Treatment of Ovarian Cancer Beyond PARP Inhibition: Current and Future Options

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Abstract

Ovarian cancer is the leading cause of gynecological cancer death. Improved understanding of the biologic pathways and introduction of poly (ADP-ribose) polymerase inhibitors (PARPi) during the last decade have changed the treatment landscape. This has improved outcomes, but unfortunately half the women with ovarian cancer still succumb to the disease within 5 years of diagnosis. Pathways of resistance to PARPi and chemotherapy have been studied extensively, but there is an unmet need to overcome treatment failure and improve outcome. Major mechanisms of PARPi resistance include restoration of homologous recombination repair activity, alteration of PARP function, stabilization of the replication fork, drug efflux, and activation of alternate pathways. These resistant mechanisms can be targeted to sensitize the resistant ovarian cancer cells either by rechallenging with PARPi, overcoming resistance mechanism or bypassing resistance pathways. Augmenting the PARPi activity by combining it with other targets in the DNA damage response pathway, antiangiogenic agents and immune checkpoint inhibitors can potentially overcome the resistance mechanisms. Methods to bypass resistance include targeting non-cross-resistant pathways acting independent of homologous recombination repair (HRR), modulating tumour microenvironment, and enhancing drug delivery systems such as antibody drug conjugates. In this review, we will discuss the first-line management of ovarian cancer, resistance mechanisms and potential strategies to overcome these.

Key Points

Poly (ADP-ribose) polymerase inhibitors (PARPi) are efficacious in ovarian cancer, but development of resistance has emerged as a critical challenge in improving treatment success.

Key mechanisms of resistance to PARPi are restoration of homologous recombination repair function, stabilization of the replication fork, changes in PARP function, and activation of alternate pathways.

Potential strategies to circumvent resistance include boosting the PARPi activity by combining with other drugs or using drugs acting on non-cross-resistant pathways.

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1 Introduction

Ovarian cancer (OC) is the eighth most common malignancy globally, accounting for 313,959 cases and 207,252 deaths annually. Although among gynecologic cancers its incidence is third after cervix and uterine, it is responsible for more deaths [1, 2]. The 5-years cause-specific survival ranges from 20% in stage IV and 40% in stage III to 70% in stage II and 90% in stage I [3]. Although >80% of cases are sporadic and without known hereditary predisposition, about 15–20% of patients have germline mutations. Half of the patients have alterations in genes involved in homologous recombination repair (HRR) pathways, an important DNA damage response (DDR) pathway [4, 5].

Poly (ADP-ribose) polymerase inhibitors (PARPi) have been extensively studied in OC and have demonstrated broad activity in both first-line and recurrent settings. In first-line and platinum-sensitive recurrent OC (PSOC), PARPi have shown efficacy in maintenance (as a single agent and with bevacizumab) as well as in combination with chemotherapy [6–13]. However, due to overlapping toxicities in combination with chemotherapy requiring dose reductions, PARPi are recommended as maintenance therapy only. PARPi have also been evaluated as treatment

in recurrent OC with BRCA mutations but this is not the preferred treatment option as recent reports demonstrated a lack of overall survival (OS) benefit [14].

2 DNA Damage Repair (DDR) Pathways

DNA damage occurs constantly in response to internal and environmental factors, and evolution has allowed for robust and overlapping repair mechanisms, to maintain DNA integrity. DNA damage due to various endogenous and exogenous influences is sensed by the cells, and repair pathways are activated based on the type of damage [15, 16]. Mismatch repair (MMR) pathways are activated in response to replication errors, bulky adducts (pyrimidine dimers produced by ultraviolet [UV] exposure) are repaired by nucleotide excision repair (NER), and single-strand DNA breaks (SSB) by base excision repair (BER). Poly (ADP-ribose) polymerase (PARP) is an enzyme involved in the repair of SSBs in the BER pathway (Fig. 1) [17]. Double-stranded DNA breaks (DSB) are produced if cells are exposed to ionizing radiations or chemotherapy drugs, and may lead to genomic instability. These are usually repaired by either the homologous recombination repair (HRR) pathway, which is a high-fidelity, error-free system as it uses sister chromatids as a template, or by the non-homologous end-joining (NHEJ) pathway, which is more efficient but prone to errors (Fig. 1). Impairment in DSB repair due to germline or somatic alterations or epigenetic silencing of genes involved in the HRR pathway is referred to as homologous recombination deficiency (HRD). These pathways are interconnected and work in concert along with cell cycle checkpoints to provide overlapping redundant repair mechanisms to ensure effective repair pathways in case one fails to repair the DNA damage. However, this also allows for an inherent vulnerability as alteration in these pathways by genetic, epigenetic, or other mechanisms can drive malignant transformation in the cells, as in the case of BRCA mutations [18–22]. This simultaneously presents a mechanism of malignant transformation as well as the potential to harness this inherent vulnerability therapeutically by exploiting synthetic lethality in malignant cells.

2.1 Biomarkers of Homologous Recombination Deficiency

HRD is widely used as a prognostic and predictive biomarker in the management of OC. Currently, validated assays such as myChoice HRD and FoundationOne CDx measure genomic scars using next-generation sequencing (NGS) and provide a threshold to quantify HRD. These tests have demonstrated good predictive value for PARPi activity

in platinum-sensitive OC. However, their application is limited in the relapse setting as they may not be precise in estimating HRD status in platinum resistance [23–25].

HRD status is dynamic and can be influenced by prior therapy and the acquisition of resistance mechanisms. Genomic scars are permanent and tend to persist even when HRR is restored. Therefore, functional assays that can reflect the dynamic HRD status by estimating RAD51 loading or BRCA1 promoter methylation are being developed [26]. RAD51 loading on single-stranded DNA is mediated by BRCA2 and is a crucial step in HRR. This is lost if there is any alteration in the HRR pathway upstream of RAD51. Initial assays, such as the REcombination CAPacity (RECAP) test, induce ex vivo DNA damage in fresh tumour tissue by ionizing radiation. HRR proficiency is assessed by the cell's ability to repair the damage by staining with RAD51, and RAD51 foci per cell are quantified by fluorescence microscopy. However, the prerequisite of fresh tumour tissue and ex vivo irradiation makes its clinical use difficult [27].

To overcome these challenges, an assay utilizing γH2Ax immunostaining to estimate endogenous DNA damage in formalin-fixed paraffin-embedded (FFPE) tissue has been developed. This can be performed on treatment-naive as well as post-chemotherapy specimens with low tumour content, thereby providing dynamic HRD monitoring. Although the assay predicted response to platinum therapy, it lacks prospective validation and predictive value for PARPi therapy [28].

Another test that can detect dynamic HRD is the BRCA1 promoter methylation assay. It can be performed on FFPE tissue by digital droplet polymerase chain reaction (ddPCR). Methylation status is altered by treatment and loss of BRCA1 methylation has been shown to restore its activity. However, its utility is limited as BRCA1 methylation is seen in only 15% of patients with OC [29]. These functional tests are promising and can extend the predictive utility of genomic scar assays, but require validation in randomized clinical trials.

