CR). The most common grade 3/4 AEs and dose-limiting toxicities (DLTs) were neutropenia and thrombocytopenia. The MTD of veliparib was established at 250 mg with carboplatin (AUC 4) plus 800 mg/m^2 gemcitabine. Therefore, the combination of veliparib with carboplatin/gemcitabine demonstrated promising preliminary antitumor activity in platinum-sensitive ovarian cancer patients with gBRCAm, with a safety profile similar to that of carboplatin and gemcitabine alone.[60] In another phase I trial, a dose-escalation study (NCT02483104), veliparib combined with carboplatin and weekly paclitaxel, was demonstrated to be tolerated and potentially beneficial for newly diagnosed advanced ovarian cancer, with no DLTs. Grade 3/4 AEs were associated with myelosuppression. The response was assessed in 5 patients (5/9, 55.9%) with measurable disease at baseline; the ORR was 100% with 4 PRs and 1 CR. The recommended phase II dose of veliparib combined with carboplatin/paclitaxel was 150 mg twice daily.[61]

Bevacizumab, which targets vascular endothelial growth factor (VEGF) A, has been approved for concurrent and/or subsequent use in combination with carboplatin and paclitaxel for stage III or IV ovarian cancer following initial surgical resection; in combination with carboplatin and paclitaxel or with carboplatin and gemcitabine for platinum-sensitive recurrent ovarian cancer; and in combination with paclitaxel, PLD, or topotecan for patients with platinum-resistant recurrent ovarian cancer who have received no more than 2 prior chemotherapy regimens.[5,62] Thus, the MTD and DLTs of veliparib combined with PLD, carboplatin and bevacizumab in recurrent, platinum-sensitive EOC were evaluated in a phase I dose-escalation study (NCT01459380). The DLTs were grade 4 thrombocytopenia and prolonged neutropenia for >7 days, grade 3 hypertension, and grade 5 sepsis. Even modest doses of veliparib administered either intermittently or continuously in combination with carboplatin resulted in significant hematologic toxicity in patients with recurrent, platinum-sensitive ovarian cancer. Moreover, the addition of bevacizumab to this regimen carried the risk of additional toxicity associated with VEGF inhibitors. Further exploration of combining PARP inhibitor administration with a lower AUC of carboplatin or administering PARP inhibitors only as maintenance therapy following treatment for platinum-sensitive relapse may be warranted.[63] In a phase I/II study (NCT01690598), the safety and efficacy of a combination of veliparib and topotecan for the treatment of platinum-resistant or partially platinum-sensitive recurrent non-gBRCA1/2-mutated EOC were evaluated. However, the best clinical response to this regimen was stable disease.[64] In another randomized phase II trial (NCT01306032), the response rate of the combination of veliparib with oral cyclophosphamide was compared with that of single-agent oral cyclophosphamide in patients with pretreated BRCA1/2-mutated ovarian cancer. Although the treatment was well tolerated, the addition of veliparib to cyclophosphamide did not improve either the response rate or the median PFS.[65]

Combination of veliparib with ionizing radiation

In a phase I dose-escalation study (NCT01264432), the efficacy and safety of low-dose fractionated whole abdominal radiation combined with veliparib were investigated in ovarian cancer patients. One (3.1%) objective response was observed in a patient with gBRCAm, platinum-sensitive disease. The MTD of veliparib combined with radiation was identified as 250 mg twice daily. The most common grade 3/4 toxicities were fatigue, myelosuppression and gastrointestinal symptoms.[66]

