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REVIEW

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Clinical approaches to overcome PARP inhibitor resistance

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Abstract

PARP inhibitors have profoundly changed treatment options for cancers with homologous recombination repair defects, especially those carrying *BRCA1/2* mutations. However, the development of resistance to these inhibitors presents a significant clinical challenge as it limits long-term effectiveness. This review provides an overview of the current understanding of resistance mechanisms to PARP inhibitors and explores strategies to overcome these challenges. We discuss the basis of synthetic lethality induced by PARP inhibitors and detail diverse resistance mechanisms affecting PARP inhibitors, including homologous recombination restoration, reduced PARP trapping, enhanced drug efflux, and replication fork stabilization. The review then considers clinical approaches to combat resistance, focusing on combination therapies with immune checkpoint inhibitors, DNA damage response inhibitors, and epigenetic drugs. We also highlight ongoing clinical trials and potential biomarkers for predicting treatment response and resistance. The review concludes by outlining future research directions, emphasizing the need for longitudinal studies, advanced resistance monitoring technologies, and the development of novel combination strategies. By tackling PARP inhibitor resistance, this review seeks to aid in the development of more effective cancer therapies, with the potential to improve outcomes for patients with homologous recombination-deficient tumors.

Introduction

Poly (ADP-ribose) polymerase (PARP) inhibitors have assumed significant therapeutic importance in cancer management, especially for homologous recombination repair (HR) deficient tumors, such as *BRCA1/2*-mutated cancers. These targeted therapies, rooted in the principle of synthetic lethality, selectively kill cancer cells and spare normal ones, thereby offering a potentially superior therapeutic index compared to conventional chemotherapy regimens. Since the approval of the first PARP inhibitor (PARPi), Olaparib, in 2014, multiple PARP inhibitors have been introduced into clinical practice, significantly advancing treatment options for various cancers, such as ovarian, breast, pancreatic, and prostate cancers, which are highlighted here due to their prominence as primary indications for PARPi therapy, their representation of diverse molecular vulnerabilities (ranging from BRCA-dependent HRD to alternative pathways), and their extensive clinical data on resistance mechanisms.

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The advent of PARP inhibitors has significantly changed the treatment landscape for malignancies with homologous recombination deficiency (HRD), a molecular phenotype initially defined by BRCA1/2 mutations but now expanded to include epigenetic dysregulation and synthetic lethal interactions [1–7]. Ovarian and breast cancers were the first approved indications for PARPi therapy due to their high prevalence of BRCA mutations, with pivotal trials like SOLO-1 and OlympiAD establishing BRCA status as a primary predictive biomarker. However, 40–70% of ovarian cancer patients develop resistance through BRCA reversion mutations, while 50% of BRCA-mutant breast cancer patients progress within 12 months of therapy, highlighting the limitations of relying solely on BRCA status [8–10].

This limitation has prompted a paradigm shift in tumor type selection, emphasizing molecular vulnerabilities beyond canonical HRD. Pancreatic cancers with PALB2 loss (POLO trial) and metastatic castration-resistant prostate cancers (mCRPC) carrying ATM deletions (PROfound trial) demonstrate PARPi sensitivity mediated by alternative HRD pathways, though secondary resistance emerges in > 50% of cases via non-BRCA DNA repair adaptations [11, 12]. This resistance phenomenon has driven intense research to understand the underlying mechanisms and develop strategies to overcome or prevent it.

This review provides a comprehensive summary of the current understanding of PARP inhibitor resistance and will explore the strategies being developed to tackle the challenge. The first section of the review will discuss the molecular basis for PARP inhibitor-induced synthetic lethality, followed by a discussion focused on the mechanisms by which the cancer cells acquire resistance to PARP inhibition. The final section will cover clinical strategies and combinations that might be promising for overcoming PARP inhibitor resistance while focusing on clinical trials and further developments in this rapidly progressing field.

PARP Inhibitor-induced synthetic lethality

The DNA Damage Response (DDR) pathway is a key pathway for genomic stability and managing cellular responses to DNA lesions induced by metabolism and environmental stressors [13]. By detecting, signaling, and repairing damage, DDR mechanisms avert the accumulation of mutations that otherwise would drive tumorigenesis. The DDR pathway integrates several repair mechanisms that include Base Excision Repair (BER), Homologous Recombination (HR), Non-Homologous End Joining (NHEJ), and Mismatch Repair (MMR). BER is a very crucial pathway primarily involved in removing base lesions from oxidative or alkylating damage, and it relies on PARP1, which is a protein that detects and binds to the single-stranded breaks (SSBs) [14]. After SSB recognition, PARP1 initiates chromatin remodeling and facilitates the recruitment of DNA repair factors to restore DNA integrity [15]. HR is a high-fidelity DNA repair mechanism that corrects DNA double-strand breaks (DSBs) during the S/G2 phases of the cell cycle. This process relies on the presence of a homologous sister chromatid as a template to ensure accurate repair. HR is mediated by a coordinated complex of proteins, including BRCA1, BRCA2, RAD51, and PALB2, along with Fanconi anemia pathway proteins. These factors collectively facilitate strand invasion, DNA synthesis, and error-free restoration of the damaged DNA [16–18]. HRD arises when mutations, epigenetic silencing (e.g., *BRCA1* promoter hypermethylation), or functional disruptions in these core components impair repair, forcing reliance on error-prone pathways like NHEJ. While BRCA1/2 mutations are the hallmark of HRD, defects in upstream regulators such as ATM, ATR, or 12 can also confer an HRD phenotype, termed "BRCAness".

PARP inhibitors exploit HRD vulnerability through synthetic lethality, a mechanism where simultaneous disruption of two pathways (e.g., HR and PARP1-mediated repair) selectively kills cancer cells while sparing normal cells. Specifically, PARPi block PARP1's enzymatic activity and trap PARP1 at DNA damage sites (e.g., unligated Okazaki fragments), converting transient SSBs into replication-associated DSBs. Beyond PARP trapping, recent studies reveal that PARP1 resolves transcription-replication conflicts (TRCs) by recruiting TIMELESS (TIM). PARPi disrupt this process, leading to unresolved TRCs that exacerbate replication stress specifically in HRD cells [19]. HR-proficient cells can repair these DSBs via homologous recombination, but HRD cells cannot, leading to genomic catastrophe [20–22]. However, the clinical definition of HRD remains contentious. FDA-approved companion diagnostics (e.g., Myriad myChoice®) use genomic "scarring" biomarkers—loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transitions (LST)—to quantify HRD, yet these assays show variable correlation with PARPi efficacy [23]. These biomarkers reflect historical HRD events during tumor evolution but may not capture real-time HR functional status, contributing to variable correlation with PARPi efficacy. PARP inhibitors exploit HRD vulnerability through synthetic lethality, yet intrinsic resistance mechanisms significantly limit their efficacy. Notably, a subset of tumors classified as HRD-positive by genomic scarring biomarkers (e.g., LOH, TAI, LST) retain functional homologous recombination (HR) capacity through compensatory mechanisms such as

BRCA-independent RAD51 loading or epigenetic plasticity (e.g., partial BRCA1 promoter demethylation), enabling escape from synthetic lethality [24]. PARP1 enzymatic activity is also critical: tumors harboring hypomorphic PARP1 variants (e.g., E988 K mutation) or baseline low PARP1 expression exhibit diminished PARP trapping and resistance, independent of HR status [25]. Furthermore, Schlafen-11 (SLFN11) deficiency is observed in 30–40% of ovarian and small cell lung cancers and confers intrinsic resistance by enabling replication fork progression under PARPi-induced stress [26, 27]. It has been evidenced by reduced progression-free survival in SLFN11-low patients across multiple clinical trials. These mechanisms collectively underscore why up to 25% of HRD-positive patients fail to respond initially, necessitating functional assays or dynamic multi-omics profiling to refine patient selection beyond static genomic scarring models [28–30].

Consequently, when SSBs remain unrepaired, they transform into DSBs during DNA replication. These trapped PARP complexes worsen the situation by blocking the replication process [31]. Cells that are efficient in homologous recombination can easily repair these DSBs. However, in the absence of functional HR, such as in cells with *BRCA* mutations, these DSBs accumulate, leading to genomic instability and cell death (Fig. 1).

This targeted approach effectively destroys cancer cells with homologous recombination deficiencies while mostly preserving healthy cells with functioning HR systems. The clinical efficacy of PARP inhibitors has been particularly notable in cancers with *BRCA1/2* mutations. A recent phase III trial (OlympiA) showed that adjuvant olaparib significantly enhanced invasive disease-free survival in patients with HER2-negative early breast cancer and *BRCA1/2* mutations [32]. Similarly, the SOLO1 trial showed that maintenance therapy with olaparib provided a substantial progression-free survival benefit in newly diagnosed advanced ovarian cancer with *BRCA1/2* mutations [33].

In solid tumors, PARPi has shown promising efficacy across various cancer types. The QUADRA study demonstrated that niraparib had antitumor activity in patients with heavily pretreated ovarian cancer, including