3 Current Management in Ovarian Cancer

3.1 Surgery and Adjuvant Chemotherapy

Initial management of OC consists of primary debulking surgery (PDS) followed by adjuvant systemic therapy [30]. The goal of surgery is to remove the tumour completely to ideally no residual disease (R0 resection), as this is the most important factor associated with long-term survival [31, 32]. Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is recommended in cases where optimal cytoreduction is not achievable or the patient is deemed unfit due to medical reasons [33–35].
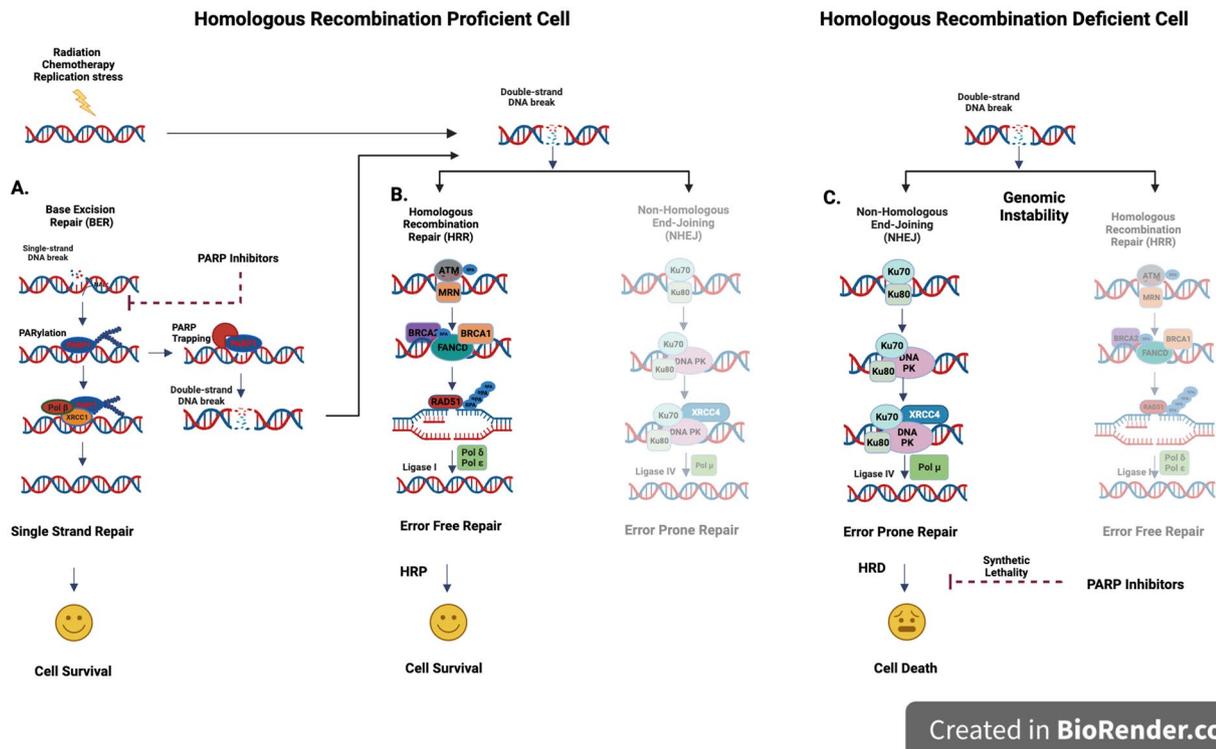
Fig. 1 Mechanisms of DDR. SSB and DSB are introduced in genome in response to external or internal stimuli. **A** BER is the major pathway for the repair of SSB. It involves recognition of SSB and the recruitment of PARP enzymes at the DNA damage site. PARylation is initiated by the transfer of ADP-ribose residues from NAD+ to PARP, relaxes chromatin. DNA polymerase and DNA ligase III are recruited to repair DNA damage. PARP inhibitors promote 'PARP trapping' by blocking PARylation and preventing dissociation of PARP from the SSB site. Unrepaired SSB is converted to DSB. **b** HRR is the predominant pathway for DSB repair in normal cells. The DSB are sensed by the MRN complex, which activate HRR by recruiting various effector proteins such as ATM, BRCA1, BRCA2, RAD51, and FANCD. It is a high-fidelity error-free system as it uses sister chromatids as a template. NHEJ is a secondary pathway that is less active in normal cells and is error prone. **c** In the HRD state, NHEJ becomes the more predominant pathway, and DNA damage is accumulated during the repair process, leading to genomic instability. *BER* base excision repair, *DDR* DNA damage repair, *DSB* double-stranded breaks, *HRD* homologous recombination deficiency, *HRR* homologous recombination repair, *MRN* Mre11-Rad50-Nbs1, *NAD+* nicotinamide adenine dinucleotide, *NHEJ* non-homologous end joining, *PARP* poly (ADP-ribose) polymerase, *PARylation* poly (ADP-ribosyl)ation, *SSB* single-stranded breaks. Created with Biorender.com

Adjuvant chemotherapy is indicated in all patients with advanced OC or early OC with stage IC or II disease, and high-grade histology [36]. Six cycles of carboplatin (area under curve [AUC] 5–6) and paclitaxel (175 mg/m^2) administered intravenously every 3 weeks is the preferred regimen [37]. Results from the Gynecologic Oncology Group (GOG) 172 trial favoured adjuvant intraperitoneal chemotherapy in patients with <1 cm residual disease post PDS-based, but more recent data from the GOG 252 trial do not support this approach [38, 39].

3.2 Antiangiogenic Agents

Bevacizumab is a humanized monoclonal antibody that prevents binding of vascular endothelial growth factor (VEGF) to the endothelial receptors and inhibits tumour angiogenesis [40]. It is the first targeted therapy to demonstrate improvement in survival in advanced OC. The role of bevacizumab as maintenance therapy in advanced OC was evaluated in two large, randomized trials. In ICON 7, patients with OC post PDS showed progression-free survival (PFS) improvement with maintenance bevacizumab (19.0 months vs. 17.3 months; hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.7–0.9). High-risk patients (stage III with residual disease >1 cm, and inoperable stage III and IV disease) showed significant improvement in both median PFS (15.9 vs. 10.5 months; HR 0.68) and median OS (36.6 vs. 28.8 months; HR 0.64) with bevacizumab [41, 42]. In GOG-0218, patients with newly diagnosed incompletely resected stage III or IV OC showed improved PFS (HR 0.7, 95% CI 0.62–0.82; $p < 0.001$) with maintenance bevacizumab. A post hoc analysis showed improved PFS as well as OS in patients who had ascites at onset [43, 44]. Intrinsic tumour chemosensitivity has been suggested as a marker to better define the population who benefit from bevacizumab. It is measured by cancer antigen (CA)-125 ELIMination rate constant K

(KELIM) score, calculated using CA-125 kinetics during the initial 100 days of treatment. Chemosensitive tumours have a KELIM score ≥1.0, while chemoresistance tumours have a KELIM score <1.0 [45]. A retrospective analysis of the ICON-7 trial showed that high-risk patients with a KELIM score <1 had better OS (median OS 29.7 vs. 20.6 months; HR 0.78, 95% CI 0.58–1.04: $p = 0.09$) [46]. Findings were confirmed in the GOG-0218 validation study in which patients with a KELIM score <1 showed improved median PFS (9.8 vs. 6.1 months; HR 0.70, 95% CI 0.59–0.82) and OS (36.3 vs. 31.8 months; HR 0.87, 95% CI 0.73–1.03). The highest benefit was observed in high-risk patients with a KELIM score of <1 [47].

3.3 Poly (ADP-Ribose) Polymerase Inhibitors (PARPi)

3.3.1 Mechanism of PARPi

PARP 1 and 2 are critical components for the repair of SSBs in the cell [48]. These recognize SSBs, bind at the site of DNA damage, and initiate poly (ADP-ribosyl)ation (PARylation), which involves the transfer of ADP-ribose or poly ADP-ribosyl (PAR) residues from nicotinamide adenine dinucleotide (NAD+) and PARP proteins to itself or other proteins [49]. PARylation causes relaxation of the chromatin and the PARP proteins are detached from the site. Various effector proteins such as DNA polymerase-β and DNA ligase III are recruited and damaged DNA is repaired [50].

PARPi act by multiple mechanisms. The most important among these is 'PARP trapping'. PARPi block PARylation and prevent the dissociation of PARP from the chromatin, leading to trapping of PARP at the sites of SSBs and preventing its repair. Furthermore, PARPi directly inhibit the activity of PARP by competitively binding to the NAD+ site and blocking the DNA repair [51]. Synthetic lethality between PARPi and defective HRR occurs as inhibition of PARP activity causes collapse of the replication fork (RF) and the consequent generation of DSBs. Repair of DSBs by error prone NHEJ results in accumulation of DNA damage, chromosomal instability, cell cycle arrest and cell death by apoptosis [52, 53].

Mechanism of PARPi activity in HRD-negative OC is not well understood. PARPi-induced immune activation, ribosome biogenesis, and regulation of gene transcription have been suggested alternative mechanisms in such cases [54–56].

3.3.2 PARPi Maintenance

Currently, three PARPi (olaparib, niraparib and rucaparib) are available as maintenance therapy after initial

platinum-based chemotherapy in newly diagnosed OC. Major trials of PARPi maintenance in first line are summarized in Table 1. In the SOLO1/GOG 3004 trial, patients with advanced OC (CR/PR post platinum-based chemotherapy) with germline or somatic BRCA mutation were randomized to olaparib 300 mg twice daily or placebo up to 2 years. Initial results showed significant improvement in PFS (56.0 vs. 13.8 months; HR 0.33, 95% CI 0.25–0.43; $p < 0.001$) [57, 58]. A recent update after a follow-up period of 7 years showed significant OS benefit, with 67.0% of patients taking olaparib still alive compared with 46.5% taking placebo (HR 0.55, 95% CI 0.40–0.76; $p = 0.0004$) [59]. In the PRIMA trial, patients with advanced high-grade serous or endometrioid OC post PR/CR to platinum-based chemotherapy were randomized to niraparib 300 mg once daily (200 mg once daily if body weight <77 kg, platelet count <150,000/mm^3, or both) and placebo for up to 3 years. That trial excluded patients who had no visible residual disease after PDS. At a median follow-up of 13.8 months, there was significant improvement in the median PFS in the overall population (13.8 months vs. 8.2 months; HR 0.62, 95% CI 0.50–0.76), HRD-positive (21.9 months vs. 10.4 months; HR 0.43, 95% CI 0.31–0.59) and HRD-negative (8.1 months vs. 5.4 months; HR 0.68, 95% CI 0.49–0.94) subgroups. OS data are not mature yet but there is a trend towards improved OS in all subgroups [7]. In the ATHENA-MONO trial, patients with advanced high-grade OC post PR/CR to platinum-based chemotherapy were randomized to rucaparib 600 mg twice daily for up to 2 years, or placebo. At a median follow-up of 24 months, the median PFS was improved with rucaparib in the overall population (20.2 months vs. 9.2 months; HR 0.52, 95% CI 0.40–0.68) and the HRD-positive (28.7 months vs. 11.3 months; HR 0.47, 95% CI 0.31–0.72), and HRD-negative subgroups (12.1 months vs. 9.1 months; HR 0.65, 95% CI 0.45–0.95) [60].