Table 5 The critical ongoing trials on PARP inhibitors in ovarian cancer

Drug	Trial	Phase	Design
Olaparib	NCT02282020 SOLO3	III	Randomized Olaparib tablets 300mg po bid vs physician choice single agent non-platinum based chemo for gBRCAm Platinum-sensitive relapsed HGS/EOC following ≥2 platinum-based chemo with progression ≥6 months after last platinum
	NCT02446600	III	Randomized Platinum-base chemo(carboplatin + paclitaxel; carboplatin + gemcitabine; carboplatin + PLD) vs olaparib vs olaparib + cediranib for Platinum-sensitive relapsed HGS/EOC or gBRCAm HGOC with any number of platinum-based chemo and ≤1 non-platinum therapy with CR to last platinum
	NCT02502266	II/III	Randomized Physician choice chemo(paclitaxel; PLD; topotecan) vs olaparib + cediranib vs olaparib vs cediranib for Platinum-resistant or refractory relapsed, HGS/EOC non-gBRCAm or HGOC gBRCAm with ≤3 prior regimens and ≤1 non-platinum
	NCT02889900 CONCERTO	IIb	Non Randomized, Non Comparative Cediranib + Olaparib for recurrent platinum resistant ovarian cancer without gBRCAm
	NCT03106987 OReO	IIIb	Randomized olaparib vs placebo maintenance re-treatment for relapsed non-mucinous EOC, who have had disease progression following maintenance therapy with a PARPi and a CR/PR to subsequent platinum-based chemotherapy
	NCT02855697 MOLTO	I	Non Randomized, Non Comparative multi-maintenance olaparib for platinum sensitive relapsed gBRCAm HGS/EOC with 2 or more courses of maintenance olaparib
	NCT03402841 OPINION	IIIb	Non Randomized, Non Comparative olaparib maintenance for platinum sensitive relapsed non gBRCAm HGS/EOC
	NCT02340611	II	Non Randomized, Non Comparative Cediranib+Olaparib after disease progression on olaparib alone in OC
	NCT03278717ICON 9	III	Randomized maintenance olaparib + cediranib vs olaparib alone for relapsed OC with disease progressed more than 6 months after first line chemotherapy or CR/PR to ≥4 cycles of platinum based chemotherapy.
	NCT03470805	II	Non Randomized, Non Comparative Olaparib maintenance after response to Trabectedin-PLD in recurrent gBRCAm or sBRCAm HGS/EOC
	NCT03117933 OCTOVA	II	Randomized Olaparib vs Olaparib + Cediranib vs weekly paclitaxel for BRCAm platinum-resistant OC
	NCT03161132 ROLANDO	II	Non Randomized, Non Comparative Olaparib + PLD for platinum resistant advanced OC
	NCT01623349	I	To determine the safety of Oral PI3kinase Inhibitor BKM120 or BYL719 + Olaparib for recurrent HGSOC
	NCT01650376	Ib	To determine the MTD of olaparib + weekly carboplatin and paclitaxel in relapsed OC
	NCT03314740 BAROCCO	II	Randomized weekly paclitaxel vs cediranib-olaparib with continuous schedule vs cediranib-olaparib with intermittent schedule for platinum refractory or resistant recurrent HGSOC
	NCT02983799	II	Non Randomized, Non Comparative Olaparib for platinum-sensitive or partially platinum-sensitive, relapsed, HGS/EOC with at least 1 prior line of platinum-based chemotherapy, in gBRCAm, sBRCAm, or HRD subgroups
	NCT02571725	I-II	Non Randomized, Non Comparative Olaparib and CTLA-4 Blockade Tremelimumab for BRCAm recurrent OC
	NCT02477644 PAOLA-1	III	Randomized olaparib vs placebo for advanced FIGO stage IIIB - IV HGS/EOC with standard first-line platinum-taxane chemotherapy and bevacizumab concurrent and in maintenance, ≥3 cycles of bevacizumab in combination with the 3 last cycles of platinum-based chemotherapy
	NCT01445418	I	Non Randomized, Non Comparative olaparib + carboplatin for gBRCAm and sporadic OC
	NCT03462342 CAPRI	II	Non Randomized, Non Comparative ATR inhibitor AZD6738 + olaparib for recurrent HGSOC (platinum-sensitive or -resistant)
	NCT03579316	II	Randomized Non-Comparative adavosertib AZD1775 alone or with olaparib for recurrent OC during olaparib progression

(*Continued*)

Table 5 (Continued).

