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PERSPECTIVE

Toward the precision use of Chinese PARP inhibitors in ovarian cancer: clinical progress, resistance mechanisms, and future perspectives

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Ovarian cancer (OC) ranks eighth in incidence and mortality among female cancers[1]. The global annual incidence of new OC cases increased from 238,700 to 324,398, while deaths rose from 151,900 to 206,839 from 2012 to 2022, respectively[1,2]. China reported the highest global numbers of OC in 2022 with 61,100 new cases and 32,600 deaths[3]. OC continues to pose a significant threat to women's health in China and worldwide.

The 5-year survival rate for early-stage OC after standardized treatment ranges from 70%–95%[4]. Due to the insidious onset and difficulty in early detection of OC, approximately 75% of patients are diagnosed at advanced stages. Treatment of advanced stage OC is frequently complicated by disease recurrence and the development of resistance to platinum-based chemotherapy, which together result in a 5-year survival rate of <40%[4]. The advent of poly(ADP-ribose) polymerase (PARP) inhibitors over the past decade has significantly expanded the therapeutic landscape of OC. Several PARP inhibitors (**Table 1**) are now approved for maintenance or later-line therapy for OC in China and internationally[5]. The series of studies involving fuzuloparib led by our team have provided high-level evidence supporting the clinical application of PARP inhibitors in China. However, acquired resistance remains a major challenge that limits therapeutic efficacy in patients. Elucidating the mechanisms underlying PARP inhibitor resistance and developing effective strategies to improve the prognosis of patients with drug resistance remain major priorities in current and future research. In this Perspective the mechanisms of action for PARP inhibitors, major clinical research progress of PARP inhibitors in China, and the mechanisms of resistance are summarized. Evidence from published cohort studies was integrated to outline the trial design strategies of PARP inhibitors to provide insights that improve efficacy and expand clinical benefit.

Mechanisms of action for PARP inhibitors

PARP inhibitors have shown remarkable clinical efficacy in OC, particularly in patients with homologous recombination deficiency (HRD), including patients harboring *BRCA1/2* mutations. The therapeutic advantage of PARP inhibitors lies in the ability to exploit synthetic lethality. Mechanistically, this effect is closely linked to a hierarchical cascade involving DNA damage, activation of the DNA damage response (DDR), and failure of homologous recombination (HR)-mediated repair (**Figure 1**). Therefore, understanding the interplay among DNA damage, DDR pathways, and synthetic lethality is essential for elucidating the antitumor effects of PARP inhibitors.

DNA damage

DNA damage is closely associated with the biology of OC. Approximately 50% of high-grade serous OCs exhibit genetic variations in DNA HR repair genes[4]. Single-strand breaks (SSBs) are the most common form of DNA damage. If not repaired, SSBs can be converted into double-strand breaks

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Table 1 Clinically approved PARP inhibitors and their first applications

Approved inhibitors	Targets	Year of first approval	Country of origin	First application	First indication	Key clinical trial	Major efficacy	Recommended dose
Olaparib	PARP1/2/3/4	2014	USA	Later-line treatment	*BRCA1/2*-mutated, advanced-stage cancer, refractory to ≥3 prior lines of therapy	NCT01078662	ORR of 34% with a median DoR of nearly 8 months	400 mg, bid, oral
Rucaparib	PARP1/2/3/4, TNKS1	2016	USA	Later-line treatment	*BRCA1/2*-mutated, advanced-stage cancer, refractory to ≥2 prior lines of therapy	NCT01482715, NCT01968213	53.8% objective response rate and a median duration of response of 9.2 months	600 mg, bid, oral
Niraparib	PARP1/2	2017	USA	Maintenance therapy	Advanced-stage, recurrent cancer, in CR or PR to platinum-based chemotherapy	NCT01847274	mPFS 21.0 months, HR = 0.27	300 mg, qd, oral
Fuzuloparib	PARP1/2	2020	China	Later-line treatment	*BRCA1/2*-mutated, advanced-stage cancer, refractory to ≥2 prior lines of therapy, CR or PR to platinum-based chemotherapy	NCT03509636	ORR of 69.9% and a median PFS of 12.0 months with an acceptable safety profile	150 mg, bid, oral
Pamiparib	PARP1/2	2021	China	Later-line treatment	*BRCA1/2*-mutated, advanced-stage cancer, refractory to ≥2 prior lines of therapy	NCT03333915	ORR of 64.6% (including 8 CRs) in gBRCA-mutated platinum-sensitive recurrent ovarian cancer and 31.6% in platinum-resistant disease, with a manageable safety profile	60 mg, bid, oral