The PAOLA-1 study was conducted to explore the role of adding olaparib maintenance in the context of standard therapy with chemotherapy plus bevacizumab in advanced OC. In this trial, patients with stage III/IV high-grade serous or endometrioid OC who were in CR/PR post platinum-based chemotherapy and bevacizumab continued bevacizumab and were randomized to olaparib 300 mg twice daily or placebo for up to 2 years. At a median follow-up of 22.9 months, PFS was significantly better in the olaparib with bevacizumab arm in the overall population (22.1 months vs. 16.6 months; HR 0.59, 95% CI 0.49–0.72) and the HRD-positive subgroup (37.2 months vs. 17.7 months; HR 0.33, 95% CI 0.25–0.45), but not in the HRD-negative (16.6 months vs. 16.2 months; HR 1.0, 95% CI 0.75–1.35) subgroup [6, 61]. Although OS data are still immature, a recent update demonstrated improved OS in the HRD-positive subgroup (65.5 months vs. 48.8 months; HR 0.62, 95% CI 0.45–0.85) but not in the overall population (47.3 months vs. 41.5 months; HR 0.92, 95% CI 0.76–1.12)

Table 1 Summary of PARP inhibitors in first-line maintenance treatment

Study	SOLO1/GOG 3004 [54–56]	PAOLA-1/ENGOT-OV25 [40, 41]	PRIMA/ENGOT-OV26/GOG-3012 [7]	ATHENA-MONO/GOG-3020/ENGOT-OV45 [57]
Number	391 (2:1)	806 (2:1)	733 (2:1)	538 (4:1)
Population	Stage III/IV high-grade serous or endometrioid OC post PR/CR to platinum-based chemotherapy	Stage III/IV high-grade serous or endometrioid OC post PR/CR to platinum-based chemotherapy plus bevacizumab	Stage III/IV high-grade serous or endometrioid OC post PR/CR to platinum-based chemotherapy[a]	Stage III/IV high-grade OC post PR/CR to platinum-based chemotherapy[+++]
CR/PR (%)	82/18	74/26	70/30	74/26
NACT	36%	49%	66.1%	51.1%
Stage	III: 85% IV: 15%	III: 70% IV: 30%	III: 65.3% IV: 34.7%	III: 75.6% IV: 24.4%
CA125 > ULN	95%	86%	92%	90%
BRCA status	BRCA-mutated	Irrespective of BRCA	Irrespective of BRCA	Irrespective of BRCA
Companion test	BRACAnalysis test, Myriad Genetics[b,c]	myChoice test, Myriad Genetics[b]	myChoice test, Myriad Genetics[b]	FoundationOne CDx[d]
Control arm	Placebo	Placebo with bevacizumab[e]	Placebo	Placebo
Experimental arm	300 mg twice daily for up to 24 months	Olaparib 300 mg twice daily for upto 24 months with bevacizumab[e]	Niraparib 200–300 mg once daily[f] for up to 36 months	Rucaparib 600 mg twice daily for up to 24 months
Primary endpoint	PFS	PFS in the overall population	PFS in HRD and the overall population[g]	PFS in HRD and the overall population[g]
Median follow-up duration	60 months	22.9 months	13.8 months	24 months
mPFS overall population	NA	22.1 months vs. 16.6 months (HR 0.59, CI 0.49–0.72)	13.8 months vs. 8.2 months (HR 0.62, CI 0.50–0.76)	20.2 months vs. 9.2 months (HR 0.52, CI 0.40–0.68)
mPFS BRCA-mutated	56.0 vs. 13.8 months (HR 0.33, CI 0.25–0.43)	37.2 months vs. 21.7 months (HR 0.31, CI 0.20–0.47)	22.1 months vs. 10.9 months (HR 0.40, CI 0.27–0.62)	NR vs. 14.7 months (HR 0.40, CI 0.21–0.75)
mPFS HRD-positive	NA	37.2 months vs. 17.7 months (HR 0.33, CI 0.25–0.45)	21.9 months vs. 10.4 months (HR 0.43, CI 0.31–0.59)	28.7 months vs. 11.3 months (HR 0.47, CI 0.31–0.72)
mPFS HRD-positive (BRCA wild-type)	NA	28.1 months vs. 16.6 months (HR 0.43, CI 0.28–0.66)	19.6 months vs. 8.2 months (HR 0.50, CI 0.31–0.83)	20.3 months vs. 9.2 months (HR 0.58, CI 0.33–1.01)
mPFS HRD-negative	NA	16.6 months vs. 16.2 months (HR 1.0, CI 0.75–1.35)	8.1 months vs. 5.4 months (HR 0.68, CI 0.49–0.94)	12.1 months vs. 9.1 months (HR 0.65, CI 0.45–0.95)
OS, BRCA-mutated	NR vs. 75.2 months (HR 0.55, CI 0.40–0.76)[++]	75.2[h] months vs. 66.9 months (HR 0.60, CI 0.39–0.93)	NA	NA
OS, overall population	NA	56.5 months vs. 51.6 months (HR 0.92, CI 0.76–1.12)	84% vs. 77% at 24 months (HR 0.70, CI 0.44–1.11)	NA
OS, HRD-positive	NA	75.2[h] months vs. 57.3 months (HR 0.62, CI 0.45–0.85)	91% vs. 85% at 24 months (HR 0.61, CI 0.27–1.39)	NA
OS, HRD-positive BRCA wild-type	NA	NR vs. 52 months (HR 0.71, CI 0.45–1.13)	NA	NA

Table 1 (continued)

Study	SOLO1/GOG 3004 [54–56]	PAOLA-1/ENGOT-OV25 [40, 41]	PRIMA/ENGOT-OV26/GOG-3012 [7]	ATHENA-MONO/GOG-3020/ENGOT-OV45 [57]
OS, HRD-negative	NA	36.8 months vs. 40.4 months (HR 1.19, CI 0.88–1.63)	81% vs. 59% at 24 months (HR 0.51, CI 0.27–0.97)	NA
Grade 3 or higher AEs	Anaemia 22%, neutropenia 8%, thrombocytopenia 1%	Hypertension 19%, anaemia 17%, neutropenia 6%, thrombocytopenia 2%	Anaemia 31.0%, thrombocytopenia 28.7%, neutropenia 12.8%	Anaemia 28.7%, neutropenia 14.6%, thrombocytopenia 7.1%
AML/MDS	1% vs, 0%	1.7% vs, 2.2%	0.3% vs, 0%	0.4% vs, 0%
Serious AEs	21% vs. 13%	31% vs. 31%	32.2% vs. 13.1%	NA
Dose reduction	32.1	39% vs. 6%	70.9%	49.4%
Dose discontinuation	11.5% vs. 2.3%	20% vs. 6%	12.0% vs. 2.5%	11.8% vs. 5.5%

AEs adverse effects, *AML* acute myeloid leukaemia, *CR* complete remission, *CI* 95% confidence interval, *HR* hazard ratio, *HRD* homologous-recombination deficiency, *LOH* loss of heterozygosity, *MDS* myelodysplastic syndrome, *mPFS* median progression-free survival, *NA* not applicable/available, a genomic instability score of ≥42 on the myChoice test, or both *NACT* neoadjuvant chemotherapy, *NR* not reported, *PARP* poly (ADP-ribose) polymerase, *PFS* progression-free survival, *PR* partial remission, *OC* ovarian cancer, *OS* overall survival, *ULN* upper normal of limit

++At a median follow-up of 88.9 months, significance was not achieved

+++Bevacizumab allowed during NACT

[a]Excluded patients with stage III disease who had no visible residual disease after primary debulking surgery

[b]HRD was defined as the presence of a *BRCA* deleterious mutation, a genomic instability score of ≥42 on the myChoice test, or both

[c]In China, germline testing by *BRCA1/2* genetic testing assay (BGI); tumour *BRCA1/2* mutation testing by Foundation Medicine

[d]FoundationOne CDx next-generation sequencing assay. HRD was defined as the presence of a *BRCA* deleterious mutation, LOH ≥16%, or both

[e]Bevacizumab at a dose of 15 mg/kg every 3 weeks for up to 15 months in total

[f]Trial amended for a starting dose of 200 mg once daily for patients with a baseline body weight of <77 kg, a platelet count of <150,000 per cubic millimetre, or both

[g]Hierarchical testing

[h]Median unstable; <50% data maturity

[62]. In this trial, patients potentially had a higher disease burden compared with SOLO1, as stage IV patients constituted 30% (vs. 17% in SOLO1) of the total population, 35% (vs. 22%) had residual macroscopic disease after surgery, and almost half (vs. 37%) of the patients received NACT. Furthermore, as there was no comparator arm with only olaparib maintenance, the role of the addition of bevacizumab to olaparib in this setting is difficult to determine.