Drug	Trial	Phase	Design
	NCT03699449 AMBITION	II	Randomized olaparib+cediranib, durvalumab + olaparib, durvalumab + chemotherapy, durvalumab + tremelimumab + chemotherapy; a biomarker-driven targeted therapy for HRD platinum-resistant recurrent OC
	NCT02345265	II	Non Randomized, Non Comparative olaparib + cediranib for recurrent OC
	NCT02121990	I	Dose-escalation study of IP cisplatin, IV/IP paclitaxel, IV bevacizumab, and oral olaparib for newly diagnosed OC
	NCT02489006 NEO	II	Randomized, neoadjuvant olaparib for platinum sensitive recurrent HGSOC prior to surgery and chemotherapy
	NCT02953457	I/II	Non Randomized, Non Comparative olaparib together with durvalumab and tremelimumab for gBRCAm recurrent or refractory OC
	NCT02898207	I	To determine the safety and best dose of olaparib + HSP90 inhibitor onalespib for recurrent OC
	NCT01116648	I/II	To determine the safety and best dose of cediranib + olaparib for recurrent OC
	NCT02208375	Ib	To determine the MTD of olaparib + oral mTORC1/2 inhibitor AZD2014 or AKT inhibitor AZD5363 for recurrent OC
Rucaparib	NCT02855944 ARIEL 4	III	Randomized rucaparib 600mg po bid vs chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, cisplatin/gemcitabine, paclitaxel, carboplatin, cisplatin) for relapsed or progressing BRCAm HGOC ≥2 prior regimens
	NCT03522246 ATHENA	III	Randomized rucaparib and nivolumab as maintenance treatment following Response to front-line platinum-based chemotherapy in newly-diagnosed ovarian cancer
	NCT03462212 MITO25	II	Randomized first line therapy of carboplatin-paclitaxel-bevacizumab (in combination and maintenance) vs carboplatin-paclitaxel-bevacizumab-rucaparib (rucaparib only in maintenance) vs carboplatin-paclitaxel-rucaparib (rucaparib only in maintenance) on PFS in patients with advanced HGOC.
	NCT03552471	I	To determine the safety and best dose of mirvetuximab soravtansine and rucaparib camsylate for recurrent OC
Niraparib	NCT02354586 QUADRA	II	Non Randomized, Non Comparative niraparib 300mg po qd for platinum-resistant or heavily pretreated HGSOC following 3 or 4 prior regimens, a response ≥6ms to first-line platinum based chemo
	NCT02655016 PRIMA	III	Randomized niraparib 300mg po qd vs placebo for first-line maintenance HGS/EOC stage III-IV with CR/PR to front-line platinum-based chemo
	NCT02354131 AVANOVA	I/II	Randomized niraparib vs bevacizumab-niraparib for platinum-sensitive relapsed HGS/EOC
	NCT03326193	II	Non Randomized, Non Comparative bevacizumab-niraparib for first-line maintenance HGS/EOC with CR/PR to front-line platinum-based chemo + bevacizumab≥1 debulking surgery
	NCT03602859 FIRST	III	Standard platinum-based chemo + Randomized [TSR-042 (anti-PD-1 antibody) + (niraparib + TSR-042) maintenance vs placebo + (niraparib + placebo) maintenance vs placebo + (placebo + placebo) maintenance for first line treatment of newly diagnosed stage III or IV non mucinous ovarian cancer
	NCT03574779 OPAL	II	To determine the safety and efficacy of niraparib + TSR-042 + bevacizumab for recurrent OC
	NCT03695380	Ib	Randomized, Non Comparative cobimetinib + niraparib ± atezolizumab for advanced platinum-sensitive OC
	NCT03598270 ANITA	III	Randomized platinum-based chemotherapy ± atezolizumab + niraparib maintenance ± atezolizumab maintenance for recurrent OC and platinum treatment-free interval >6 months
	NCT02657889 TOPACIO	I/II	Non Randomized, Non Comparative niraparib + pembrolizumab for recurrent OC
	NCT03586661	Ib	To determine the best dose and safety of niraparib and copanlisib for recurrent OC
	NCT03651206	II/III	Randomized (TSR-042 + niraparib vs niraparib) vs chemotherapy for metastatic or recurrent ovarian carcinosarcoma after first line chemotherapy
	NCT03154281	I	To determine the safety of niraparib + everolimus for advanced OC

(*Continued*)

Table 5 (Continued).