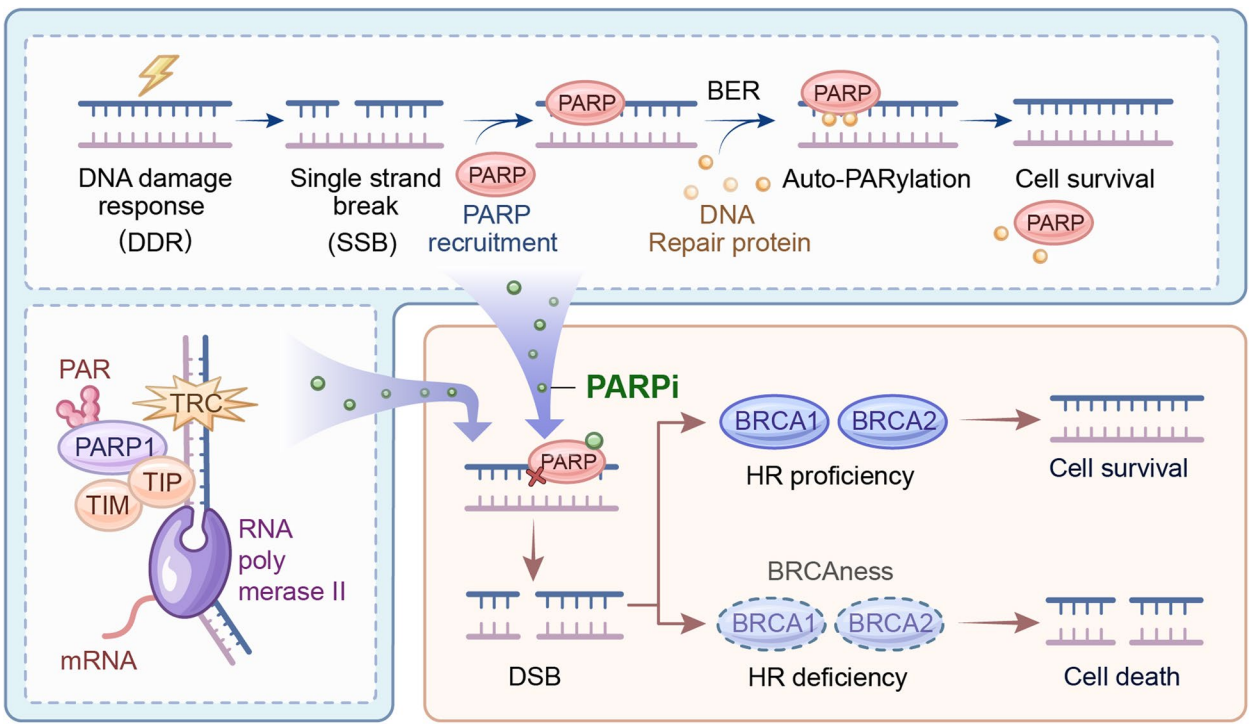

Fig. 1 Mechanism of synthetic lethality mediated by PARP inhibitors in HR-deficient cells. PARP inhibitors induce synthetic lethality by disrupting DNA damage repair mechanisms and transcription-replication conflicts (TRCs). PARPs normally bind to single-strand break sites, initiating repair processes. They also interact with TIMELESS and TIPIN to resolve TRCs, which are major sources of genome instability and double-strand breaks (DSBs). PARP inhibitors competitively bind to PARPs, preventing their normal function and trapping them on damaged DNA. This leads to an accumulation of unrepaired single-strand breaks and unresolved TRCs, which evolve into DSBs during DNA replication. In HR-deficient tumor cells, these DSBs cannot be effectively repaired, forcing cells to rely on error-prone NHEJ repair. The resulting genomic instability ultimately triggers cell death, demonstrating the selective toxicity of PARP inhibitors in HR-deficient cancers

those without *BRCA* mutations or HRD [34]. In metastatic castration-resistant prostate cancer (mCRPC), the PROFOUND trial suggested that olaparib improved radiographic progression-free survival in men harboring mutations in homologous recombination repair genes, including but not limited to *BRCA1/2* [35]. This evidence supported the FDA approval of rucaparib and olaparib based on HRD deficiencies, which can occur in *BRCA*-wildtype tumors. In non-small cell lung cancer (NSCLC), a traditionally *BRCA*-independent cancer, the phase II ORION study explored olaparib monotherapy in patients with homologous recombination repair gene mutations beyond *BRCA1/2*, showing promising clinical activity [36].

In hematological malignancies, the concept of HRD as a predictive biomarker for PARPi efficacy is also gaining traction. While *BRCA1/2* mutations are rare in blood cancers, HRD is often associated with other genetic alterations, such as *TET2*, *DNMT3 A*, *IDH1/2*, or *STAG2* mutations, which impair homologous recombination repair and sensitize these malignancies to PARP inhibition [37]. Recent trials, such as the use of veliparib in combination with temozolomide or carboplatin, have demonstrated meaningful clinical responses in subsets of patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), particularly those with HRD-driven disease [38, 39].

Notably, in adult T-cell leukemia/lymphoma (ATLL), a highly aggressive form of leukemia associated with HTLV-I infection, genetic heterogeneity and chemotherapy resistance present significant treatment challenges. A study investigating the PARP inhibitor PJ-34 demonstrated its ability to induce G2/M cell cycle arrest, reactivate p53 transcriptional activity, and trigger caspase-3-dependent apoptosis in HTLV-I-transformed and patient-derived ATLL cells [40]. However, resistance to PJ-34 therapy was observed in certain HTLV-I-transformed cell lines, such as MT-2 cells, which showed reduced caspase-3 cleavage and upregulation of RelA/p65. These findings indicate that HRD testing, similar to its application in solid tumors, could be crucial in pinpointing blood cancer patients most likely to respond well to PARP inhibitors, thereby enabling more tailored treatment approaches.

The capacity of PARP inhibitors to specifically target cancer cells with HRDs is a key factor in their success in treating *BRCA1/2* mutated cancers. While this has spurred exploration of PARPi in other HRD-positive malignancies, including prostate and pancreatic cancers, emerging data reveal critical exceptions within molecularly defined subgroups. A notable example is microsatellite instability-high (MSI-H) pancreatic cancer, which constitutes 1–2% of cases. Despite sporadic BRCA1/2 monoallelic mutations in this subgroup, PARPi resistance arises due to the mutual exclusivity between MSI-H (driven by mismatch repair deficiency) and functional HRD [41]. This biological dichotomy is further evidenced by the elevated tumor mutational burden (TMB) in MSI-H tumors, which renders them highly responsive to immune checkpoint inhibitors (ICIs). The KEYNOTE-158 trial demonstrated a 34% response rate to pembrolizumab in this population, establishing ICI as the preferred first-line therapy [42]. Ongoing studies aim to decipher resistance mechanisms, such as HR restoration and dynamic biomarker evolution, to refine PARPi utility across heterogeneous tumor contexts.

Mechanisms of resistance to PARP inhibition

PARP inhibitors have improved outcomes in HRD-associated cancers, but intrinsic and acquired resistance remain major challenges. Several acquired resistance mechanisms have been identified, including HR restoration, reduced PARP trapping, increased drug efflux, and enhanced replication fork protection, revealing potential therapeutic targets for overcoming PARPi resistance (Fig. 2).

HR Restoration

PARP inhibitors exert their therapeutic effects by disrupting the HR pathway, thereby impairing DNA damage repair and selectively targeting HR-deficient tumor cells. However, the restoration of HR activity is a prominent mechanism of acquired resistance, particularly in initially responsive HR-deficient tumors. A key pathway through which resistance arises involves secondary mutations that partially or fully restore the function of critical HR genes, such as *BRCA1* or *BRCA2*, thereby reinstating HR repair capacity [43]. Using liquid biopsy or circulating cell-free DNA (cfDNA), these secondary mutations, often involving insertions or deletions that correct frameshift mutations, have been identified to restore the open reading frame of *BRCA1/2*, enabling full transcription and activity of the repair proteins [44–46] (Fig. 2). In the presence of functional HR, the synthetic lethality mechanism between *BRCA1/2* mutations and PARP inhibition, which is essential for inducing cancer cell death, is disrupted, resulting in the loss of clinical efficacy for PARP inhibitors [47]. In metastatic castration-resistant prostate cancer (mCRPC) patients with *BRCA* mutations treated with Rucaparib, *BRCA* reversion mutations were detected in 39% after progression, with higher rates associated with prolonged therapy, subclonal evolution, and clinical responses such as objective or prostate-specific antigen-based improvements [48, 49]. A longitudinal ctDNA analysis by E. Harvey-Jones et al. demonstrated that 60% of PARPi-resistant breast cancer patients

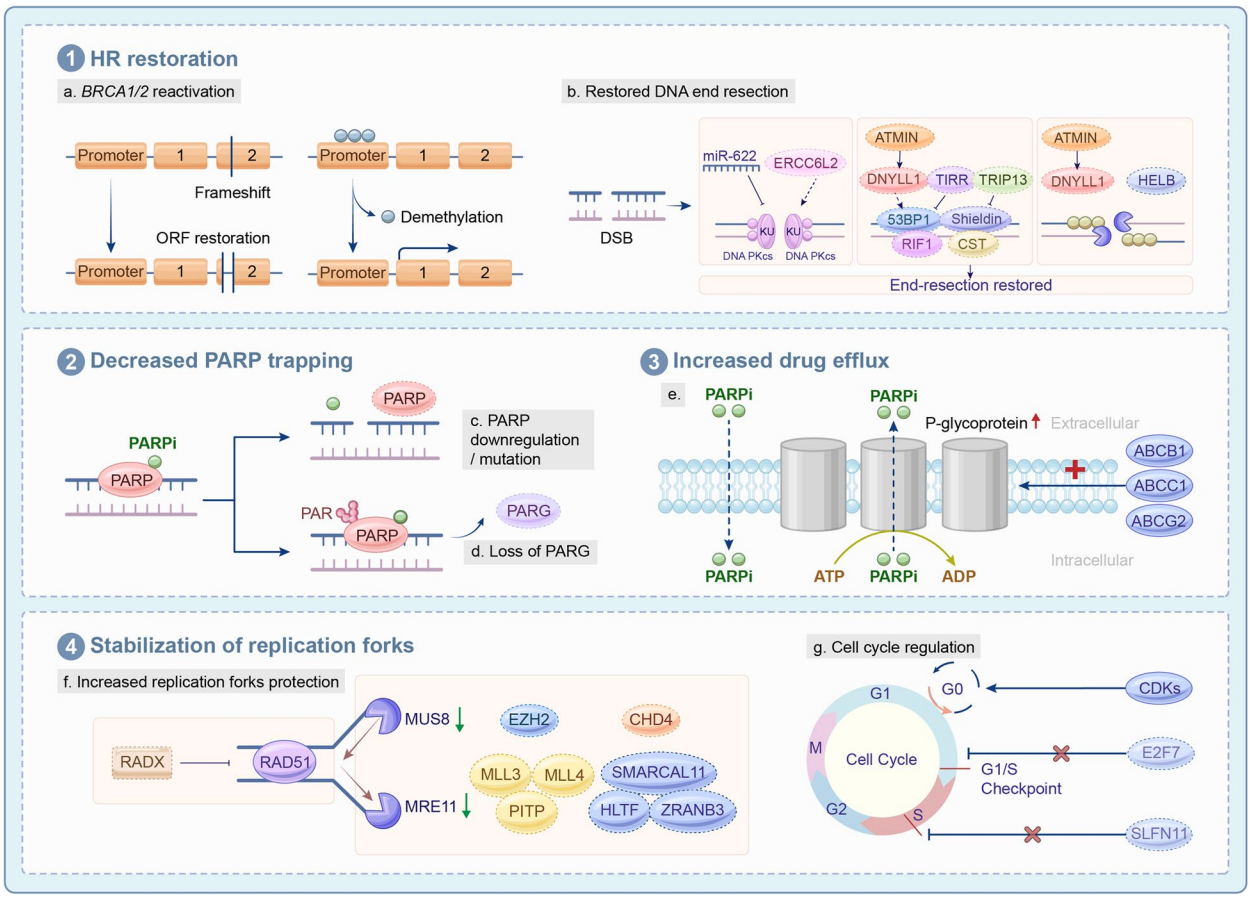

Fig. 2 Mechanisms of Resistance to PARP inhibitors. (1) HR restoration can occur through *BRCA1/2* reactivation(**a**) and restored DNA end resection(**b**). (2) Both downregulation or mutations in PARP1(**c**) and loss of poly (ADP-ribose) glycohydrolase (PARG) (**d**) can reduce PARP inhibitor trapping. (3) Overexpression of ABC transporters, such as ABCB1, ABCC1, and ABCG2, leads to increased drug efflux, resulting in reduced intracellular concentrations of PARP inhibitors and contributing to treatment resistance. (4) PARPi resistance can emerge through mechanisms that enhance fork stability, such as loss of fork reversal factors (SMARCAL1, ZRANB3, HTLF and CHD4), reduced EZH2-mediated MUS81 recruitment, loss of PTIP/MLL3/MLL4-mediated MRE11 recruitment, decreased PTIP expression, or loss of SLFN11-dependent and E2 F7-dependent cell cycle checkpoint activation