PARPi maintenance has consistently shown higher benefit in BRCA-mutated and HRD-positive patients, and even in HRD-proficient patients, albeit this was more modest. Although benefit was observed in the HRD-negative population with niraparib maintenance in the PRIMA trial, the magnitude of benefit is lower compared with that of the HRD-positive population (HR 0.43 vs. 0.68). Similarly, benefit was observed with rucaparib in the ATHENA-MONO trial in the HRD-negative subgroup (HR 0.47 vs. 0.65). It should be noted that in all these trials, patients qualified for participation if they had demonstrable benefit to platinum—this functional predictive biomarker is quite important and may influence the predictive value of HRD status, particularly in the homologous recombination proficient (HRP) setting. Therefore, PARPi as maintenance are recommended in patients with advanced OC who respond to initial platinum-based therapy. Olaparib is recommended in patients with somatic or germline BRCA mutations, while olaparib in combination with bevacizumab is recommended in HRD-positive patients. Niraparib and rucaparib may be used irrespective of BRCA or HRD status. However, the optimal duration of maintenance is unclear. Olaparib ± bevacizumab and rucaparib were studied in maintenance for up to 2 years, while niraparib was administered for 3 years [6, 7, 57, 60]. If patients have not received maintenance PARPi in first-line therapy, they should be considered for PARPi after response to platinum-based therapy in the recurrent setting [9, 10].

It is noteworthy that 70–80% of patients with advanced OC respond to initial platinum-based therapy, while outcomes are poor in the remaining patients who do not respond to first-line platinum-based therapy. As such, options are limited in such patients because of a lack of data due to exclusion from clinical trials. Bevacizumab concurrently and in maintenance is an important drug in patients with suboptimally debulked and advanced disease, as well as patients who are HRP. Based on current data, patients who have advanced disease or who are at high risk should ideally be able to access both bevacizumab and PARPi, particularly if they have BRCA mutations or HRD.

4 Resistance to PARPi

With increasing use of PARPi as maintenance in the first-line setting, PARPi resistance has emerged as a major challenge in the management of OC. Many patients progress during the maintenance phase while others progress after discontinuation of PARPi. Two years of maintenance with olaparib was completed in 47.3% (123/260) of patients in SOLO1 (19.6% discontinued due to progression) and only 27.5% (148/537) of patients in PAOLA1 (36.5% discontinued due to progression). Similarly, in the PRIMA trial at a median follow-up of 13.8 months, 47% of patients were continuing niraparib (45% discontinued due to progression). Therefore, 35–45% of patients discontinue PARPi due to the development of resistance. Potential mechanisms of PARPi resistance (Fig. 2) include restoration of HRR activity, alteration of PARP function, stabilization of the RF, drug efflux by multidrug resistance (MDR) pumps, and activation of alternate pathways [63].

4.1 Restoration of Homologous Recombination (HR) Activity

PARPi act by blocking DNA damage repair via homologous recombination, and restoration of this activity is one of the common pathways of resistance. This can occur due to restoration of the functional homologous recombination repair pathway via reversion mutation in BRCA, loss of BRCA promoter methylation, presence of BRCA splice variants, or amplification of wild-type BRCA. Alternatively, homologous recombination repair activity may also be restored by activation of alternative DNA repair pathways, epigenetic changes and re-ignition of end resection due to loss of 53BP1.

Secondary mutations are be observed in 20–30% of patients with PARP resistance in BRCA-positive OCs [64]. These may restore the amino acid sequence similar to wild-type BRCA, restore the reading frame, or reverse epigenetic silencing. Most reversion mutations involve deletions of more than one base pair. These are usually subclonal and patients may demonstrate a heterogenous pattern of progression. Multiple mutations may be detected simultaneously by cell-free DNA analysis, which may result due to the emergence of multiple subclones due to the heterogenous nature of progression [65]. It occurs due to the inherent mutagenic nature of BRCA-mutated cancers as a result of dependence on error-prone DNA repair by NHEJ coupled with heterogeneity leading to multiple sites undergoing change, or as a result of evolutionary adaptation to therapy-induced alterations [64–66]. Furthermore, epigenetic changes such as methylation may cause silencing of HRR genes. Loss of promoter methylation may occur during the course of therapy and can also promote resistance to PARPi by activating silenced genes [67, 68]. Methylation status may predict response to PARPi therapy in recurrent OC [69].

Hypomorphic proteins with partial loss of activity may result due to alternative splicing of BRCA1. The BRCA1-Δ11q alternative splice isoform contains all functional
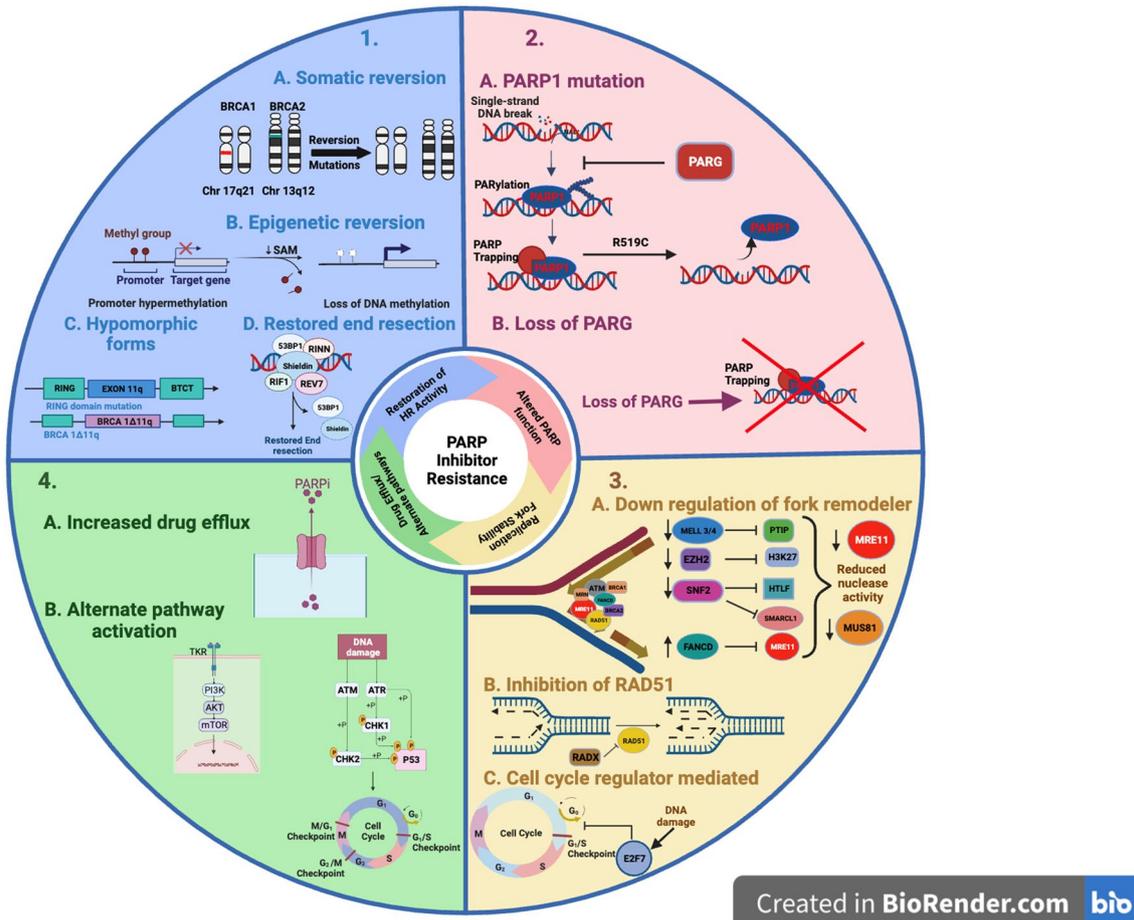
Fig. 2 Mechanisms of PARPi resistance. (**1**) Restoration of homologous recombination repair. **a** Somatic reversion mutation restores the open reading frame and activity of HRR genes. **b** Epigenetic reversion by loss of methylation can restore BRCA1/RAD51 function. **c** Hypomorphic proteins, viz. BRCA1D11q isoform, retains partial activity due to an intact functional domain. **d** Restoration of end resection through loss of 53BP1 and Shieldin also promote PARPi resistance. (**2**) Alteration in PARP function due to **a** PARP1 mutations (R519C), or **b** Loss of PARG can inhibit PARylation and PARP trapping. (**3**) Stabilization of the RF. **a** HRD leads to collapse of the replication fork due to unchecked activity of nucleases such as MRE11, DNA2 and MUS81. Downregulation of these nucleases by loss of RF remodelers (MLL, EZH2, PTIP, SMARCAL1, HLTF) and FANCD2 overexpression promotes fork stabilization and promotes PARPi resistance. **b** RADX depletion restores fork stabilization by regulating RAD51. RF can also be stabilized by loss of regulation of G1/S cell cycle checkpoint secondary to E2F7 depletion. (**4**) Drug efflux and activation of alternate pathways can also cause PARPi resistance. *53BP1* TP53-binding protein, *HRD* homologous recombination deficiency, *HRR* homologous recombination repair, *PARG* poly (ADPribose) glycohydrolase, *PARPi* poly (ADP-ribose) polymerase inhibitor, *PARylation* poly (ADP-ribosyl)ation, *RF* replication fork. Created with Biorender.com

domains except for exon 11 and is associated with resistance to platinum and PARPi [70]. Similarly, BRCA1 with mutations in the RING domain retain function and are associated with PARPi resistance [71].