Drug	Trial	Phase	Design
Veliparib	NCT01113957	II	Randomized veliparib + temozolomide vs PLD for recurrent HGSOC
	NCT02470585	III	Randomized carboplatin/paclitaxel + veliparib or placebo + veliparib or placebo maintenance for newly diagnosed HGSOC (stage III or IV)
	NCT01012817	I/II	To determine the safety and best dose of veliparib + topotecan for relapsed or refractory OC after prior platinum containing first-line chemotherapy
	NCT01459380	I	To determine the safety and best dose of veliparib + PLD + carboplatin + bevacizumab for recurrent OC
	NCT01145430	I	To determine the safety and best dose of veliparib + PLD for recurrent OC
	NCT01749397	I	To determine the safety and best dose of veliparib + floxuridine for metastatic OC
	NCT00892736	I	To determine the safety and best dose of veliparib for BRCAm cancer or platinum-refractory OC
	NCT00989651	I	To determine the safety and best dose of intravenous carboplatin/paclitaxel or intravenous and intraperitoneal paclitaxel/cisplatin in combination with continuous or intermittent veliparib and bevacizumab for newly diagnosed stage II-IV OC
Talazoparib	NCT03642132	III	Randomized avelumab + chemotherapy + maintenance of avelumab + talazoparib for untreated advanced OC
	NCT02326844	II	Non Randomized, Non Comparative talazoparib for BRCAm OC with prior PARP inhibitor treatment
	NCT03330405	Ib/II	To evaluate safety and anti-tumor activity of avelumab + talazoparib for recurrent platinum sensitive OC

Abbreviations: OC, epithelial ovarian, fallopian tube or primary peritoneal cancer; EOC, epithelial ovarian cancer; HGOC, High-grade epithelial ovarian, fallopian tube or primary peritoneal cancer; HGSOC, High-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer; HGS/EOC, High-grade serous or endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer; CR/PR, complete response or partial response; MTD, maximum-tolerated dose; g/sBRCAm, germline or somatic BRCA1/2 mutation; PLD, Pegylated liposomal doxorubicin. PFS, Progression-free survival; HRD, homologous recombination deficiency.

Combination of PARP inhibitors with antiangiogenic agents

Combination of olaparib with antiangiogenic agents

Cediranib is a highly potent inhibitor of VEGF receptors 1–3. Single-agent cediranib resulted in a response rate of 17% in a single-arm study of ovarian cancer patients, and the response rate increased to 26% in platinum-sensitive patients.[67,68] Cediranib has been shown to cause or augment local tumor hypoxia and has demonstrated an important role in modulating the tumor microenvironment in ovarian cancer.[62] In a randomized phase II study (NCT01116648) comparing single-agent olaparib and combined cediranib/olaparib in patients with platinum-sensitive recurrent HGOC, the response rate was high (79.6%) in the combination group, with equally notable PFS times of 17.7 months in the combination cohort and 9.0 months in the single-agent olaparib cohort (p=0.005). The gBRCAm status was equally distributed between the combination and single-agent olaparib groups. A PFS time of 5.7 months with single-agent olaparib and 16.5 months (p=0.008) with combination therapy was observed in the wild-type BRCA group. A PFS time of 16.5 months with single-agent olaparib and 19.4 months (p=0.16) with combination therapy was seen in gBRCAm carriers. Fatigue, diarrhea, and hypertension were the most common grade 3/4 AEs in the combination group, but these AEs were manageable and reversible with supportive care.[69]

Overview of ongoing studies with PARP inhibitors in ovarian cancer

As of November 2018, 123 clinical trials on PARP inhibitors, including olaparib (n=59, 48.0%), rucaparib (n=9, 7.3%), niraparib (n=19, 15.4%), veliparib (n=26, 21.1%), and talazoparib (n=10, 8.1%), in ovarian cancer registered in the ClinicalTrials.gov database are ongoing or completed with results yet to be published. Most of these studies focus on combination strategies, including combinations with antiangiogenic agents, chemotherapeutics, and the newly approved bevacizumab. The aims of the combination strategy are to overcome the requirement of BRCA mutation or HRD and to further enhance the efficacy of PARP inhibitors without additional toxicity. Some studies emphasize the role of somatic BRCA mutations, aberrations in other genes in the BRCA pathway or other biomarkers to predict the response to PARP inhibitors. The