exhibited *BRCA1/2* reversion mutations. Furthermore, resistance was not confined to reversion mutations; loss-of-function mutations in key HR pathway regulators such as *TP53BP1*, *RIF1*, and *PAXIP1* were also observed, with some cases showing co-occurrence of these alterations alongside *BRCA1/2* reversions [50].

Resistance to PARP inhibitors can also arise through *BRCA*-independent mechanisms, including additional mutations in key HR-related genes such as *RAD51 C*, *RAD51D*, and *PALB2*, epigenetic modifications affecting repair pathways, or the functional loss of critical HR suppressors, such as p53-binding protein 1 (53BP1) and MAD2L2 (also known as REV7). These alternative routes bypass *BRCA* dependency and contribute to the reactivation of homologous recombination, undermining the therapeutic efficacy of PARP inhibitors [48, 51–54].

Beyond these pathways, epigenetic regulation and RAD51-related mechanisms synergistically modulate HR restoration. For instance, complete methylation of the BRCA1 promoter silences its expression, enhancing PARPi sensitivity, whereas loss of methylation restores BRCA1 transcription and HR repair, leading to resistance. This mechanism has been observed in patient-derived xenograft (PDX) models of triple-negative breast cancer (TNBC) and ovarian cancer [55, 56]. Similarly, homozygous methylation of the RAD51 C promoter (meRAD51 C) drives HR deficiency and predicts PARPi sensitivity [57]. The role of methylation in HR restoration is further supported by a phase I clinical trial in acute myeloid leukemia (AML) combining a DNMT inhibitor with a PARP inhibitor, which demonstrated altered HR repair dynamics [58].

Importantly, RAD51-mediated HR reactivation is tightly regulated by key suppressors such as 53BP1 and REV7. The 53BP1-RIF1-REV7-shieldin pathway acts as a barrier to HR in BRCA1-deficient cells by protecting

DNA ends from resection, thereby favoring NHEJ over HR [59–61]. 53BP1 is recruited to DSBs and serves as a scaffold for downstream factors. RIF1 is then recruited by 53BP1, followed by REV7, which recruits the shieldin complex (SHLD1, SHLD2, and SHLD3). This assembled complex prevents excessive DNA end resection, suppressing HR. Loss of 53BP1, REV7, or shieldin components disrupts this protection, enabling resection and partial HR restoration even without functional BRCA1 [62] (Fig. 2).

Other regulators of DNA end resection further fine-tune this balance. The CTC1-STN1-TEN1 (CST) complex, operating downstream of the 53BP1-RIF1-REV7-shieldin pathway, prevents end resection at DSBs [63]. Loss of CST complex components restores end resection in BRCA1-deficient cells, leading to PARP inhibitor resistance [63]. However, this effect is less pronounced compared to the disruption of 53BP1-RIF1-REV7-shieldin signaling, indicating the involvement of additional protective mechanisms.

HELB and DYNLL1 act downstream of 53BP1 to antagonize various components of the DNA end resection machinery [64, 65]. Their loss results in hyper-resected DNA ends and confers PARP inhibitor resistance in BRCA1-deficient tumor cells. DYNLL1 also promotes NHEJ by stimulating 53BP1 oligomerization, enhancing its recruitment to DSBs [65]. Upstream factors like ERCC6L2, an accessory NHEJ factor, also play a role. Loss of ERCC6L2 restores DNA end resection, partially rescuing HR and inducing PARP inhibitor resistance in BRCA1-deficient cells [66]. Overexpression of factors promoting HR and suppressing NHEJ, such as TIRR, TRIP13, and miRNA-622, rescues HR and reduces PARP inhibitor sensitivity in BRCA1-deficient cells [67–69]. These findings highlight the complex regulation of DNA repair pathway choice and PARP inhibitor sensitivity.

PARP inhibitor resistance often arises through the loss of DNA end protection in cells lacking functional BRCA1. This allows for the restoration of end resection and partial reactivation of HR, even without BRCA1. However, while BRCA1 may be partially dispensable for the distal steps of RAD51-mediated HR, BRCA2 remains crucial for this pathway.

Decreased PARP trapping

Decreased PARP trapping, a crucial mechanism underlying PARP inhibitor resistance, stems from a reduced ability of PARP enzymes, primarily PARP1, to become stably bound to DNA lesions [70, 71]. This diminished trapping can arise from several factors (Fig. 2). Downregulation of PARP1 expression, for instance, limits the overall amount of enzyme available to bind DNA damage [72]. Furthermore, mutations within PARP1, especially those impacting its DNA-binding domain, can impair its ability to recognize and bind damaged DNA. Counterintuitively, loss of PARG activity, the enzyme responsible for reversing PARylation, also contributes to reduced trapping [73, 74]. While PARG activity typically facilitates PARP release from DNA, its absence leads to hyper-PARylation [75]. This excessive modification can trigger accelerated PARP1 degradation, effectively depleting the pool of PARP1 available for trapping at DNA damage sites and ultimately promoting resistance, similar to observations with PARG inhibitors enhancing resistance.

Increased drug efflux

Increased drug efflux contributes to PARP inhibitor resistance, primarily through the overexpression of ATP-binding cassette (ABC) transporters like ABCB1 (P-gp), ABCC1 (MRP1), and ABCG2 (BCRP), which actively pump PARP inhibitors out of cells, reducing intracellular drug concentrations (Fig. 2). This overexpression can be driven by the activation of transcription factors such as Nrf2, which regulates the expression of these transporter genes, ultimately leading to decreased drug efficacy and treatment failure. Preclinical studies in *BRCA*-deficient mouse models demonstrated that Olaparib resistance can arise through ABCB1 overexpression, and that this resistance is reversible with the ABCB1 inhibitor tariquidar, confirming the role of drug efflux [76–78]. Elizabeth L. et al. identified recurrent SLC25 A40–ABCB1 genomic fusions in 15.7% of patients with high-grade serous ovarian carcinoma, with similar fusion events observed in 30% (9/30) of metastatic or end-stage breast cancer cases [76]. In BRCA1/2-deficient murine mammary tumor models, ABCB1 mRNA expression was 20-fold higher in PARP inhibitor-resistant tumors compared to treatment-sensitive counterparts [77]. Liu, et al. demonstrated that the PARP1-DOT1L-PLCG2/ABCB1 regulatory axis significantly modulates PARPi responses in BRCA wild-type ovarian cancer cells [79]. Mechanistically, DOT1L-mediated H3 K79 methylation facilitates recruitment of methylated H3 K79 to the promoter regions of PLCG2 and ABCB1, thereby enhancing their transcriptional activation [79]. Comparative analysis revealed elevated *ABCB1* mRNA expression in control SKOV-3 cells relative to DOT1L-knockout counterparts, underscoring the functional relevance of this epigenetic modification in chemoresistance regulation [79]. The overexpression of ABCC1 and ABCG2 transporters on cancer cell membranes reduces the therapeutic efficacy of Talazoparib in ovarian cancer treatment by enhancing drug efflux and decreasing its cytotoxicity [80, 81].

Stabilization of replication forks

Stabilization of replication forks is a critical mechanism of PARP inhibitor resistance, particularly in cells deficient in BRCA1 or BRCA2, distinct from restoring HR. Enhanced fork stability contributes to PARP inhibitor resistance in cells with loss of BRCA1/2, underscoring their essential roles in maintaining fork integrity under replicative stress (Fig. 2). This resistance arises from a complex interplay of factors that protect stalled forks from detrimental processing. For example, MRE11, crucial for processing stalled forks, can become overactive in *BRCA1/2* deficient cells, leading to excessive resection and fork collapse [82–85]. Fork remodeling by chromatin remodelers like SMARCAL1, ZRANB3, and HLTF is required for this MRE11-dependent nascent DNA degradation [86, 87]. Consequently, depleting these remodelers and factors like PTIP and CHD4 involved in MRE11 recruitment/activation leads to fork protection and PARP inhibitor resistance [88]. Similarly, limiting the activity of other nucleases like MUS81, potentially through EZH2 inhibition, can also promote resistance, although MUS81's precise role remains context-dependent [89]. Another key player, RADX, is implicated in fork protection in BRCA2-deficient cells; its depletion confers resistance by stabilizing forks [90]. Recent research has identified E2 F7, a transcriptional repressor, as a modulator of therapeutic resistance and a potential biomarker for early diagnosis, survival prediction, and a marker to monitor disease relapse [91]. In BRCA2-deficient cells, E2 F7 regulates RAD51 expression, thereby influencing HR repair and replication fork stability, contributing to PARP inhibitor and cisplatin resistance [92]. Critically, these resistance mechanisms operate independently of HR restoration, as depletion of PTIP, EZH2, or RADX does not rescue HR deficiency. This highlights fork stabilization as a potent, distinct driver of PARP inhibitor resistance. Beyond these factors, PARP1 itself plays a complex role at stalled forks, recruiting MRE11 and potentially influencing the outcome of combination therapies. SLFN11 also critically modulates replication stress responses independent of HR. Its presence enforces cell cycle arrest upon replication stress, increasing sensitivity to PARP inhibitors [93, 94]. Loss of SLFN11, therefore, allows cell cycle progression despite DNA damage, diminishing PARP inhibitor efficacy [95].