Resection of break ends is a crucial step in HRR. In BRCA1 mutation, failure of resection of break ends prevents recruitment of RAD51 and further DNA repair. This is mediated by the TP53-binding protein (53BP1) pathway, which also involves the Shieldin and RIF1 proteins. In vitro loss of 53BP1 and Shieldin have been shown to be associated with resistance to PARPi [72, 73].

Mutation in the BRCT domain of BRCA1 leads to formation of the truncated form, which is degraded by proteosomes. Inhibition of proteasomal degradation by Hsp90-mediated stabilization promotes accumulation of these truncated proteins. As these truncated proteins retain some activity, accumulation may promote PARPi resistance [74].

4.2 Stabilization of the Replication Fork

In addition to BER, PARP1 plays an important role in stabilization of the RF during replication. The

MRE11-RAD50-NBS1 (MRN) senses DSB and binds the break site to initiate HRR. MRE11 possess endonuclease activity, RAD50 is an ATPase and has a DNA-binding site, while NBS1 is a regulatory protein that activates other proteins involved in HRR, viz. ATM and ATR [75]. Endonuclease activity of MRE11 is responsible for initiating end resection to create single-stranded DNA (ssDNA), which are essential for HRR. However, unchecked activity may lead to the collapse of the RF. BRCA prevents MRE11-mediated degradation of nascent DNA at RF [76]. In the presence of BRCA mutations, PARPi promote RF instability and collapse by nuclease (MRE11, DNA2 and MUS81)-mediated DNA degradation [77]. Fork stabilization by other pathways can therefore promote PARPi resistance.

Multiple remodelers are involved in fork collapse in HRD cells. EZH2 mediates H3K27 methylation and MUS81 recruitment to facilitate restart of the halted fork in BRCA-deficient cells. MELL3/4 triggers H3K4 methylation, which enhances PTIP accumulation and causes MRE11 recruitment. Members of the SNF2-family fork remodellers, including SMARCAL1, HLTF, and ZRANB3, are involved in MRE11-induced RF collapse, but is suppressed by FANCD2. Loss or depletion of these remodelers (EZH2, PTIP, SMARCAL1, HLTF, and ZRANB3) and FANCD2 overexpression promotes fork stabilization and causes resistance to PARPi [77–82].

RADX is an ssDNA-binding protein recruited to RFs and prevents fork collapse by regulating RAD51. In cancer cells, loss of RADX allows unchecked RAD51 activity, leading to the formation of DSB, while RADX depletion restores fork protection without restoring HRD in BRCA2-deficient cells [83].

E2F7 is a transcription factor regulating G1/S cell cycle checkpoint and is induced by DNA damage. It causes suppression of HRR by interfering with BRCA/RAD51 action. Depletion of E2F7 in BRCA-deficient cell lines has shown to confer resistance to platinum as well as PARPi [84].

4.3 Alteration of PARP Function

PARP1 attaches to the damaged DNA through its zinc finger DNA-binding domain. This interaction is also modified by allosteric effects of PARPi joining at the catalytic site. PARP1 function can be affected due to mutations or post-translational modifications in PARP1. Mutations within the DNA-binding domain are known to alter PARP trapping by preventing binding to DNA damage sites and resulting in resistance, while mutations in other sites may also cause resistance due to the allosteric effects of these mutations on DNA binding [85, 86].

PARylation is crucial for DNA repair by the homologous recombination pathway and involves the transfer of PAR residues from NAD+ and PARP. This leads to relaxation of the chromatin and recruitment of effector proteins (DNA polymerase-β and DNA ligase) at the site of DNA damage [49, 50]. The enzyme poly (ADPribose) glycohydrolase (PARG) can break PAR strands and reverse PARylation. PARP1-dependent DNA damage signalling is maintained and eventually results in PARPi resistance [87, 88]. PARG overexpression has been observed in OC cell lines and inhibition of PARG can augment the therapeutic effect of PARPi in OC cells [89, 90].

4.4 Drug Efflux

Another well-known mechanism of drug resistance is activation of drug efflux pumps. Multidrug-resistance protein 1 (MDR1), or P-glycoprotein (P-gp), is encoded by the ABCB1 gene. Long-term PARPi treatment can stimulate ABCB1 upregulation as a result of fusions or translocations [91]. Drug efflux as a mechanism of resistance may be observed in up to 15% of patients post progression on PARPi [92].

5 Managing PARP Resistance and Therapies Beyond PARPi

Understanding the mechanism of resistance is the key step before deciding further therapies. The resistant mechanisms discussed above can be targeted to resensitize the resistant OC cells to further therapy. Various modalities (Fig. 3) have been clinically evaluated, including the combination of PARPi with antiangiogenic agents, immune checkpoint inhibitors (ICIs), signal transduction pathway inhibitors, and targeting cell cycle checkpoints. These act by either overcoming resistance by enhancing the activity of PARPi using a combination with other targets in the DDR pathway, or bypassing the resistance mechanism through non-cross-resistant therapies. Alternatively, patients who had received PARPi as maintenance may still respond to PARPi rechallenge as monotherapy or as maintenance after chemotherapy.

5.1 Rechallenge PARPi

Many patients progress after completion of PARPi maintenance therapy. Thus, the rechallenge strategy has been tried in platinum-sensitive patients who respond to platinum-based chemotherapy, as these patients may not be truly resistant to PARPi. In the Quadra trial, niraparib monotherapy was evaluated in recurrent OC post three or more lines of therapy. Among 37 patients who had received prior PARPi therapy, one patient had a confirmed partial response (3%), and the clinical benefit rate at 16 weeks was 20% [93]. In the OReO trial, relapsed PSOC patients who had received one prior line of PARPi (irrespective of
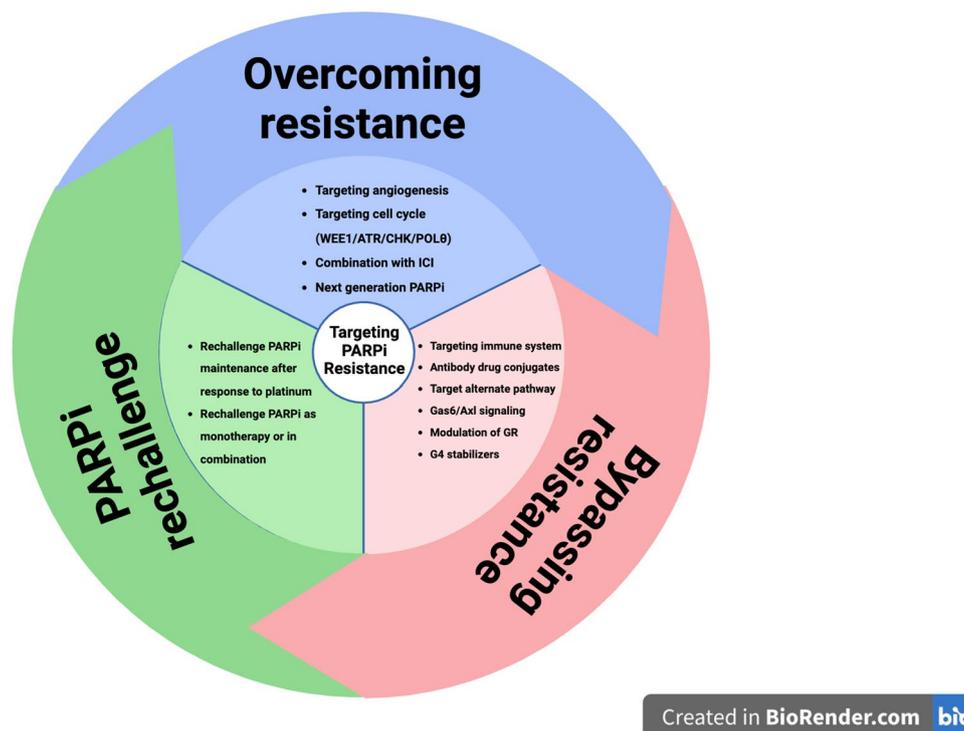
Fig. 3 PARPi resistance can be managed by either **a** PARPi rechallenge, especially in the context of platinum sensitivity; **b** Overcoming resistance: resistance mechanisms can be overcome through inhibiting angiogenesis, targeting cell cycle regulators, or combining with immune checkpoint inhibitors; or **c** Bypassing resistance: an alternative strategy is targeting the non-cross-resistant pathways that are independent of HRR. *GR* glucocorticoid receptors, *HRR* homologous recombination repair, *ICI* immune checkpoint inhibitor, *PARPi* poly (ADP-ribose) polymerase inhibitor. Created with Biorender.com

BRCA/HRD status), were randomized to either olaparib or placebo maintenance. PFS was significantly better in the BRCA-mutated cohort (median PFS 4.3 months vs. 2.8 months; HR 0.57, 95% CI 0.37–0.87; $p = 0.022$) as well as the non-BRCA-mutated cohort (median PFS 5.3 months vs. 2.8 months; HR 0.43, 95% CI 0.26–0.71; $p = 0.002$) [94]. The results were statistically significant but, clinically, of modest value. The trial suggests that PARPi retain activity in platinum-sensitive relapsed OC, and prior PARPi exposure does not essentially indicate complete resistance to therapy.