CR, complete response; DoR, duration of response; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

(DSBs). To prevent the cascade collapse triggered by DNA damage, OC cells frequently rely on DDR pathways.

DDR

DDR has a crucial role in repairing DNA damage and maintaining genomic stability. As a coordinated network, DDR pathways maintain genomic integrity through multiple repair pathways, including base excision repair (BER), HR, and non-homologous end joining (NHEJ). Among these repair pathways, BER is the primary pathway for repairing SSBs and is highly dependent on PARP proteins, particularly PARP1, PARP2, and PARP3. In addition to SSB repair, PARP1 also contributes to replication fork stability and chromatin regulation, underscoring a central role for PARP1 in DDR and the potential as a therapeutic target.

Synthetic lethality mechanism of PARP inhibitors

PARP1 functions as an early sensor in DDR when an SSB occurs. The zinc finger domain of PARP1 quickly recognizes and binds to the lesion, triggering conformational activation and catalyzing the transfer of ADP-ribose units from nicotinamide adenine dinucleotide $(NAD)^+$ to PARP1 and surrounding proteins, a process known as PARylation (**Figure 1**). This catalysis leads to the synthesis of linear and branched poly(ADP-ribose) chains. In this way, PARP1 functions as a molecular scaffold, recruiting key downstream repair factors, such as XRCC1, DNA polymerase β, and DNA ligase III, enabling the efficient repair SSBs[6].

PARP inhibitors exert antitumor effects through two primary mechanisms. First, PARP inhibitors competitively bind to the catalytic domain of PARP, inhibiting PARylation and preventing SSB repair. The accumulation of unrepaired SSBs ultimately leads to DSBs and cell death. Second, PARP inhibitors stabilize the PARP–DNA complex, a phenomenon known as "PARP trapping," which impedes replication fork progression and promotes replication fork collapse (**Figure 1**).

Although PARP inhibitors can induce the formation of DSBs, cells have evolved several pathways to repair DSBs, among which HR is one of the most important. In cells with intact HR, such as *BRCA1/2* wild-type cells, *BRCA1* is involved in the end resection of DSBs, generating ssDNA and providing a template for HR repair. *BRCA1* also regulates the recruitment of other repair factors to ensure efficient repair progression. Compared to BRCA1, BRCA2 facilitates this process by