Metabolic pathways involved in PARPi resistance

In many cancer cells, glycolysis is upregulated, known as the Warburg effect [96]. Increased lactate production from glycolysis can lead to intracellular acidosis, promoting DNA damage and increasing replication stress [97]. Additionally, increased glycolytic flux may help cancer cells bypass the need for oxidative phosphorylation and other DNA repair mechanisms (e.g., NAD + regeneration, which is critical for PARP activity) [98–100]. These adaptive changes create vulnerabilities that can be therapeutically exploited. For instance, glycolysis inhibition using agents like 2-deoxyglucose (2-DG) or targeting key glycolytic enzymes (e.g., Hexokinase 2) could impair NAD + regeneration, directly interfering with PARP activity and enhancing PARPi sensitivity [101]. Other glycolytic inhibitors, such as 3-bromopyruvate (3-BrPA), have shown significant efficacy, particularly in hepatocellular carcinoma and pancreatic cancer [102, 103]. Similarly, targeting the NAD + salvage pathway by inhibiting nicotinamide phosphoribosyltransferase (NAMPT), a rate-limiting enzyme in this pathway, has been shown to enhance the cytotoxicity of PARP inhibitors, particularly in triple-negative breast cancer (TNBC) cells. NAMPT inhibitors like FK866, OT-82, and GMX1777(8) combined with PARPi show improved efficacy in various cancer models [104, 105]. OT-82 exhibits potent anti-tumor activity in hematological malignancies, while GMX1777(8) demonstrates synergistic effects with PARPi in multiple solid tumor types [105, 106].

Beyond glycolysis, mitochondrial metabolism plays a dual role in resistance. While OXPHOS inhibition through metformin or IACS-10759 (a mitochondrial complex I inhibitor) depletes NAD + and suppresses DNA repair, making cells more dependent on PARP-mediated repair and thus more sensitive to PARPi [107–109]. OXPHOS inhibition can also exacerbate oxidative stress, further diminishing cancer cell viability [110]. Additionally, mitochondrial-targeted therapies may synergize with PARPi in tumors that are resistant due to high oxidative capacity [108].

Lipid metabolic adaptations further complicate resistance dynamics. Fatty acid oxidation (FAO) and lipogenesis are critical for maintaining membrane integrity and mitochondrial function [111]. Increased intracellular FAO may provide tumor cells with additional sources of acetyl-CoA and NADPH, which can enhance DNA repair and counteract PARPi toxicity [112]. Inhibiting lipid metabolism using drugs like C75 (which inhibits fatty acid synthase) or etomoxir (which blocks carnitine palmitoyltransferase I) could impair lipid biosynthesis and mitochondrial function, leading to increased DNA damage and PARPi sensitization [113].

Emerging insights highlight the therapeutic potential of metabolic contexture. Neomorphic isocitrate dehydrogenase (IDH) mutations in gliomas exemplify how oncometabolites modulate PARPi response [114]. These mutations decrease NAD + levels by downregulating nicotinate phosphoribosyltransferase (NAPRT1), making tumors hypersensitive to NAD + depletion, while producing D-2-hydroxyglutarate (D-2HG) that inhibits

homologous recombination, creating dual metabolic sensitivities [115, 116]. Current preclinical exploration focuses on optimizing combination strategies. The simultaneous use of PARPi (e.g., Olaparib, Niraparib) with metabolic inhibitors like metformin (targeting OXPHOS) and 2-DG (targeting glycolysis) is being investigated for synthetic lethality in HR-deficient tumors [117, 118]. Collectively, glycolytic reprogramming, OXPHOS dependency, lipid metabolism adaptations, and oncometabolite-driven sensitivities are synthetically targeted in combinatorial strategies (Fig. 3).

Future directions emphasize precision targeting through metabolic profiling, where tumor-specific signatures of glycolytic flux, OXPHOS activity, or lipid metabolism could guide the selection of PARPi combination regimens. These metabolic signatures help design rational drug combinations that address resistance mechanisms arising from metabolic adaptations. The tumor microenvironment significantly affects treatment outcomes. Metabolites released by stromal cells can create protective microenvironments that promote resistance. Targeting specific metabolic processes, such as lactate transport or pH regulation mechanisms, may disrupt these protective environments and restore drug sensitivity. Advances in non-invasive metabolic biomarkers will enable clinicians to monitor treatment responses in real time. This monitoring capability allows for timely adjustments to therapy as tumors adapt. Additionally, emerging immunometabolic approaches target both resistance mechanisms and immune suppression simultaneously. Metabolic reprogramming strategies show particular promise by restoring PARPi sensitivity while activating anti-tumor immune responses. By integrating precise metabolic analysis with microenvironment modulation and immune system engagement, researchers can develop more effective strategies to overcome PARPi resistance across various cancer types.

Role of ncRNAs in PARP inhibitors resistance

miRNAs can modulate key genes involved in homologous recombination repair (HRR) and base excision repair (BER), pathways that are directly affected by PARP inhibition [119]. For example, miR-182, miR-155, and miR-30a have been shown to regulate the expression

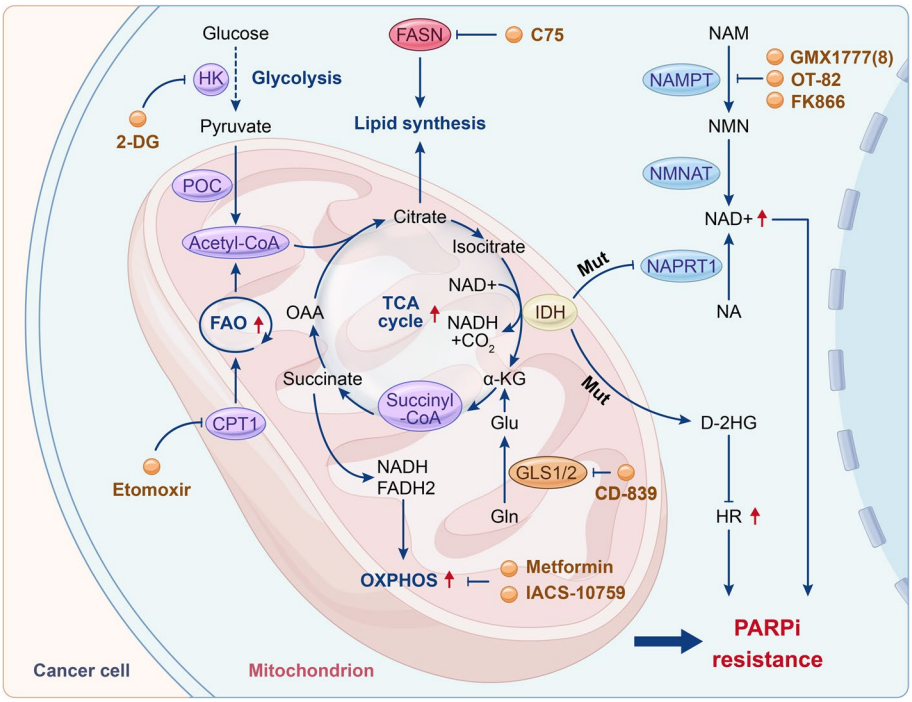

Fig. 3 Metabolic pathways driving PARP inhibitor resistance and its potential therapeutic targets. Metabolic reprogramming, including upregulated glycolysis, enhanced oxidative phosphorylation (OXPHOS), and altered lipid metabolism, contributes to resistance against PARP inhibitors (PARPi) in cancer. Potential therapeutic strategies targeting these pathways, such as glycolytic inhibitors (e.g., 2-DG), OXPHOS inhibitors (e.g., metformin, IACS-10759), lipid metabolism inhibitors (e.g., C75, etomoxir), or NAD + salvage pathway inhibitors (e.g., FK866, OT-82, GMX1777(8)), are depicted as combinatorial approaches to enhance PARPi sensitivity and overcome resistance mechanisms in tumors. Notably, tumors with neomorphic isocitrate dehydrogenase (IDH) mutations exhibit dual metabolic vulnerabilities: NAD + depletion via downregulation of NAPRT1 and accumulation of the oncometabolite D-2-hydroxyglutarate (D-2HG), which impairs homologous recombination repair. These mechanisms highlight how metabolic and genetic alterations synergistically sensitize tumors to PARPi combination therapies

of BRCA1/2, RAD51, and other DNA repair factors. Upregulation or downregulation of these miRNAs could impact the efficiency of DNA repair and influence PARPi sensitivity. In addition, some miRNAs can directly target PARP1 or PARP2. For example, miR-34a has been shown to suppress PARP1 expression, potentially influencing the response to PARPi [120]. Besides directly modulating genes involved in HRR or BER, miRNA can impact PARPi sensitivity through other mechanisms. miR-181a has been determined to downregulate the STING pathway, thereby driving PARPi resistance in TNBC and ovarian cancer [121]. miR-622 can induce PARPi resistance by interacting with Ku70 and Ku80, and impacting NHEJ-mediated repair of DSBs [69].

Certain lncRNAs, such as HOTAIR and MALAT1, have been implicated in the regulation of DNA repair genes [122]. For example, MALAT1 has been shown to modulate the expression of HR repair genes and could impact PARPi sensitivity by influencing BRCA1/2 expression or other repair pathway genes [123]. PANDAR, a lncRNA, has been associated with DNA damage repair and may modulate PARP inhibitor response by influencing the repair machinery [124]. Several lncRNAs are involved in regulating the DDR, an essential process in determining cell fate after DNA damage [125]. XIST, for instance, can influence DNA repair pathways, and its expression may be altered in PARPi-resistant cells, contributing to resistance [126]. Interestingly, a recent study uncovered that inhibition of lncRNA PART1 conferred resistance to PARPi through promoting the downregulation of PHB2, an inner mitochondrial membrane mitophagy receptor, which may play a role in cellular senescence [127]. CircRNAs can serve as potential vaccine platforms, drug targets, and act as miRNA sponges in PARPi resistance [128–130]. Circ-ARID1 A has been shown to sponge miR-370-3p, leading to the upregulation of its target gene ARID1 A, which is involved in the regulation of DNA repair [118, 131]. By modulating miRNA activity, circRNAs can influence the expression of genes involved in PARPi sensitivity, contributing to resistance [132, 133].