In the phase II MOLTO study, relapsed high-grade serous OC (HGSOC) patients with germline BRCA mutations were administered with two courses of olaparib maintenance. Patients who did not receive PARPi therapy were treated with platinum-based chemotherapy, followed by olaparib maintenance if they achieved CR/PR after platinum therapy. Patients who had previously received PARPi or who relapsed after receiving initial olaparib were retreated (if they had CR/PR or stable disease to platinum-based therapy) with olaparib (if platinum-free interval $\geq$ 6 months after initial

PARPi therapy) or olaparib with cediranib (if platinum-free interval < 6 months after initial PARPi therapy). Of the 27 patients who began trial treatment (17 PARPi-naive and 10 prior PARPi), 19 started platinum-based therapy at progression on prior PARPi. Among these patients, 12 (63%) received a second course of olaparib $\pm$ cediranib, and the duration of second olaparib maintenance was >6 months in 4 (33%) patients. No new safety concerns were identified with the olaparib rechallenge. There was a significant difference in the duration of first and second olaparib maintenance (12.1 months vs. 4.4 months; $p < 0.001$). Functional HRD evaluation and somatic copy-number alteration (SCNA) assays did not predict PFS after platinum therapy. This study showed that PARPi rechallenge is feasible but it would be difficult to conclude on its efficacy due to small numbers and the lack of a comparator placebo group [95].

Current evidence suggests that PARPi rechallenge is possible in some patients. Fresh tumour biopsy and liquid biopsy may detect BRCA reversion mutation when PARPi are ineffective. Further research is ongoing to select appropriate patients and is crucial to optimizing this strategy.

5.2 Overcoming PARPi Resistance

Enhancing the PARPi activity by combining it with other agents that can overcome the resistance mechanisms has been extensively studied. This includes targeting angiogenic pathways, cell cycle checkpoints, immune system, and using next-generation PARPi.

5.2.1 Antiangiogenic Agents

Antiangiogenic agents inhibit tumour angiogenesis and cause hypoxia in the tumour. Hypoxic changes in the tumour microenvironment (TME) exert multiple effects, including abnormal DNA damage and repair signals, leading to genetic instability. Inhibition of VEGFR3 also downregulates BRCA1/2 gene expression in the tumour cells. Thus the combination of PARPi with antiangiogenic agents may help overcome resistance [96–98].

In PSOC, a combination of niraparib and bevacizumab was evaluated in the AVANOVA2 trial. Patients were randomized to either niraparib and bevacizumab or niraparib alone. Improvement in median PFS was observed in the intention-to-treat (ITT) population (11.9 months vs. 5.5 months; HR 0.35, 95% CI 0.21–0.57), bevacizumab-naive patients (14.4 months vs. 6.0 months; HR 0.39, 95% CI 0.22–0.68) and patients without BRCA mutation (11.3 months vs. 4.2 months; HR 0.32, 95% CI 0.17–0.578), but not in patients who were previously exposed to bevacizumab (5.9 months vs. 3.1 months; HR 0.51, 95% CI 0.21–1.26) [99]. Cediranib is an oral multikinase inhibitor of VEGF receptors 1–3, and c-kit has been evaluated in recurrent OC but failed to show much promise. In a phase II trial in PSOC or presence of deleterious germline *BRCA1/2* mutation, 90 patients were randomized to olaparib with or without cediranib. The median PFS was significantly improved with the combination (16.5 vs. 8.2 months; HR 0.50; *p* = 0.007) but OS failed to reach statistical significance (44.2 vs. 33.3 months; HR 0.64; *p* = 0.11) [100]. No benefit was seen in a phase III trial evaluating olaparib with or without cediranib and platinum-based chemotherapy in platinum-sensitive relapsed OC [87]. In the EVOLVE trial, a translational phase II study in recurrent OC, patients (irrespective of platinum sensitivity) who had progressed on any prior PARPi received olaparib in combination with cediranib. Although responses were seen in only 8.8% of patients, about 50% were progression free at 16 weeks. Reversion mutations (19%), *CCNE1* amplification (16%), and *ABCB1* upregulation (15%) were common genomic alterations after prior PARPi exposure [92].

5.2.2 Targeting Cell Cycle

Dividing cells transverse through various phases of the cell cycle, viz G1, S, G2 and M. There are certain checkpoints that ensure genetic integrity of the cell while it passes from one phase to another through proteins that act in synergy to regulate this process of transition. The first checkpoint when the resting cell (G1 phase) commits to division is G1/S and is dependent on retinoblastoma (Rb) gene phosphorylation, which in turn is controlled by various cyclins (D and E), cyclin-dependent kinases (CDK) 2 and 4, p16/INK4 and p53. In the S phase, genetic material is duplicated, and in the G2 phase, cells prepare for mitosis by forming various proteins and organelles required in the M phase. G2/M transition is dependent on cyclin B and CDK1 phosphorylation, which is controlled by WEE1, checkpoint kinase (CHK) 1, polo-like kinase 1 (PLK1) and Aurora A. As p53 is universally mutated in serous OC, there is increased reliance on G2/M checkpoint, and blockage at this checkpoint can prevent cell cycle progression and growth of the tumour. Several cell cycle proteins, including cyclins, CDKs, CHK1 and 2, PLK1, and aurora kinases (Aurora A and Aurora B), are overexpressed in malignancies and are involved in carcinogenesis. Agents that act to inhibit these regulators of cell cycle have been shown to prevent tumour progression [101].

5.2.2.1 WEE1 Inhibition
WEE1 is a tyrosine kinase that regulates G2/M checkpoint by inhibiting CDK1 and regulates DNA synthesis in the S phase by inhibiting CDK2. Inhibition of WEE1 by adavosertib (AZD1775) promotes unchecked transition through the G2/M checkpoint, accumulation of damaged DNA, and sensitization to chemotherapy in p53-deficient cells [102]. In a randomized, phase II trial, patients with recurrent platinum-resistant/refractory OC were treated with gemcitabine plus either oral adavosertib or placebo. The adavosertib arm demonstrated significant improvement in objective response rate (ORR; 23 vs. 6%) and median PFS (4.6 vs. 3.0 months; HR 0.55, 95% CI 0.35–0.90). There was also a significant improvement in median OS (11.4 vs. 7.2 months; HR 0.56, 95% CI 0.35–0.91) [103]. In another four-arm, phase II study, two doses of adavosertib were combined with either gemcitabine, paclitaxel, carboplatin, or pegylated liposomal doxorubicin. In all patients, the ORR was 32% and 66.7% in combination with paclitaxel [104]. Both these trials showed that responders were enriched with high CCNE1-amplified tumours. The IGNITE trial investigated the efficacy of single-agent adavosertib in CCNE1-amplified (FISH) or overexpressed (IHC) platinum-resistant OC. Results from the cohort with overexpressed CCNE1 showed an ORR of 53% [105].

The efficacy of adavosertib post progression on PARPi was evaluated in the phase II EFFORT trial. Patients were randomized to either adavosertib alone or adavosertib with olaparib, and there was improvement in ORR (29 vs. 23%) and median PFS (6.8 vs. 5.5 months). BRCAwt patients

showed improved ORR compared with BRCAm patients in both arms [106].

5.2.2.2 ATR Inhibition

ATR plays a very important role in cell cycle by inducing RF stalling, and activates CHK1, cell division cycle 25 (CDC25A/C), and WEE1, which prevents the progression of the cell cycle. ATR inhibition can reverse PARPi resistance due to RF protection by promoting the division of cells with DNA damage [107]. In a phase II trial, patients with recurrent OC (≤1 line for platinum resistance) were randomized to gemcitabine with/without berzosertib. The median PFS was significantly better in the berzosertib arm (22.9 vs. 14.7 weeks; HR 0.57, 90% CI 0.33–0.98; $p = 0.044$) [108]. Authors identified replication stress as an important biomarker of response to gemcitabine. Patients with high replication stress (defined as at least one genomic alteration due to the dysregulated RB pathway and/or oncogene-induced replication stress) [109]. Single-agent activity of the oral ATR inhibitor RP3500 in advanced OC was recently demonstrated in the phase I TRESR trial, with an ORR of 25% in patients with synthetic lethal genomic alterations [110]. In the CAPRI trial, olaparib and ceralasertib combination showed an ORR of 46% in patients with BRCAm or HRD-positive PSOC post progression on PARPi [111].