striking improvement in PFS with olaparib maintenance in gBRCA1/2-mutated ovarian cancer patients has not translated into improved OS. Since a substantial proportion of BRCA1/2-mutated HGSOC patients retain sensitivity to platinum following progression on olaparib, it is appropriate to offer a further course of olaparib to these patients. A further course of olaparib might consolidate the gains from the first course of olaparib, improving PFS such that OS also increases. Thus, two or more courses of PARP inhibitor maintenance therapy are initiated, aiming to retain the OS advantage. In addition, more clinical trials are ongoing to investigate the efficacy of PARP inhibitors compared with that of standard-of-care chemotherapy in platinum-resistant or progressive ovarian cancer with or without BRCA mutations. Table 5 shows the critical ongoing trials of PARP inhibitors (olaparib, rucaparib, niraparib, veliparib and talazoparib) in ovarian cancer.

Critical ongoing trials of olaparib in ovarian cancer

SOLO3 (NCT02282020), a phase III trial of olaparib as maintenance monotherapy, is in progress.[31,36] SOLO3 aims to confirm whether olaparib is superior to single-agent non-platinum-based chemotherapy (including weekly paclitaxel, topotecan, PLD, or gemcitabine) for patients with gBRCA1/2-mutated platinum-sensitive relapsed ovarian cancer treated with at least two prior platinum-based lines of chemotherapy. Two phase III studies (NCT02446600 and NCT02502266) exploring the combination of cediranib and olaparib in ovarian cancer are ongoing. The first study (NCT02446600) aims to evaluate the efficacy and safety of single-agent olaparib or the combination of cediranib and olaparib versus standard platinum-based chemotherapy to assess the efficacy of these regimens in patients with recurrent platinum-sensitive ovarian cancer. The second study (NCT02502266) aims to evaluate the efficacy and safety of monotherapy with either olaparib or cediranib and the combination of cediranib and olaparib versus non platinum-based standard-of-care chemotherapy in a population of patients with recurrent platinum-resistant or refractory HGSOC enriched for non-gBRCAm patients, based on the improved clinical benefit observed with the combination of olaparib and cediranib in patients with BRCA wild-type/unknown status in the phase II study.[69] The combination strategy might overcome the requirement for BRCA mutation or HRD and achieve an optimal therapeutic effect.[62,69–71]

Critical ongoing trials of rucaparib in ovarian cancer

ARIEL2 Part 2 is in progress and will continue to evaluate the HRD status and rucaparib efficacy in ovarian cancer patients treated with at least 3 prior chemotherapy regimens. ARIEL4, a phase III trial (NCT02855944), is underway to further evaluate rucaparib versus standard-of-care chemotherapy regimens, such as carboplatin/paclitaxel, carboplatin/gemcitabine, cisplatin/gemcitabine, or single-agent paclitaxel/carboplatin/cisplatin, in patients with relapsed or progressive, BRCA1/2-mutated HGOC following at least two prior chemotherapy regimens.

Critical ongoing trials of niraparib in ovarian cancer

QUADRA, a phase II single-arm study, is underway to evaluate the safety and efficacy of niraparib in patients with advanced recurrent HGSOC who have received three or four previous chemotherapy regimens and have previously experienced a response lasting at least 6 months to first-line platinum-based chemotherapy (NCT02354586). QUADRA aims to evaluate the efficacy and safety of niraparib in the setting of 4th-/5th-line treatment for recurrence and the treatment of platinum-resistant or heavily pretreated disease. PRIMA (NCT02655016), a phase III randomized placebo-controlled study, aims to evaluate the efficacy and safety of niraparib maintenance treatment in patients with advanced (FIGO stage III-IV) HGS/EOC who demonstrate clinical CR/PR following the completion of first-line platinum-based chemotherapy. Patients with stage IV disease irrespective of residual disease after primary or interval debulking, inoperable stage III or IV disease, or stage III disease with visible residual disease after primary surgery are eligible for inclusion in this trial. Two trials aiming to evaluate the safety and efficacy of bevacizumab-niraparib combination therapy are ongoing. AVANOVA (NCT02354131) is a two-part, open-label study in which phase I aims to evaluate the safety and tolerability of bevacizumab-niraparib combination therapy, and phase II aims to evaluate the efficacy of niraparib versus bevacizumab-niraparib combination therapy in patients with platinum-sensitive ovarian cancer. Another phase II single-arm study aims to evaluate the safety and efficacy of bevacizumab-niraparib combination therapy as maintenance treatment in patients with advanced ovarian cancer following a response to first-line platinum-based chemotherapy with bevacizumab and

at least one prior attempt at debulking surgery (NCT03326193).