Tumor microenvironment (TME)-mediated PARPi resistance

TME can promote proliferation signaling, generating blood vessels, inhibiting cell apoptosis and evading immune surveillance. Due to its complex function, TME plays a crucial role in cancer initiation, promotion, and drug resistance [134]. As vital components of TME, M2-like tumor-associated macrophages are associated with suppression of CD8 + T cell function and treatment tolerance [135]. A study found that PARPi-induced DNA damage can upregulate STAT3 signaling pathway in BRCA-deficient ovarian cancer cells. JAK2-STAT3 pathway activation upregulates several STAT3-regulated chemokines like CCL2, CX3 CL1, CCL20, and CXCL1, thereby promoting protumor M2-like macrophage polarization, which can lead to PARPi resistance [136]. Similarly, another study demonstrated that PARP inhibition modulates the TME and results in phenotypic changes of immunosuppressive macrophages. These changes subsequently turn on an immune-suppressive signaling pathway, manifested by increased PD-L1 and CSF-1R expression, limiting the efficacy and contributing to PARPi resistance [137]. Collectively, TME-mediated PARPi resistance involves multidimensional immune remodeling, and future studies should focus on developing TME-targeted combination strategies.

Clinical strategies to overcome PARP inhibitor resistance

Researchers are actively exploring various combination strategies in clinical trials to address the challenge of PARPi resistance and improve patient outcomes. As summarized in Table 1, current clinical investigations are not limited to monotherapy regimens. Emerging combination strategies with chemotherapy, targeted agents, or immunotherapies are being actively explored to enhance therapeutic efficacy. Notably, current research prioritizes three principal combination categories designed to circumvent resistance mechanisms and prolong treatment effectiveness (Table 2). These combinations include ICIs to enhance anti-tumor immune responses, DNA damage response inhibitors to further exploit cancer cell vulnerabilities, and epigenetic drugs to modulate gene expression and potentially resensitize resistant cells. These diverse approaches are being evaluated across various cancer types and treatment settings to develop more effective and durable treatment options for patients resistant to PARPi monotherapy.

Combining PARP inhibitors with ICIs

The synergistic potential of PARPi and ICI is underpinned by several interconnected mechanisms (Fig. 4). These integrated mechanisms, including genomic instability-driven immunogenicity, cGAS-STING-IFN-I activation, PD-L1-mediated checkpoint targeting, and TME immune reprogramming, collectively define the synergistic framework of PARPi-ICI combinations, as comprehensively illustrated in Fig. 4. Primarily, PARPi-induced DNA damage escalates genomic instability, leading to an increased TMB [138]. This heightened TMB is a proxy for neoantigen load, a critical factor in ICI efficacy [139]. The augmented neoantigen presentation enhances tumor immunogenicity, potentially sensitizing malignancies to immunotherapeutic interventions. PARPi

Table 1 Ongoing clinical trials of PARP inhibitors in cancer treatment

Type of cancer	PARPi agent	Identifiers	Phase	Population	Intervention/Treatment	Primary endpoints	Estimated completion date
Ovarian cancer	Rucaparib	NCT03522246	3	Newly diagnosed ovarian cancer patients	Rucaparib; Nivolumab; Placebo Oral Tablet; Placebo IV Infusion	PFS	2030/12/30
	Olaparib	NCT01844986	3	Patients with *BRCA* mutated advanced ovarian cancer	Olaparib	PFS	2028/08/29
	Olaparib	NCT03737643	3	Patients with newly diagnosed advanced ovarian cancer	Bevacizumab; Durvalumab; Olaparib; Placebo olaparib; Durvalumab placebo; Carboplatin + Paclitaxel	PFS	2028/03/30
	Pamiparib	NCT0351923	3	Chinese participants with recurrent ovarian cancer who achieved a complete response or partial response after platinum-based chemotherapy	Pamiparib; Placebo	PFS	2026/6/30
	Olaparib	NCT04729387	3	Patients with platinum resistant or refractory high-grade serous ovarian cancer, with no germline *BRCA* mutation detected	Alpelisib; Olaparib; Paclitaxel; Pegylated liposomal doxorubicin	PFS	2026/01/31
	Niraparib	NCT02655016	3	Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy	Niraparib; Placebo	PFS	2025/09/30
	Rucaparib	NCT04227522	3	Patients with histologically confirmed, advanced high grade serous or high grade endometrioid ovarian cancer, fallopian tube cancer, primary peritoneal cancer and clear cell carcinoma of the ovary	Rucaparib; Placebo	PFS	2025/01
Prostate cancer	Saruparib	NCT06120491	3	mCSPC	Saruparib; Placebo; Abiraterone Acetate; Darolutamide; Enzalutamide	rPFS	2031/04/30
	Talazoparib	NCT04821622	3	mCSPC	Talazoparib + Enzalutamide; Placebo + Enzalutamide	rPFS	2027/08/07
	Niraparib	NCT04497844	3	Patients with deleterious germline or somatic HRR gene-mutated mCSPC	Niraparib; Abiraterone acetate; Prednisone; Placebo for Niraparib	rPFS	2027/05/27
	Niraparib	NCT03748641	3	mCRPC	Niraparib; Abiraterone Acetate; Prednisone; Placebo; New Formulation of Niraparib and Abiraterone Acetate	rPFS	2027/02/19
	Rucaparib	NCT04455750	3	mCRPC	Enzalutamide; Rucaparib camsylate; Placebo; Leuprolide Acetate; Goserelin Acetate; Degarelix	rPFS, OS	2026/09/01
	Talazoparib	NCT03395197	3	mCRPC	Talazoparib + enzalutamide; Placebo + enzalutamide	rPFS	2025/12/31
	Olaparib	NCT03150576	3	Patients with TNBC and/or gBRCA breast cancer	Olaparib; Paclitaxel + Carboplati	Number of participants with treatment-related adverse events as assessed by NCI CTCAE v4.03; pCR rate	2034/06

Table 1 (continued)

Type of cancer	PARPi agent	Identifiers	Phase	Population	Intervention/Treatment	Primary endpoints	Estimated completion date
Breast cancer	Saruparib	NCT06380751	3	Patients with *BRCA1*, *BRCA2*, or *PALB2*m, HR-positive, HER2-negative advanced breast cancer	Saruparib; Camizestrant; Abemaciclib; Ribociclib; Palbociclib; Fulvestrant; Letrozole; Anastrozole; Exemestane	PFS	2030/10/18
	Olaparib	NCT02032823	3	Patients with g*BRCA1/2* mutations and high risk HER2 negative primary breast cancer	Olaparib; Placebo	iDFS	2029/05/28
	Niraparib	NCT04915755	3	Participants with either HER2-negative BRCA-mutated or triple-negative breast cancer with molecular disease	Niraparib; Placebo	Number of participants with treatment emergent adverse event (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs)	2025/12/31
	Niraparib	NCT04475939	3	Patients with advanced or metastatic non-small cell lung cancer	Niraparib; Pembrolizumab; Placebo	PFS, OS	2025/02/19
Lung cancer	Niraparib	NCT04475939	3	Patients with advanced or metastatic non-small cell lung cancer	Niraparib; Pembrolizumab; Placebo	PFS, OS	2025/02/19

Abbreviations: iDFS Invasive disease-free Survival, *PFS* Progression-free Survival, OS: Overall survival, *rPFS* Radiological progression free survival, *mCRPC* Metastatic castration-resistant prostate cancer, NHA: New hormonal agent, *mCSPC* Metastatic castration-sensitive prostate cancer, *HRR* Homologous Recombination Repair

Table 2 Comprehensive List of Clinical Trials Involving Combination Therapies with PARP Inhibitors

Cancer type	Year		Phase	PARPi agent	Combination agent	Combination therapy	No. of Patients	Design	Primary endpoints	Results	Recruitment status	Identifiers
	First submitted	Last verified										
Ovarian, Fallopian Tube, Peritoneal cancer	2015	2023	3	Veliparib	Carboplatin and Paclitaxel	PARPi + Platinum chemotherapeutic + Anti-microtubule agent	1140	Previously untreated stages III or IV high-grade serous epithelial OC, fallopian tube, or primary peritoneal cancer	PFS	Veliparib + Carboplatin + Paclitaxel → Veliparib: 34.7 (31.8-NA), Mo; Veliparib + Carboplatin + Paclitaxel → Placebo: 21.1 (17.0–25.5), Mo	Terminated	NCT02470585
	2015	2024	2/3	Olaparib	Cediranib	PARPi + VEGFRi	587	Recurrent platinum-resistant or refractory ovarian, fallopian tube, or primary peritoneal cancer	PFS, OS	NA	Active, not recruiting	NCT02502266
	2015	2024	3	Olaparib	Cediranib	PARPi + VEGFRi	579	Recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer	PFS	10.4 (8.5–12.5), Mo	Active, not recruiting	NCT02446600
	2017	2022	3	Olaparib	Cediranib	PARPi + VEGFRi	330	Relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer	PFS	NA	Unknown status	NCT03278717
	2018	2023	3	Talazoparib	Avelumab + Carboplatin + Paclitaxel	PARPi + immunotherapy + Platinum chemotherapeutic + Anti-microtubule agent	79	Stage III/IV epithelial OC, fallopian tube, or primary peritoneal cancer with high-grade serous component	PFS	NA	Terminated	NCT03642132
	2021	2024	3	Olaparib	Alpelisib	PARPi + PI3 Ki	358	Platinum resistant or refractory high-grade serous or endometrioid OC, fallopian tube cancer, or primary peritoneal cancer with no g*BRCA*m detected	PFS	NA	Active, not recruiting	NCT04729387

Table 2 (continued)