5.2.2.3 Checkpoint Kinase Inhibition

CHK1 and CHK2 are kinases regulating the G2/M cell cycle checkpoint by phosphorylating CDC25C and CDC25A. In response to DNA damage, these are activated by ATM/ATR and arrest cell cycle at the G2/M checkpoint to permit DNA damage repair [112, 113]. Prexasertib, a selective inhibitor of CHK1/CHK2, prevents activation of the CHK and allows cell cycle progression under persistent replication stress. It was evaluated as monotherapy in recurrent BRCA wild-type OC in a phase II study. Partial response was observed in 8/24 evaluable patients (PR 33%), while grade 4 neutropenia was observed in 79% [114] of patients. In another phase II study in platinum-resistant or -refractory OC, PR was seen in 12.1% and 6.9% of patients, respectively [115]. Prexasertib and olaparib combination was studied in a phase I trial in advanced solid tumours. Among 18 patients with BRCA-mutated OC who had progressed on prior PARPi, 4 (22%) had confirmed PR [116].

5.2.2.4 POLθ Inhibition

DNA polymerase theta (Polθ) is an enzyme involved in theta-mediated end joining (TMEJ), an error-prone backup pathway of DSB repair. Inhibition of Polθ has shown synthetic lethality in BRCA-deficient cells. ART558 is an inhibitor of Polθ and can reverse PARPi resistance secondary to defects in the 53BP1/Shieldin complex [117].

5.2.3 Immune Checkpoint Inhibitors

PARPi have synergistic activity in combination with ICIs, primarily via action on the cGAS-cGAMP-STING pathways. PARPi upregulate STING, which promotes the release of proinflammatory cytokines in the TME and also upregulates expression of programmed cell death-ligand 1 (PD-L1) on OC cells [118, 119]. In the phase I/II TOPACIO/KEYNOTE-162 trial in women with recurrent OC or advanced triple-negative breast cancer (TNBC), niraparib was administered in combination with pembrolizumab. Among patients with OC, responses were modest, with an ORR of 18% and a disease control rate (DCR) of 65%. Furthermore, responses were observed irrespective of BRCA, platinum sensitivity, or prior bevacizumab administration [120].

5.2.4 Next-Generation PARPi

AZD5305 is a specific PARP1 inhibitor with better efficacy and safety profile compared with current PARPi. A phase I/IIa PETRA trial is currently evaluating AZD5305 in patients with advanced metastatic ovarian, breast, pancreatic or prostate cancer with loss-of-function mutation in BRCA1/2, PALB2, RAD51C or RAD51D and prior PARPi treatment. Initial reports showed an ORR of 28% [121]. At present, there are limited data to indicate whether second-line PARPi are effective at overcoming resistance to first-generation agents.

5.3 Bypassing PARPi Resistance

PARPi resistance can be bypassed through targeting non-cross-resistant pathways acting independently of HRR. Several approaches have been investigated, including modulating the TME, enhancing drug delivery to tumour cells, and targeting different pathways.

5.3.1 Targeting the Immune System

ICIs have thus far failed to demonstrate meaningful benefit in OC, both in first-line maintenance and in the treatment of recurrent OC. The mechanism of immune resistance in OC is not universal and several genetic, immune, and metabolic factors contribute to establish an immunosuppressive milieu and lack of response to ICIs [122, 123]. T cells infiltrating OC express inhibitory receptors, such as programmed cell death protein 1(PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte activation gene-3 (LAG-3), leading to impaired function of T cells. Tumour-infiltrating CD8-positive T cells secrete interferon-γ, which further upregulates PD-L1 expression on OC cells and macrophages [124–126]. Additionally, the impact of mutational

profile and anatomic sites has been suggested to contribute to the immunosuppressed and hostile TME [127]. However, a recent press release from sponsors of the DUO-O trial suggest significant PFS benefit with the addition of durvalumab to platinum-based chemotherapy and bevacizumab followed by durvalumab/olaparib/bevacizumab maintenance in newly diagnosed advanced OC [128]. DUO-O was a three-arm, placebo-controlled, randomized trial evaluating the efficacy of durvalumab in combination with platinum-based chemotherapy and bevacizumab, followed by maintenance with durvalumab and bevacizumab with or without olaparib in newly diagnosed patients with advanced OC.

In Javelin Ovarian 100, patients with newly advanced OC were randomized to chemotherapy (six cycles of carboplatin/paclitaxel) followed by avelumab maintenance, chemotherapy plus avelumab followed by avelumab maintenance (avelumab combination group), or chemotherapy followed by observation (control group). After interim analysis, the trial was stopped as PFS crossed the futility boundary (median PFS 16.6 months vs. 18.1 months vs. not reached) [129]. In Javelin Ovarian 200, recurrent platinum-resistant or -sensitive OC patients were randomized to avelumab, avelumab plus liposomal doxorubicin, or liposomal doxorubicin alone; no benefit was observed in median PFS [130]. In the IMagyn050 trial in newly advanced OC, patients were randomized to atezolizumab or placebo with paclitaxel/carboplatin and bevacizumab; median PFS was 19.5 vs. 18.4 months (HR 0.92, 95% CI 0.79–1.07; $p = 0.28$) in the overall population and 20.8 vs. 18.5 months (HR 0.80, 95% CI 0.65–0.99; $p = 0.038$) in the PD-L1-positive population [131].

In the ATALANTE/ov29 trial, patients with platinum-sensitive relapsed OC were randomized to atezolizumab or placebo with chemotherapy and bevacizumab. The median PFS in the overall population was 13.5 vs. 11.2 months (HR 0.83, 95% CI 0.69–0.99; $p = 0.041$), and 15.2 vs. 13.1 months (HR 0.86, 95% CI 0.63–1.16; $p = 0.30$) in PD-L1+ patients [132].

Currently, there are many trials exploring adoptive cell therapy, vaccine-based therapies, bispecific antibodies (BiTEs), chimeric antigen receptor therapy (CART), and oncolytic viruses, which may provide opportunities to bypass PARP resistance.

Nemvaleukin alfa is an engineered cytokine that selectively binds to the intermediate-affinity interleukin (IL)-2 receptor to preferentially activate and expand CD8+ T cells and natural killer (NK) cells with minimal expansion of CD4+ Tregs. It does not bind to high-affinity receptors due to steric hinderance, thereby avoiding adverse effects associated with it. In a phase I/II trial in multiple solid tumours, nemvaleukin alfa in combination with pembrolizumab showed an impressive ORR of 28.6% (including two

complete responses) and a DCR of 71.4% in heavily pretreated OC patients [133]. ARTISTRY-7 (NCT05092360), a phase III randomized study of nemvaleukin alfa and pembrolizumab versus chemotherapy in platinum-resistant OC is currently recruiting.

Ubamatamab is an MUC16/CD3 bispecific antibody. In this first-in-human phase I study in patients with recurrent platinum-resistant OC and elevated CA125, an ORR of 14.3% was observed in those receiving one or more full doses [134].

Maveropepimut-S (DPX-Survivac) is a T-cell-activating vaccine with T-cell epitopes derived from survivin (tumour-associated antigen). In combination with low-dose cyclophosphamide, Maveropepimut-S showed robust T-cell response in OC patients [135]. In the phase I PESCO trial, maveropepimut-S in combination with pembrolizumab and low-dose cyclophosphamide demonstrated tolerable adverse effects, with a response rate of 16% in the initial 24 patients [136]. Similarly, OSE2101 (a multiple-neoepitope vaccine restricted to HLA-A2-positive patients targeting TP53, MAGE2, MAGE3, CEA and HER2) is under evaluation as maintenance therapy (post platinum-based chemotherapy) alone or in combination with pembrolizumab in the TEDOVA trial [137].

5.3.2 Antibody Drug Conjugates

Antibody drug conjugates (ADCs) are monoclonal antibodies conjugated to a cytotoxic payload that aim to deliver the cytotoxic agents directly to the cancer cells, thereby minimizing the toxicity associated with its systemic exposure. These bind the cell surface antigens and are internalized by endocytosis. The antibodies are selective against tumour-associated antigens and are connected to the cytotoxic agent by a linker that is stable while in circulation but is dissociated after entering the cells [138]. Various antigens of interest in OC that are in clinical trials include folate receptor-α (FRα), NaPi2, tissue factor (TF), mesothelin, MUC16, protein tyrosine kinase 7 (PTK7), and Trop2 [139]. Mirvetuximab soravtansine is an ADC against FRα with soravtansine (microtubule inhibitor), as the cytotoxic payload has been studied as a single agent in a recurrent setting as well in combination with chemotherapy and bevacizumab. In the phase III FORWARD 1 trial, patients with platinum-resistant OC who had received one to three prior lines of therapy and had positive FRα expression (≥50% of tumour cells with any FRα membrane staining visible at ≤10× microscope objective) on their tumours were randomly assigned to receive mirvetuximab (6 mg/kg) or chemotherapy. Although the ORR (24% vs. 10%) and CA-125 responses (53% vs. 25%) were improved, there was no difference in terms of PFS in the ITT population (4.1 vs. 4.4 months) as well as high FRα expression (≥75%) [94]. In the

phase II, single-arm SORAYA trial, patients with platinum-resistant OC (PROC) who had received one to three prior lines of therapy and had high FRα expression (≥75% of viable tumour cells exhibiting ≥2+ level membrane staining intensity in the Ventana FOLR1 assay) were enrolled. All patients had received prior bevacizumab and about half of the patients had received prior PARPi therapy. At a median follow-up of 13.4 months, the ORR was 32.4% (95% CI 23.6–42.2%) and the median duration of response (DOR) was 6.9 months (95% CI 5.6–9.7 months). The most common adverse events (all grade) were blurred vision (41%), keratopathy (29%), and nausea (29%) [140].