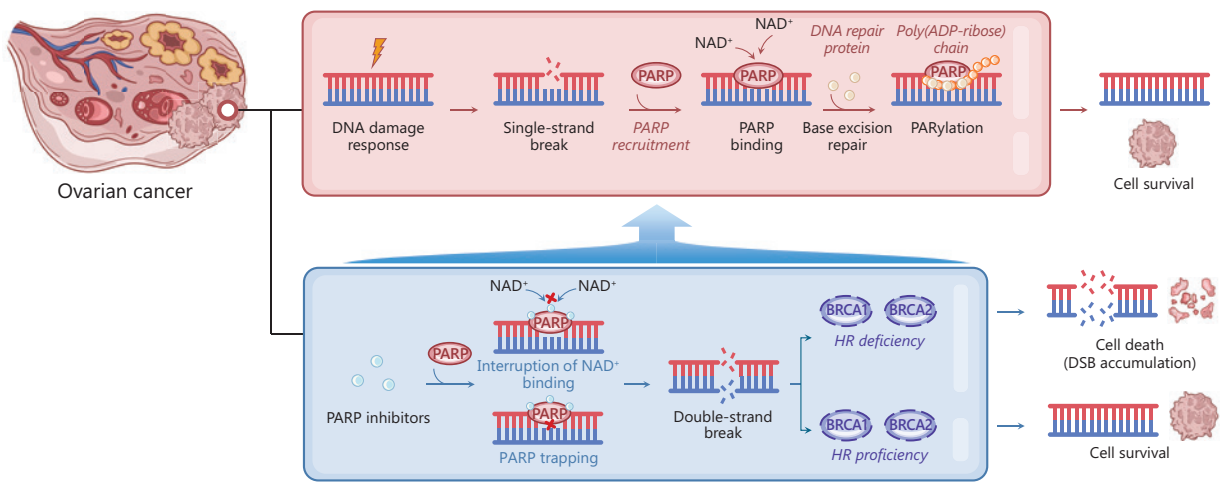


Figure 1 The synthetic lethality mechanism underlying PARP inhibitors. The HR repair mechanism efficiently repairs DSBs in *BRCA1/2* wild-type cells, preventing cell death. In contrast, HR repair is defective in *BRCA1/2*-mutant and BRCAness-like cells, which leads to the accumulation of unrepaired DSBs. In addition, PARP inhibitors block PARP activity, which prevents SSB repair and further promotes the accumulation of DSBs. This accumulation triggers synthetic lethality in *BRCA1/2*-mutant and BRCAness-like cells, ultimately resulting in tumor cell death. BER, base excision repair; BRCA1, breast cancer type 1 susceptibility protein; BRCA 2, breast cancer type 2 susceptibility protein; DSB, double-strand break; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase; SSB, single-strand break. All elements shown in this figure were created by Procreate and Adobe Illustrator.

binding to RAD51, which helps stabilize its accumulation on ssDNA, promoting homologous pairing and completing the repair. The combined actions of BRCA1 and BRCA2 ensure the accuracy and efficiency of HR, thereby preventing cell death from PARP inhibitors. However, HR repair is defective in *BRCA1/2* mutant cells or cells exhibiting a BRCAness phenotype. As a result, DSBs induced by PARP inhibitors cannot be repaired through the HR pathway. Instead, these cells rely on the error-prone NHEJ repair mechanism, resulting in further accumulation of DNA damage and ultimately leading to cell death. This phenomenon, known as synthetic lethality (**Figure 1**), accounts for the potent antitumor effects of PARP inhibitors in *BRCA1/2*-mutant and BRCAness-like tumors[5].

Major clinical research progress involving PARP inhibitors in China

Given the role in suppressing DNA damage repair, PARP inhibitors have been developed and translated into clinical applications, providing novel options for patients with OC. To date, multiple clinical studies have investigated the role of PARP inhibitors in different scenarios, including later-line treatment for recurrent disease, maintenance therapy for recurrent platinum-sensitive OC (PSOC), and first-line maintenance therapy for newly diagnosed advanced OC. In particular, the emergence of Chinese PARP inhibitors, such as fuzuloparib and pamiparib, has further advanced the clinical management of OC in China. The major clinical research progress involving PARP inhibitors in these therapeutic settings will be briefly summarized.

Later-line treatment for recurrent OC

Initially, PARP inhibitors were used to explore the efficacy and safety as a later-line treatment for recurrent OC. In 2020 fuzuloparib received initial approval in China for the later-line treatment of recurrent PSOC in patients harboring germline *BRCA1/2* mutations. This approval was based on a phase II, open-label, multicenter, single-arm study (Registration No. NCT03509636)[7]. Among 113 enrolled patients, fuzuloparib treatment achieved an Independent Review Committee (IRC)-assessed objective response rate (ORR) of 69.9% and a median progression-free survival (PFS) of 12.0 months. These findings supported fuzuloparib as an active later-line option for recurrent *BRCA1/2*-mutant OC in China.