Cancer type	Year		Phase	PARPi agent	Combination agent	Combination therapy	No. of Patients	Design	Primary endpoints	Results	Recruitment status	Identifiers
	First submitted	Last verified										
Breast Cancer	2014	2023	3	Veliparib (ABT-888)	Carboplatin + Paclitaxel	PARPi + Platinum chemotherapeutic + Anti-microtubule agent	509	HER2-negative metastatic or locally advanced unresectable *BRCA* -associated BC	PFS	14.5 (12.5–17.7), Mo	Completed	NCT02163694
	2024	2024	3	Fluzoparib	Dalpiciclib + Fulvestrant/AI	PARPi + CDK4/6i + Endocrine therapy	307	HR +/HER2- advanced BC	PFS	NA	Active, not recruiting	NCT06612814
	2024	2024	3	Fluzoparib	Camrelizumab	PARPi + immunotherapy	310	High-risk non-pCR TNBC	iDFS	NA	Recruiting	NCT06533384
Prostate Cancer	2019	2024	3	Niraparib	Abiraterone Acetate	PARPi + ARSI	750	Metastatic hormone-sensitive and castration-resistant prostate cancer	PFS	NA	Recruiting	NCT03903835
	2021	2024	3	Talazoparib	Enzalutamide	PARPi + ARSI	599	DDR gene mutated mCSPC	Radiological PFS	NA	Active, not recruiting	NCT04821622
	2024	2024	3	Niraparib	Abiraterone Acetate	PARPi + ARSI	8000	Metastatic hormone sensitive prostate cancer	Radiographic PFS, OS	NA	Recruiting	NCT06320067
Non-small cell lung cancer	2020	2024	3	Olaparib	Pembrolizumab + Carboplatin + Cisplatin	PARPi + immunotherapy + Platinum chemotherapeutic + Radiotherapy	870	Unresectable, locally advanced, stage III NSCLC	PFS, OS	NA	Active, not recruiting	NCT04380636
Uterine leiomyosarcoma	2022	2024	2/3	Olaparib	Temozolomide	PARPi + Alkylating agents	190	Advanced uterine leiomyosarcoma after progression on prior chemotherapy	PFS, OS	NA	Active, not recruiting	NCT05432791
Endometrial, ovarian carcinosarcoma	2018	2024	2/3	Niraparib	Dostarlimab (TSR-042)	PARPi + immunotherapy	196	Metastatic or recurrent endometrial or ovarian carcinosarcoma	ORR, OS	NA	Active, not recruiting	NCT03651206

Abbreviations: PFS progression-free survival; OS, overall survival; ORR, objective response rate, *iDFS* invasive disease-free survival; BC, breast cancer; OC, ovarian cancer, *mCSPC* metastatic castration-sensitive prostate cancer; Mo, Month; NA, not available, *NSCLC* non-small cell lung cancer, *ARSI* androgen receptor signaling inhibitors, *gBRCAm* germline *BRCA* mutated, *DDR* DNA damage repair

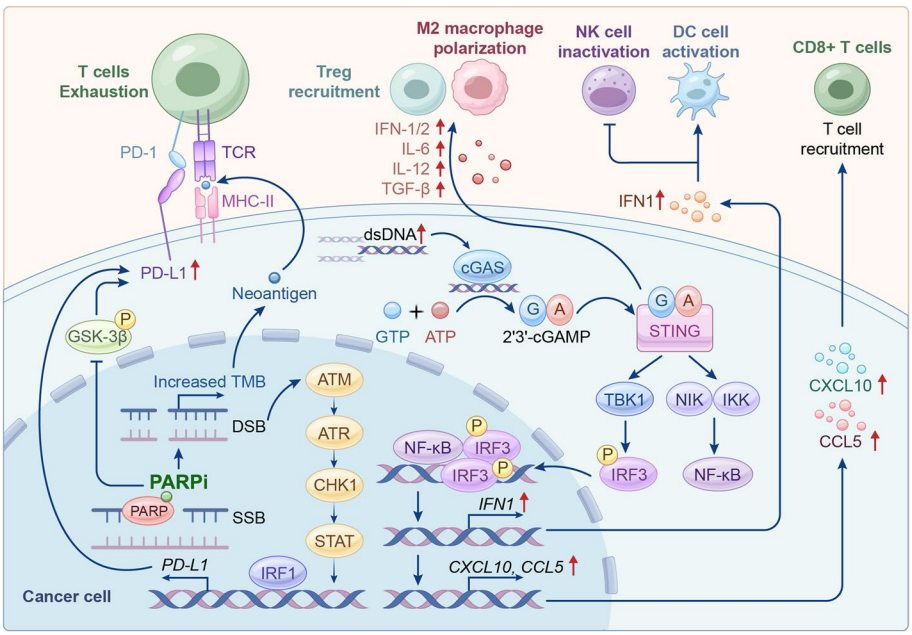

Fig. 4 Mechanisms underlying the synergistic effects of PARP inhibitors with immunotherapies. PARP inhibitors enhance anti-tumor immunity by (1) increasing tumor mutational burden (TMB) and neoantigen production through DNA damage-induced genomic instability; (2) activating the cGAS-STING pathway via cytoplasmic double-stranded DNA accumulation, thereby stimulating type I interferon (IFN-I) production to promote dendritic cell maturation, cytotoxic T lymphocyte activation, and chemokine-mediated T cell infiltration; (3) upregulating PD-L1 expression via both IFN-dependent and DNA damage-triggered pathways, creating targetable immune checkpoints for PD-1/PD-L1 blockade; and (4) remodeling the tumor microenvironment by shifting chronic inflammation to acute Th1-polarized immunity, enhancing CD8 +T cell infiltration, suppressing myeloid-derived suppressor cells (MDSCs)

in *LKB1*-mutant NSCLC can simultaneously exploit synthetic lethality due to DNA repair deficiencies and restore IFN-γ signaling, creating a more immunogenic tumor microenvironment that synergizes with PD-1 blockade [140].

PARPi-mediated DNA lesions trigger the cytosolic DNA sensing pathway. Accumulation of cytoplasmic double-stranded DNA activates the cGAS-STING axis, culminating in robust type I interferon (IFN-I) production [141–145]. This interferon surge orchestrates a cascade of immunostimulatory events: enhancing dendritic cell maturation and antigen presentation, augmenting T cell trafficking via chemokine modulation, and bolstering cytotoxic T lymphocyte function through elevated perforin and granzyme B expression [146, 147]. Moreover, IFN-I attenuates regulatory T cell suppressive capacity, further tilting the balance towards an anti-tumor immune response. A preclinical trial demonstrated the therapeutic efficacy of the combination of PARPi and STING agonist, which can overcome TME-dependent adaptive resistance to Olaparib by remodeling TME and reprogramming myeloid cells [136]. Currently, several clinical trials have been conducted on STING agonists either as monotherapy or in combination therapies. For example, a phase I trial (NCT04144140) assessed the safety and clinical activity of a STING agonist E7766 in patients with advanced solid tumors or lymphomas. Another phase I/II trial (NCT04020185) evaluated the efficacy of a STING agonist IMSA101 monotherapy and combination therapy with ICI. However, no clinical trials have been initiated to evaluate the combination of STING agonists with PARPi, and the efficacy of such combination therapy remains unknown.

PARPi treatment has been observed to upregulate PD-L1 expression on tumor cells through both IFN-dependent and independent mechanisms [148]. While this might initially appear counterproductive, it provides additional targets for anti-PD-1/PD-L1 therapies, potentially enhancing their efficacy. This adaptive response to PARPi-induced DNA damage creates a therapeutic window for ICI intervention.

Furthermore, PARPi administration instigates a profound remodeling of the tumor immune microenvironment. In contrast to the chronic, low-grade inflammation associated with baseline DNA damage, PARPi elicits an acute inflammatory response. This shift from smoldering inflammation to an acute surge recalibrates the immune landscape, fostering a Th1-polarized milieu conducive to anti-tumor immunity [149]. The resultant microenvironment is characterized by enhanced CD8 +T cell

infiltration, diminished myeloid-derived suppressor cell presence, and altered macrophage phenotypes [150]. The intricate interplay between DNA damage response pathways and immune system modulation forms the cornerstone of PARPi-ICI combinatorial strategies [137, 151]. By leveraging these multifaceted mechanisms, this therapeutic approach aims to overcome immune evasion strategies employed by malignant cells and reinvigorate anti-tumor immune responses.

The ongoing phase III trials ATHENA and FIRST are evaluating PARPi combined with ICIs in newly diagnosed advanced ovarian cancer. FIRST (NCT03602859) is a randomized, adaptive phase III trial investigating Rucaparib plus Nivolumab, while ATHENA (NCT03522246) is a randomized, placebo-controlled, four-arm phase III trial studying Niraparib plus Dostarlimab. FIRST included 1402 ovarian cancer patients, while ATHENA included 1097 patients. Both trials focus on patients with advanced (FIGO stage III or IV) high-grade serous or endometrioid ovarian cancer who have responded to first-line platinum-based chemotherapy. These studies aim to determine if the combination therapy improves progression-free survival compared to PARP inhibitor monotherapy or placebo. Results are expected around 2024 and could significantly impact first-line treatment strategies in ovarian cancer, potentially improving outcomes for patients with advanced ovarian cancer.

PARP inhibitors with DNA damage response inhibitors

The strategic combination of DNA damage response inhibitors, such as ATR and CHK1, with PARPi emerges as a promising approach to overcome PARPi resistance and increase therapeutic efficacy.

ATR regulates HR repair by phosphorylating key HR-related proteins. One of its downstream targets, CHK1, enhances the transcription of RAD51, thereby facilitating the HR repair process [152]. Up to now, combining PARPi with ATR, CHK1, AXL inhibitors, and other targets has shown promising results in cancer therapy. (Fig. 5) [153]. In line with these findings, several studies have demonstrated that ATR and CHK1 inhibitors induce synthetic lethality with PARP inhibitors by causing HRD, highlighting their therapeutic potential to overcome PARP inhibitor resistance [154, 155]. SLFN11 is actively recruited to DNA damage sites to inhibit HR. Loss of SLFN11, which is common in cancer cells, could confer resistance to PARPi [156]. However, the addition of ATRi VE-821 can reverse such resistance, providing an option in treating SLFN11-negative cancer [157]. In ovarian cancer, the CHK1 inhibitor SRA737 has shown notable single-agent activity in PARPi-resistant cells. Although the synergistic effects of PARPi and CHK1 inhibitors (CHK1i) are well known, it has been shown that SRA737 can sensitize PARP inhibitor-resistant ovarian cancer by increasing replication stress and the accumulation of DNA double-strand breaks [158].