Critical ongoing trials of veliparib in ovarian cancer

A phase III clinical trial (NCT02470585) is ongoing to assess the efficacy and safety of veliparib in combination with concurrent and/or subsequent carboplatin/paclitaxel administration for patients with newly diagnosed advanced HGSOC (stage III or IV). In this study, PFS is the primary outcome, and OS and disease-related symptom scores are the secondary outcomes. Four other clinical trials are ongoing to evaluate the role of veliparib in combination with conventional cytotoxic chemotherapy (topotecan, carboplatin/paclitaxel/bevacizumab, PLD, or floxuridine) in first-line and recurrent treatment of ovarian cancer (NCT01012817, NCT00989651, NCT01145430, and NCT01749397).

Critical ongoing trials of talazoparib in ovarian cancer

A phase II trial (NCT02286687) is in progress to evaluate the efficacy of talazoparib for advanced cancer patients with somatic BRCA mutations, mutations/deletions in PTEN or PTEN loss, HRD, or mutations/deletions in other BRCA pathway genes. In addition, a phase I trial (NCT02316834) is in progress with an aim to determine whether certain characteristics of DNA affect the response of the disease to talazoparib therapy in patients with advanced ovarian cancer that has spread to other anatomical sites and usually cannot be cured or controlled with treatment.

Discussion and conclusion

Before PARP inhibitors, the only demonstrated efficient strategy for ovarian cancer maintenance treatment was bevacizumab maintenance, which delayed the PFS time to 3–4 months.[72–75] However, in SOLO2, the PFS was delayed to 15 months,[36] and in SOLO1, the PFS was delayed to up to 3 years.[39] Three patients with somatic BRCA1/2-mutated HGSOC were treated for >5 years with olaparib monotherapy and reported to achieve durable and long-term responses to olaparib (>5 years), and one of these maintained a response to olaparib for >7 years. Notably, at diagnosis, the last patient had a tumor with biallelic somatic deletion and loss-of-function mutation and thereby lacked a functional allele for the recovery of BRCA1 activity, indicating a potential cure.[76] The safety profiles of PARP inhibitors were mild to moderate, and AEs were manageable and reversible with supportive care. PARP inhibitors confer a certain risk for MDS/AML and should be administered with caution. This risk warrants further investigation.

PARP inhibitor maintenance therapy achieved substantial PFS benefit among patients with platinum-sensitive recurrent ovarian cancer after a CR/PR to the most recent regimen. SOLO1 demonstrated that olaparib maintenance therapy following a CR/PR to first-line platinum-based chemotherapy confers PFS benefits on patients with advanced primary BRCA1/2-mutated ovarian cancer; moreover, PRIMA, which aims to demonstrate the same indication for niraparib in these patients, is ongoing. Notably, to date, PARP inhibitor clinical trials have focused on serous and endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancers rather than on the mucinous or clear cell subtypes of EOC, carcinosarcoma or undifferentiated ovarian cancer. The significantly improved PFS benefit did not translate into an OS benefit in olaparib trials. The hypothesis that olaparib is insufficiently potent is unlikely to be supported, given the notable HRs in its favor, especially in patients with BRCA mutations. Thus, the most likely explanation for the lack of OS benefit is that effective post-progression therapy overcomes this benefit. Patient crossover to PARP inhibitor treatment after post-progression therapy has been demonstrated to be a confounding factor in analyzing the OS of patients with BRCA mutations.[35] The effect of PARP inhibitors on prolonging the chemotherapy-free interval might greatly improve patients' quality of life, and studies have shown that resistance to PARP inhibitors does not affect the subsequent response to platinum-based chemotherapy.[37,38]