Pamiparib is the first PARP inhibitor approved in China for the later-line treatment of recurrent PSOC and platinum-resistant OC (PROC). This approval was based on a phase II, open-label study (NCT03333915)[8]. Among 113 enrolled patients, the IRC-assessed ORR was 64.6% in the PSOC group and 31.6% in the PROC group. These results demonstrated the antitumor activity and manageable safety profile of pamiparib.

Maintenance therapy for recurrent PSOC

Following the application for later-line treatment, PARP inhibitors were further investigated as maintenance therapy for patients with recurrent PSOC. Several international multicenter studies have shown that PARP inhibitors significantly improve the median PFS in maintenance therapy for recurrent PSOC. FZOCUS-2 (NCT03863860) was the first phase III clinical trial conducted exclusively in a Chinese population to evaluate fuzuloparib in this setting[9]. Patients were randomly assigned to receive fuzuloparib or placebo with blinded IRC-assessed PFS as the primary endpoint. Fuzuloparib significantly improved the PFS compared to placebo in the overall population and showed a consistent benefit in germline *BRCA1/2* mutation-positive and -negative subgroups. These findings supported the approval of fuzuloparib as maintenance therapy for recurrent PSOC in China.

Maintenance therapy for newly diagnosed advanced epithelial OC

Notably, the FZOCUS-1 trial, which was led by our team, suggested that fuzuloparib monotherapy may be sufficient to achieve substantial clinical benefit for HRD patients without the need for additional anti-angiogenic therapy, thereby reducing the treatment burden and potential toxicity. Specifically, the FZOCUS-1 trial (Registration No. NCT04229615) compared the combination of fuzuloparib with apatinib (a VEGFR-2 inhibitor) to fuzuloparib monotherapy and placebo in patients with newly diagnosed advanced OC[10]. A total of 674 patients were randomized into 3 groups. Both fuzuloparib plus apatinib and fuzuloparib monotherapy significantly improved the median PFS compared to placebo after a median follow-up of 40 months [26.9 and 29.9 *vs.* 11.1 months; hazard hatio (HR) = 0.57 and 0.58, respectively] regardless of BRCA1/2 mutation status. Although fuzuloparib alone exhibited clinical benefit in HRD patients, the addition of apatinib showed a trend toward improved PFS compared to fuzuloparib monotherapy for patients with HR proficiency [HRP] (16.6 *vs.* 11.0 months; HR = 0.73), indicating the necessity of drug combination in HRP patients.

In addition, although PARP inhibitors were generally well-tolerated, hematologic adverse events, particularly anemia and neutropenia, were frequently reported across the above-mentioned clinical trials. Therefore, future strategies should focus on improving efficacy and reducing treatment-related toxicity. It has been reported that the specific inhibition of PARP-1, rather than PARP-2, can reduce the toxicity and side effects[11]. Furthermore, rational dose optimization, dynamic toxicity monitoring, and biomarker-guided patient enrollment may collectively enhance the durability and precision of PARP inhibitor therapy in OC.

In addition to the side effects, drug resistance also warrants attention. Current clinical studies of Chinese PARP inhibitors have primarily focused on efficacy and safety outcomes, whereas specific resistance mechanisms have not been systematically investigated. These unresolved issues also highlight the importance of integrating clinical outcomes with molecular analyses of resistance.

Biological mechanism underlying resistance to PARP inhibitors

Despite the substantial clinical benefit of PARP inhibitors in OC, acquired resistance has emerged as a major challenge limiting long-term efficacy. Tumor cells can evade PARP inhibition through multiple mechanisms, including restoration of HR repair, reduced PARP trapping, replication fork stabilization, and metabolic alternation (**Figure 2A**). The major biological mechanisms underlying PARP inhibitor resistance are discussed below.