Mirvetuximab soravtansine was recently granted FDA accelerated approval for platinum-resistant OC patients with high FRα expression [141]. The results differed in the two studies due to variable estimation criteria for FRα expression. In FORWARD1, patients with tumours having any level of expression on tumour cells were included, while in SORAYA, ≥2+ level membrane staining intensity was required. An exploratory analysis demonstrated that the predictive biomarker assay in the FORWARD 1 trial did not sufficiently enrich for high folate expressors. Therefore, careful selection of patients is required before considering them for these agents. MIRASOL, a randomized, phase III trial to evaluate the efficacy of mirvetuximab soravtansine compared with chemotherapy (weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan) in PROC (post one to three lines) has completed accrual. FRα testing was performed by the Ventana FOLR1CDx assay and high expression was defined as ≥75% of cells with PS2+ staining intensity. A recent press release by the sponsors reported improved ORR with mirvetuximab soravtansine (42.3 % vs. 15.9 %). Significant improvement in PFS (5.62 vs. 3.98 months; HR 0.65; $p < 0.0001$) and OS (16.46 vs. 12.75 months; HR 0.67; $p = 0.0046$) was also reported [142, 143].

In a phase Ib/II study, mirvetuximab was evaluated in combination with carboplatin and bevacizumab in patients with PSOC with one to two prior lines of therapy. ORR was observed in 81% of patients, with a median DOR of 10.7 months and median PFS of 12.0 months [144]. Mirvetuximab in combination with bevacizumab demonstrated an ORR of 39% and a median PFS of 6.9 months in heavily pretreated patients with PROC [145]. Similarly, an ORR of 43%, with a median PFS of 5.2 months, was observed in combination with pembrolizumab in PROC with two to four prior lines of therapy [146].

NaPi2B, a sodium-dependent phosphate transport protein, is expressed in 80–100% of OC cells, but not on normal ovarian tissue [147]. The anti-NaPi2b ADC lifastuzumab vedotin was evaluated in a phase II randomized trial in PROC. A higher ORR was observed compared with liposomal doxorubicin (34% vs. 15%), but PFS was not significantly improved [148]. Another anti-NaPi2b, upifitamab

rilsodotin, showed an ORR of 23% in the ITT population and 34% in patients with high NaPi2b expression in pretreated PROC [149]. TF is involved in the extrinsic pathway of coagulation and aberrant expression may be observed in a variety of solid tumours, including epithelial OC [150]. In a phase I/II trial of tisotumab vedotin (ADC against TF) in multiple advanced solid tumours, the ORR in OC patients was 13.9% [151]. Mesothelin is a glycoprotein important for cellular adhesions and is overexpressed in up to 88% of OC patients [152]. Anetumab ravtansine (AR) is a fully human ADC against mesothelin conjugated to a microtubule inhibitor. In a phase II randomized trial in platinum-resistant/refractory OC, a combination of anetumab with bevacizumab failed to show any benefit over paclitaxel/bevacizumab. The ORR was 55% with paclitaxel/bevacizumab compared with 18% in the experimental arm. The median PFS was 9.6 months with paclitaxel/bevacizumab compared with 5.3 months with anetumab/bevacizumab (HR 1.7, 95% CI 0.9–3.4) [153].

5.3.3 Modulation of Glucocorticoid Receptors

Cortisol binds to glucocorticoid receptors (GRs) and inhibits cell death by apoptosis, leading to chemotherapy resistance. GRs are abundantly expressed on OC cells and high expression is associated with poor outcomes [154]. Relacorilant is a selective modulator of GRs, which compete with cortisol and can reverse the cortisol-induced chemotherapy resistance in multiple solid tumours [155]. In a phase II, randomized study, recurrent PROC patients were randomized to nab-paclitaxel alone or nab-paclitaxel with intermittent (150 mg/day the day before, of, and after nab-paclitaxel administration) or a continuous schedule of relacorilant (100 mg daily). The intermittent schedule was associated with a significantly improved median PFS compared with nab-paclitaxel alone (5.55 vs. 3.76 months; HR 0.6, 95% CI 0.44–0.98; $p = 0.038$), but OS failed to reach statistical significance (13.9 vs. 12.2 months; HR 0.67, 95% CI 0.43–1.03; $p = 0.066$) [156, 157].

5.3.4 Gas6/Axl Signalling

Axl is a receptor tyrosine kinase associated with chemotherapy resistance and poor outcomes in various cancers. It is activated by the binding of its ligand Gas6 (growth arrest specific 6), which acts as growth factor and activates signalling pathways to promote cellular proliferation, invasion, migration, epithelial-mesenchymal transition, angiogenesis, immune evasion, and survival [158]. Axl is expressed on serous OC cells but not on healthy ovarian cells [159]. Batiraxcept (AVB-500) is a fusion protein containing the Fc region of heavy chain immunoglobulin (Ig) G1 fused to the extracellular region of Axl. It acts as a decoy receptor

and binds Gas6 with 200-fold high affinity. Batiraxcept was evaluated in phase Ib trial in patients with platinum-resistant OC in combination with paclitaxel or pegylated liposomal doxorubicin. In patients receiving paclitaxel, the ORR was 34.8% and the median PFS and OS was 3.1 and 10.3 months, respectively [160]. GOG-3059/ENGOT OV66 (NCT04729608) is a randomized, phase III study comparing the efficacy of batiraxcept (AVB-S6-500) in combination with paclitaxel in patients with platinum-resistant OC, and is currently recruiting.

5.3.5 G-Quadruplex Stabilizers

G-quadruplexes (G4) are transient guanine-rich tertiary structures that are found at promoter sites and telomeric regions in human genome. These are believed to be involved in gene regulation and other processes during cell division, but the precise role of G4 is still undetermined. G4 unwinding proteins/helicases remove these G4 structures in normal cells [161, 162]. Alteration in this process can cause transcriptional changes and DNA breaks, leading to genome instability. HRR is the predominant pathway involved in DNA damage repair in response to G4 alterations [163]. G4-induced genomic instability has been linked to carcinogenesis, although synthetic lethality in this context is being explored as a therapeutic target in HRD cancers [164]. CX-5461 (Pidnarulex) is a G4 stabilizer that promotes tertiary structure and RF arrest, leading to cancer cell death in HRD tumours. It was evaluated in phase I trial in multiple solid tumours and response was observed in 1 (14.2%) patient with BRCA2 mutations among 7 patients with OC. Overall responses were observed in 4/29 patients (ORR 13.8%) with BRCA2 and PALB2 alterations (breast, ovarian, pancreatic cancer) [165]. CX-5461 is currently being evaluated in a phase Ib trial in patients with HRD [166].

5.3.6 Chemotherapy

Chemotherapy remains an option in patients post progression on PARPi. Although there is an overlap between resistance mechanisms of PARPi and platinum, PARPi resistance does not necessarily denote platinum resistance. In ARIEL 4, a phase III study in relapsed OC patients with deleterious germline or somatic BRCA alterations and no prior PARPi, patients were randomized to rucaparib or chemotherapy (based on platinum sensitivity). Fully platinum-sensitive patients (platinum free interval >12 months) were administered platinum-based chemotherapy, while others received weekly paclitaxel. The primary endpoint was investigator-assessed PFS in the efficacy population (deleterious BRCA mutations without BRCA reversion mutations). Median PFS was significantly improved with rucaparib in the efficacy population (7.4 months vs. 5.7 months; HR 0.64, 95% CI

0.49–0.84); however, the median OS was better in patients receiving chemotherapy (25.4 months vs. 19.4 months; HR 1.31, 95% CI 0.99–1.72). This was mainly driven by the platinum-resistant subgroup. Similarly, in patients with BRCA reversion mutations, the median PFS was greater with chemotherapy (5.5 months vs. 2.9 months; HR 2.77, 95% CI 0.99–7.76). As crossover was permitted, 80 (69%) patients randomized to chemotherapy crossed-over to rucaparib, while 42.1% of patients in the rucaparib arm did not receive subsequent anticancer treatment. PFS2 (PFS during the first subsequent anticancer treatment) was better in patients crossing over to rucaparib. Furthermore, translational analysis showed that there was a decrease in BRCA reversion mutations in three of four patients randomized to paclitaxel (in the pre- and post-treatment plasma samples). This suggests that paclitaxel may reverse PARPi resistance due to BRCA reversion mutations [14, 167].

6 Conclusion

PARPi resistance has emerged as a major challenge in the management of OC. Ongoing research has provided valuable insight into the mechanisms of resistance to PARPi. Restoration of HRR and RF stability appears to be the major pathways involved. However, it may be difficult to ascertain the exact mechanism in a single patient due to complex interplay between the various pathways. This presents a challenge to develop newer therapies to overcome or bypass the resistance. Multiple trials are currently evaluating the newer agents and combinations targeting these pathways. Further translational research is warranted in this area, with the incorporation of biomarkers to direct the management strategy.

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