WEE1 can inhibit CDK and activate the cell cycle checkpoint to allow DNA damage repair. Therefore, inhibiting WEE1 or CDK, which can induce cell cycle arrest, apoptosis, and suppression of transcription [159], presents another potential strategy for combination therapy [160]. Several studies have shown that combining PARPi with WEE1 inhibitors induces synthetic lethality, supporting the therapeutic potential of this combination for cancer treatment [153, 154]. The underlying mechanisms of overcoming PARPi resistance have been explored. Targeting WEE1 can downmodulate the key enzyme in dNTP synthesis RRM2 thereby inducing replication fork stalling and replication stress response, delaying the acquired resistance to PARPi in BRCA1-altered PDX models [161]. WEE1 inhibition sensitize *BRCA1/2* wild-type TNBC to PARPi through increasing DNA damage, apoptosis, replication stress, and STING pathway activation [162]. A growing body of research is highlighting the potential of combining PARPi and CDK inhibitors (CDKi), providing new hope and perspectives for cancer treatment. Talazoparib-induced apoptosis was increased by Palbociclib, a CDK4/6 inhibitor. Talazoparib/Palbociclib combination therapy can induce both G0/G1 and G2 arrest, thereby leading to synergism. The combination of Palbociclib and Talazoparib effectively enhances bladder cancer therapy, and RB is a molecular biomarker of response to this treatment regimen [163]. Besides, in Olaparib-resistant BRCA-deficient TNBC models, CDKi can reinstate sensitivity to Olaparib by reverting the functional HR restoration, which is frequently associated with PARPi resistance [164]. Dinaciclib, a CDK inhibitor that can downregulate MYC expression and impair the HR pathway by inhibiting RAD51 and BRCA1 activity, induces TNBC sensitivity to PARPi. Treatment with Dinaciclib and Niraparib can overcome acquired resistance to PARPi [165].

Other DNA damage response inhibitors are also emerging as promising candidates in combination therapy, opening up exciting new possibilities for treatment. For example, by preventing RPA2/CHK1-mediated HR, AXL inhibitor Bemcentinib can augment PARPi Olaparib sensitivity, uncovering that AXL acts as a prognostic biomarker. A combination therapy with Bemcentinib can expand the application of PARPi in HCC patients, especially those with AXL expression [166]. Numerous studies have shown that RAD51 plays a key role in identifying PARP inhibitor sensitivity, correlating with the functional status of BRCA1/2 proteins [167–169]. Silencing of RAD51 C enhanced the sensitivity to Olaparib, and RAD51 C deficiency may be considered a biomarker for

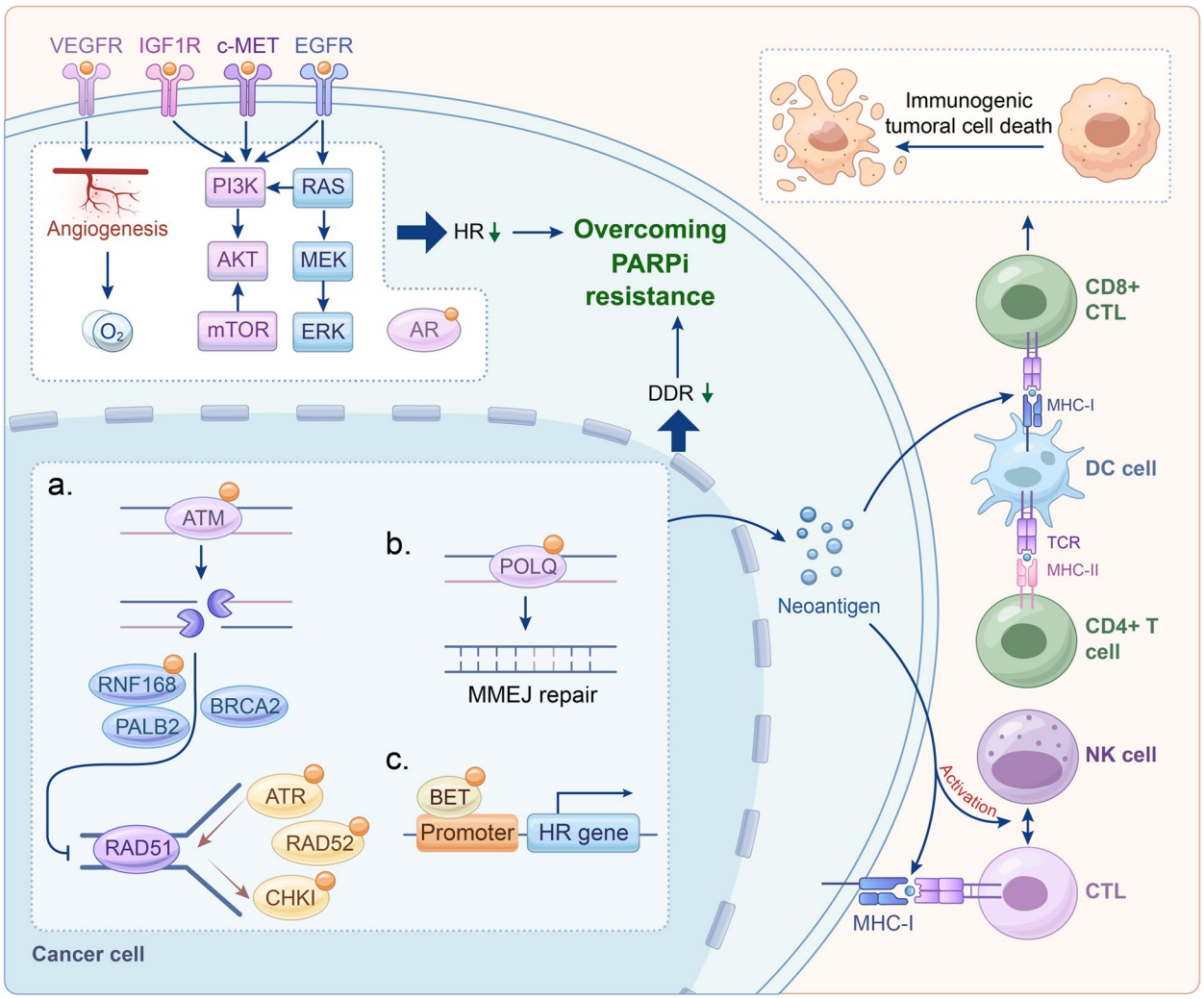

Fig. 5 Mechanisms underlying the synergistic effects of PARP Inhibitors in combination with other drugs. Mechanisms involve targeting various cellular processes to overcome resistance and enhance therapeutic efficacy. These strategies include suppression of HR pathway reactivation through tyrosine kinase inhibitors and epigenetic regulators, enhancement of PARPi cytotoxicity via NAD + synthesis inhibition, and disruption of restored replication fork protection in resistant cells by targeting factors such as ATR and RAD52. The inhibition of alternative DNA repair pathways, particularly microhomology-mediated end-joining (MMEJ), presents a novel approach, with polymerase θ (POLQ) inhibitors emerging as promising agents. Importantly, combination therapies with PARPi can also modulate the tumor immune microenvironment. Tyrosine kinase inhibitors used in combination with PARPi may alter the infiltration and function of CD4 + and CD8 + T cells. Epigenetic drugs, such as HDAC inhibitors, when combined with PARPi, can enhance the expression of immunogenic markers on tumor cells, potentially increasing their recognition by immune cells. Some DNA damage response inhibitors used in combination strategies may influence the activation state of tumor-infiltrating lymphocytes and alter the balance between effector and regulatory T cells

predicting the efficacy of treating with Olaparib [170]. In agreement with these observations, Ksenija et al. found that homozygous RAD51 C methylation is a positive predictive biomarker for sensitivity to PARPi [171]. Besides the dominant DNA repair pathway HR, DSBs can be repaired by other pathways, including NHEJ and microhomology-mediated end joining (MMEJ). These pathways promote DSB repair, especially in HR-deficient cells. Activation or upregulation of the main factor of these pathways can promote DNA repair and compensate HR pathway [172]. Upregulation of DNA polθ, a crucial factor in MMEJ, results in enhancement of DNA repair and Olaparib resistance in HR-deficient ovarian cancer cells [173]. Thereby, targeting DNA polθ can suppress DSB repair and improve PARPi therapeutic efficacy. Furthermore, a study has demonstrated that ART558, a Polθ inhibitor, enhances the effects of a PARPi, presenting

a promising strategy to overcome PARPi resistance in HRR-deficient cancer [174].

ATM is a nuclear protein that participates in the initiation of DNA repair signaling and cell-cycle checkpoints during DNA damage. ATM deficiency was found to be associated with enhanced sensitivity to Veliparib and TOP1 inhibitor irinotecan. Combining PARP and TOP1 inhibitors could improve drug efficacy and increase the sensitivity of gastric cancer cells to chemotherapy in ATM-driven cancers, offering a potential strategy to overcome drug resistance [175]. Chu et al. discovered that ALK promotes HRR and PARP inhibitor resistance by phosphorylating CDK9 at tyrosine-19. Moreover, inhibiting ALK was shown to overcome PARP inhibitor resistance. These results suggest that ALK is a predictive biomarker for PARP inhibitor resistance, and that combining ALK and PARP inhibitors may represent a promising approach to enhance the effectiveness of PARPi [176].

Several studies have indicated that small molecules engaged in DNA damage response can serve as predictive biomarkers, potentially predicting the efficacy of PARPi treatment. *BRCA1* expression continues to be one of the most widely studied biomarkers, despite the exploration of many others. Loss of BRCA1 methylation and biallelic loss of BRCA1/2 may serve as potential markers of PARP inhibitor resistance [177]. Additionally, the expression level of other molecules, like GLI1 [178], LIG3 [179], PPP2R2 A [180], ERCC1 [181], MED12 [182], and others, may also represent prognostic and predictive biomarkers for PARPi treatment.

PARPi and writers/erasers epigenetic drugs

Epigenetic dysregulation, recognized as a pivotal factor in tumor genesis and maintenance, regulates PARPi sensitivity. This presents opportunities for combining epigenetic drugs with PARPi to overcome acquired resistance to therapy, as demonstrated in studies of DNMT and HDAC inhibitors [18, 183, 184]. Up to now, a variety of epigenetic drugs have come into focus, showing promising therapeutic effects when combined with PARPi. Some epigenetic drugs, like DNMT, HDAC, and EZH2 inhibitors, have already been approved by the FDA in cancer therapy [185, 186].