HR restoration

PARP inhibitors exert therapeutic effects by blocking PARP-mediated DNA damage repair and inducing the formation of DSBs, thereby selectively targeting HRD tumors through synthetic lethality. However, restoration of HR function can induce resistance to PARP inhibitors, particularly in patients with a recurrence who initially responded to PARP inhibitors.

Reversion mutations, which are capable of restoring function of crucial HR genes, such as *BRCA1/2*, represent the most prevalent mechanism of resistance. Specifically, these mutations typically involve insertions or deletions, which result in frameshift mutations that can restore the open reading frame

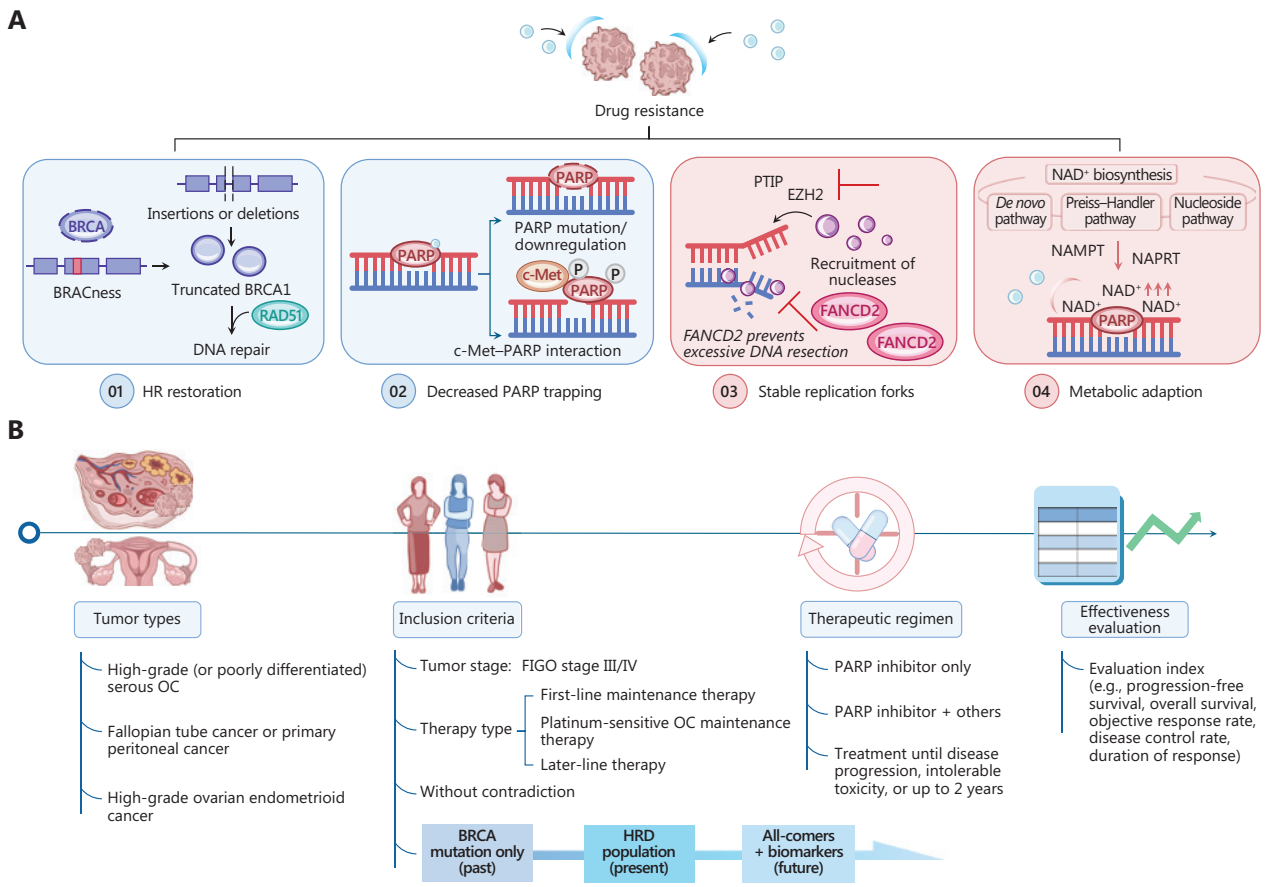


Figure 2 PARP inhibitor resistance mechanisms and evolving clinical trial strategies in ovarian cancer. (A) Main mechanisms of acquired resistance to PARP inhibitors, including HR restoration, reduced PARP trapping, replication fork stabilization, and metabolic adaptation. (B) Schematic summary of PARP inhibitor trial design in ovarian cancer, including tumor type, inclusion criteria, therapeutic regimen and endpoint evaluation, and the trend of patient selection progresses from *BRCA*-mutant patients (past) to patients with HRD (present) and biomarker-guided populations (future). HR, homologous recombination; HRD, homologous recombination deficiency; OC, ovarian cancer. All elements shown in this figure were created by Procreate and Adobe Illustrator.

of *BRCA1/2* and potentially lead to the complete restoration of BRCA1/2 protein function. In addition, translation initiation downstream of frameshift mutations can drive the expression of truncated BRCA1 proteins. The truncated BRCA1 can be recruited to DNA damage sites, facilitating RAD51 binding and enhancing HR repair capacity, thereby contributing to PARP inhibitor resistance.

Interestingly, *BRCA* gene reversion is not the only mechanism that can lead to HR restoration. It has been reported that *BRCA1/2* reversion mutations only account for a subset of resistant cases, suggesting that additional mechanisms, such as epigenetic reactivation of *BRCA1*, may also contribute to treatment failure.