Clinical trials of chemotherapeutics in combination with PARP inhibitors demonstrated the PFS benefit of the concurrent and sequential combination of olaparib with platinum-based chemotherapy compared with that of platinum-based chemotherapy alone and showed that the benefits are mainly derived from the maintenance monotherapy phase. However, it is unknown whether the regimen of dose-decreasing concurrent chemotherapy with olaparib followed by olaparib maintenance therapy is safer and more efficient than the standard dosing schedule of platinum-based chemotherapy followed by olaparib maintenance therapy for platinum-sensitive recurrent ovarian cancer patients. Considering the increased bone marrow suppression with concurrent use, the optimum strategy

is sequential rather than concurrent administration.[57] Some combination strategies expand the utility of PARP inhibitors to HR-proficient tumors. The combination of olaparib and cediranib greatly improved the efficacy of PARP inhibition in gBRCA1/2-mutated ovarian cancers and was also surprisingly active in non-BRCA1/2-mutated ovarian cancers, thus overcoming the requirement for underlying high-level HRD.[69]

To date, three trials have compared the efficacy of PARP inhibitors with that of chemotherapeutic agents in ovarian cancer treatment. PLD, a second-line chemotherapeutic drug, was not significantly different from olaparib in terms of efficacy measured by PFS in patients with BRCA1/2-mutated, recurrent ovarian cancer (disease recurrence within 12 months after prior platinum-based chemotherapy, including platinum-sensitive and platinum-resistant disease).[29] In SOLO3, the efficacy of olaparib is being compared with that of various single-agent non-platinum chemotherapies for the treatment of BRCA1/2-mutated, platinum-sensitive recurrent ovarian cancer. In ARIEL4, the efficacy of rucaparib is being compared with that of standard chemotherapy regimens (including platinum-based chemotherapy) for the treatment of BRCA1/2-mutated, relapsed or progressive ovarian cancer. The latter two trials are ongoing.

Patients with ovarian cancer undergo many relapse and treatment cycles, and the intervals between recurrences shorten with no available chemotherapeutics; moreover, patients die after treatment cessation. Some patients cannot tolerate the toxic effects of chemotherapeutics; thus, drugs cannot be administered at the required time and at the full dose, significantly reducing the effectiveness of chemotherapy, increasing the risk of chemotherapy resistance, and hastening the point at which no further drug is available. With the advent of the era of PARP inhibitors, patients with BRCA1/2-mutated ovarian cancer are treated with PARP inhibitor maintenance therapy following a CR/PR to platinum-based chemotherapy. As duration of PARP inhibitor maintenance therapy increases, recurrence is expected to be delayed indefinitely. In the near future, BRCA mutation-associated ovarian cancer is expected to become a chronic disease, and an OS benefit will be gained from PARP inhibitor maintenance. This occurrence will be a landmark in ovarian cancer treatment. The death curve for ovarian cancer patients will soon level out. Given the unprecedented PFS benefit of PARP inhibitor maintenance therapy in patients with BRCA1/2-mutated ovarian cancer, clinical trials specifically on PARP inhibitor maintenance therapy for non-BRCA1/2-mutated ovarian cancer should be initiated as soon as possible to augment the understanding of the benefits of PARP inhibitor maintenance therapy and inform the use of PARP inhibitors in this patient population.

Abbreviation list

PARP, Poly (ADP-ribose) polymerase; BRCA, Breast Cancer Susceptibility Gene; FDA, Food and Drug Administration; EMA, European Medicine Agency; EOC, Epithelial ovarian cancer; PFS, progression-free survival; OC, ovarian cancer; HRD, homologous recombination-deficient; EU, Europe; US, the United States; SSBs, single-strand breaks; DSBs, double-strand breaks; HR, homologous recombination; NHEJ, nonhomologous end-joining; g/s, germline and/or somatic; HGSOC, high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer; CR/PR, complete or partial response; gBRCAm, germline BRCA mutation; HGOC, high-grade ovarian carcinoma; ORR, objective response rate; OS, overall survival; MTD, maximum tolerated dose; HR, hazard ratio; 95% CI, 95% confidence interval; HGS/EOC, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian tube cancer; LOH, loss of heterozygosity; AEs, adverse events; MDS/AML, myelodysplastic syndrome/acute myeloid leukemia; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; PLD, pegylated liposomal doxorubicin; DLTs, dose-limiting toxicities; VEGF, vascular endothelial growth factor.

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Disclosure

The authors report no conflicts of interest in this work.

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