Decreased PARP trapping

The primary target of PARP inhibitors is PARP1. Mutations in *PARP1* can alter the DNA-binding properties and impair PARP trapping at sites of DNA damage, ultimately resulting in resistance.

The CRISPR-Cas9 "tag-mutation-enrichment" screening results indicated that mutations both within and outside the DNA-binding zinc finger domain of *PARP1* contribute to PARP inhibitor resistance[12]. Moreover, the receptor tyrosine kinase, C-Met, has been shown to interact with PARP1, promoting phosphorylation at the Y907 site within the catalytic domain, thereby impeding the interaction of PARP inhibitors[13].

In addition to *PARP1* mutations, the inhibited or absent activity of poly (ADP-ribose) glycohydrolase (PARG), an enzyme responsible for removing PAR chains after DNA repair, may also contribute to resistance by attenuating the synthetic lethality.

Stable replication forks

Another key mechanism of PARP inhibitor resistance is maintenance of replication fork stability. As mentioned above, BRCA1/2 are essential for DSB repair. Factors, such as EZH2 and PTIP, promote the recruitment of nucleases, including MUS81 and MRE11, to stalled replication forks in BRCAness-like cells, leading to fork collapse and cell death. However, the inhibited or absent activity of EZH2 or PTIP can prevent nuclease recruitment, stabilize replication forks, and ultimately confer resistance to PARP inhibitors[14,15]. FANCD2 can prevent excessive DNA resection by nucleases, such as MRE11 and DNA2, during fork stalling and reversal in contrast to the functions of EZH2 and PTIP, thereby preserving fork stability. Studies have shown that in *BRCA1/2*-mutant breast cancer, FANCD2 induces PARP inhibitor resistance by maintaining fork stability[16]. In addition, the loss of SLFN11 expression in *BRCA1/2*-deficient cells reduces the accumulation of replication gaps, thereby decreasing sensitivity to PARP inhibitor treatment, which is consistent with reduced SLFN11 expression in OC patients and poor PARP inhibitor efficacy[17].

Metabolic pathways contributing to PARP inhibitor resistance

Because NAD^+ serves as the ADP-ribose donor for PARylation, increased NAD^+ availability may reduce the inhibitory effect of PARP inhibitors and contribute to resistance. It is well-known that NAD^+ can be synthesized through multiple pathways, including the *de novo* pathway (derived from tryptophan), the Preiss–Handler pathway (derived from nicotinic acid), and the nucleoside pathway (derived from nicotinic acid riboside or nicotinamide riboside)[18]. NAMPT and NAPRT are key regulatory enzymes in these pathways. In addition, metabolic reprogramming, including enhanced oxidative phosphorylation (OXPHOS) and fatty acid oxidation, may further promote resistance by supporting energy production and facilitating DNA damage repair. Together, these findings suggest that metabolic adaptation is another important mechanism underlying PARP inhibitor resistance.

Conclusions

Currently, PARP inhibitors have shown significant clinical benefits for OC patients through synthetic lethality. The results of FZOCUS-1 trial, which was conducted by our team, supported the use of fuzuloparib monotherapy in patients with HRD, whereas the addition of anti-angiogenic therapy may provide further benefit in patients with HRP, suggesting the importance of personalized treatment strategies in future OC therapy.

Existing studies on resistance mechanisms provide essential theoretical foundations for the development of targeted therapies and combination strategies with PARP inhibitors. For example, targeting *FANCD2* to reduce replication fork stability or activating *SLFN11* to increase replication fork gap accumulation are potential strategies for enhancing PARP inhibitor efficacy. Furthermore, preclinical studies have shown that NAMPT inhibitors, such as FK866, potentiate anti-tumor effects when combined with olaparib by reducing NAD^+ synthesis. However, there are currently no clearly established Phase I/II trials specifically testing NAMPT inhibitors or *FANCD2*-targeted strategies in combination with fuzuloparib or pamiparib. In addition, the PDBAG1 peptide increases sensitivity to the PARP inhibitor, PJ34-HCL, treatment by inhibiting OXPHOS activity. Thus, targeting metabolic pathways and inhibiting metabolic adaptation in tumor cells represents another promising combination therapy strategy to overcome resistance.

Furthermore, recent studies demonstrated that USP1 inhibition can overcome PARP inhibitor resistance *in vitro and in vivo*[19,20]. These results suggested that *USP1* targeting may provide a potential translational strategy for overcoming PARP inhibitor resistance.

Another important trend in the clinical development of PARP inhibitors is the evolution of patient selection strategies (**Figure 2B**). Early studies mainly focused on *BRCA1/2*-mutant populations, in whom the therapeutic benefit of PARP inhibition were most evident. Subsequent trials were expanded to include HRD populations because HR impairment may also result from other genomic or epigenetic alterations. It can be predicted that the field is moving toward a more refined biomarker-guided framework, in which *BRCA* and HRD status may be integrated with additional molecular and functional markers to improve patient selection and extend the benefit of PARP inhibitor therapy. This refinement is also essential to avoid the unnecessary side effects of PARP inhibitors in patients with limited likelihood of benefit, thereby reducing potential toxicity and alleviating the treatment burden on patients.

In conclusion, future research should focus on the systematic analysis of the mechanisms underlying PARP inhibitor resistance, followed by the development of novel combination therapies. The use of biomarker-based screening and dynamic monitoring of treatment responses, such as ctDNA-based liquid biopsy, will support personalized treatment strategies. These measures are expected to overcome resistance, ultimately improving the survival rate and quality of life for OC patients.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Lingying Wu, Wei Cui, Jing Yu and Maochen Li.
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Wrote the paper: Jing Yu and Maochen Li.
Illustrated the table and figures: Jing Yu and Maochen Li.
Reviewed and revised the paper: Lingying Wu and Wei Cui.

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