BET inhibitors (BETi) disrupt the binding of BET proteins to acetylated lysine residues on chromatin, thereby suppressing the transcription of various genes. The synergy between BETi and PARPi has triggered synthetic lethality and improved therapeutic sensitivity [187]. Whereas utilizing BETi in conventional chemotherapy has shown limited effectiveness, there is a growing need to explore additional combination strategies and identify sensitive biomarkers [188]. Guadecitabine, a DNMT inhibitor, in combination with Talazoparib, has been shown to enhance the efficacy of PARPi and further sensitize breast and ovarian cancer cells to PARPi regardless of the BRCA status. Possible mechanisms are PARP trapping, ROS accumulation, and subsequent PKA activation [189]. However, a recent study demonstrated that malignant DNMT3 A-deficient leukemia cells were resistant to PARPi treatment both in vitro and in vivo [190]. HDAC inhibitors (HDACi) can inhibit histone deacetylases, thereby regulating gene expression [191]. In a preclinical trial, HDACi SAHA can enhance the antitumor effects of Olaparib in TNBC cells. The expression level of functional PTEN may serve as a biomarker to predict response to this combination therapy [192]. Similar results were also observed in the MDA-MB-231 xenograft model in vivo [193]. Finally, studies have shown that the downregulation of EZH2, which can methylate H3 K27 and exert a transcriptional repressor activity, prevents MUS81 recruitment and causes replication fork stabilization, promoting PARPi resistance in *BRCA2*-deficient cells [89].

Targeting other repair pathways

In addition to the aforementioned strategies, targeting other repair pathways could also hold significant promise for combination therapy. Vascular endothelial growth factor (VEGF) is a secreted molecule that contributes to angiogenesis and vascular permeability, which participates in oncogenesis. A combination of VEGF and VEGFR can enhance PI3 K/AKT signaling [194]. Additionally, VEGFR and PI3 K/AKT pathways have been shown to modulate HR function, providing rationale for combination therapy with PARPi [195]. VEGFR3 inhibition can downregulate BRCA1 and BRCA2 mRNA, resulting in cell cycle arrest and chemosensitization [196]. Another study demonstrated that VEGF/VEGFR/PI3 K signaling enhances HR activity by upregulating CRY1 expression [197], with parallel research showing spliceosome components such as SF3B4 regulate HR-related transcripts via alternative splicing [198]. Interestingly, several evidence have uncovered the interaction of androgen receptor (AR) signaling and HRR pathway [199, 200]. AR signaling activation can upregulate HRR genes, including BRCA1 and RAD51, so inhibiting this signaling may downregulate HRR genes. AR signaling inhibition may also upregulate PARP and induce sensitivity to PARPi, indicating the potential role of AR signaling inhibitors (ARSI) in reversing PARPi resistance [201]. These complementary mechanisms jointly promote DNA repair and cell survival.

A phase IIb clinical trial combining anti-VEGFR Cediranib and Olaparib in patients with ovarian cancer showed clinical activity despite failing to meet the target ORR of 20%. Further exploration for combination

therapy and biomarkers are required [202]. Several clinical studies have shown that combining PARP inhibitors with PI3 K/AKT pathway inhibitors results in synergistic anti-tumor activity. In a phase I clinical trial, antitumor activity was observed when combining PARPi and AKT inhibitor Capivasertib in patients with *BRCA1/2*- and non-*BRCA1/2*-Mutant Cancers [203]. Furthermore, preliminary clinical evidence suggests synergistic activity between Olaparib and the PI3 K inhibitor Alpelisib [204]. Additionally, a phase III clinical trial has been initiated investigating the combination of PARP and PI3 K inhibition in ovarian cancer (NCT04729387). This study included patients with platinum-resistant or refractory high-grade serous ovarian cancer with no germline BRCA mutation detected, aiming to assess the efficacy and safety of the combination of Alpelisib and Olaparib. The primary endpoint is progression-free survival, and the estimated completion date of this study is June 2025. Two phase III trials are assessing the therapeutic effect of PARPi combined with ARIS in metastatic castration-sensitive prostate cancer. Both of these trials investigated whether the combination of Talazoparib with ARSI Enzalutamide improves patients' survival compared to Enzalutamide monotherapy. Results of one trial demonstrated a hazard ratio (HR) of 0.447 in favor of the Talazoparib + Enzalutamide group compared to the placebo + Enzalutamide, indicating a formidable therapeutic effect of combination therapy (NCT03395197). Another trial is still ongoing, with an estimated completion date of August 2027 (NCT04821622). These trials may provide novel therapeutic options for combination therapy.

PARPi and ionizing radiation (IR)

IR can induce DNA damage and trigger cell death. The combination of PARPi and IR could enhance the cytotoxicity mediated by reactive oxygen species, preferentially targeting cancer cells with mutant *TP53* [205].

A study in pancreatic ductal adenocarcinoma suggests that combining radiotherapy with the PARP inhibitor Olaparib could enhance treatment efficacy, with DDB2 expression serving as a potential predictive biomarker for response. Through patient stratification by DDB2 expression level, it is possible to expand the therapeutic options for Olaparib as a radiosensitizer in a wide range of patients [206]. Niraparib BMN673, a PARPi with unique radiosensitizing ability via unique mechanisms causing profound shifts in the balance among DNA double-strand break (DSB) repair pathways, sheds light on combining PARPi and IR to overcome PARPi resistance [207]. Combining Niraparib with IR shows significant potential, as indicated by several preclinical and clinical studies. However, further research is needed to identify biomarkers that could predict the response to this combination.

Future direction

Recent advances in understanding PARPi mechanisms and resistance patterns have significantly improved their clinical application. However, as PARP inhibitors expand beyond breast and ovarian cancers, acquired resistance remains a critical challenge, necessitating further investigation [208]. While laboratory studies have identified various resistance mechanisms, clinical scenarios often differ due to prior treatment-induced cross-resistance. This discrepancy underscores the need for more comprehensive clinical studies to elucidate real-world resistance patterns.

Future research directions should focus on several key areas to address these challenges. Longitudinal studies will be crucial to track the evolution of resistance mechanisms throughout treatment courses, particularly comparing first-line versus later-line PARPi use. For molecularly defined subgroups such as MSI-H pancreatic cancer, dedicated trials are needed to validate ICI as the preferred first-line therapy over PARPi. Additionally, developing combinatorial strategies (e.g., PARPi + ICI in MSS/HRD tumors vs. ICI monotherapy in MSI-H tumors) may maximize therapeutic efficacy while avoiding futile treatments. Utilizing liquid biopsy analysis of circulating tumor DNA can provide non-invasive, real-time monitoring of resistance development. Advanced single-cell omics technologies will enable the dissection of intratumoral heterogeneity and the identification of resistant subclones.

In-depth analysis of exceptional responders to PARPi may uncover novel sensitivity determinants, potentially leading to new therapeutic strategies. Further exploration of synergistic drug combinations, particularly concerning POLQ inhibitors and other emerging targets, is warranted. Identifying and validating predictive biomarkers for PARPi response and resistance will be essential for guiding personalized treatment approaches.

Investigating novel drug delivery systems, such as nanoparticle-based or targeted delivery approaches, as well as leveraging tumor-associated microbiota as a delivery pathway, may enhance PARPi efficacy and overcome resistance mechanisms [209–212]. A recent study developed a genomic-guided biomimetic co-delivery system using B7H3-targeted metal–organic frameworks (MOFs) to simultaneously deliver CDK4/6 inhibitors and PARP inhibitors, which not only achieved tumor microenvironment-responsive drug release but also amplified DNA damage through photodynamic therapy while

reprogramming the immunosuppressive microenvironment via enhanced CD8 + T cell infiltration, demonstrating a 4.2-fold improvement in tumor targeting efficiency compared to non-targeted nanoparticles [213]. Nanoparticles can be designed to deliver RNA-based therapeutics (such as siRNA or miRNA) that target resistance mechanisms, such as restored HRR (via BRCA1/2 or RAD51 overexpression). In addition, nanoparticles could deliver siRNA targeting RAD51 to inhibit the HR pathway, thereby sensitizing tumors to PARPi [214, 215]. Preclinical models demonstrate that PARPi-loaded nanoparticles prolong drug retention in the cerebrospinal fluid with eightfold tumor accumulation, significantly enhancing antitumor activity over free drugs in BRCA-deficient cancers [216]. Furthermore, nanoparticles co-delivering PARPi and immune checkpoint inhibitors boost tumor penetration by 3.7-fold through hyaluronidase-mediated matrix remodeling while blocking PD-L1 upregulation, leading to sustained cytotoxic T-cell infiltration and improved survival [217, 218]. These advances underscore the potential of nanocarriers to overcome drug solubility limitations, minimize off-target effects, and enable combination therapies through controlled spatiotemporal release.

Examining the role of the tumor immune microenvironment in PARPi resistance and exploring immunomodulatory combination strategies could yield valuable insights. Tumor-associated fibroblasts (TAFs) and the extracellular matrix (ECM) contribute to the tumor microenvironment's mechanical properties, affecting drug delivery, immune infiltration, and PARPi resistance. TAFs can produce collagen, fibronectin, and other ECM components, creating physical barriers to immune cell infiltration and drug diffusion [219]. Developing new strategies to target fibroblasts or alter ECM composition would enhance the penetration of PARPi into the tumor and promote more efficient immune cell infiltration. In addition, cytokines such as IL-10, TGF-β, and IL-6 are abundant in the tumor microenvironment and play critical roles in immune suppression and PARPi resistance. Cytokine-targeted therapies can be developed to block immunosuppressive cytokines and boost antitumor immunity. Furthermore, TGF-β is a key mediator of immune suppression in tumors, and blocking its signaling can reverse immune evasion, sensitize tumors to immune checkpoint inhibitors, and enhance the efficacy of PARPi.

Targeting key signaling pathways involved in DNA repair, cell cycle regulation, and tumor survival can sensitize tumors to PARPi by inhibiting alternative repair pathways or overcoming resistance mechanisms. Targeting specific kinases may provide a powerful tool to enhance PARP therapy efficacy. For example, Olaparib has been tested in the presence of Lapatinib (HER2 Inhibitor). Clinical studies in HER2-positive breast cancer are evaluating the synergistic effects of Olaparib and Lapatinib. This combination targets HER2-mediated signaling and DNA repair, aiming to overcome resistance and increase treatment efficacy. In some leukemia models, the combination of Imatinib (BCR-ABL inhibitor) and Olaparib is being tested in clinical trials, particularly in CML and Ph + ALL, where BCR-ABL signaling contributes to DNA repair and survival, and PARPi can exacerbate DNA damage.

Leveraging artificial intelligence and machine learning algorithms to predict resistance patterns and optimize treatment strategies represents an exciting frontier in PARPi research [220]. Cutting-edge AI tools are revolutionizing PARPi drug design. AlphaFold2 now accurately predicts PARP1–ligand binding interfaces, while Rosetta's COMBS algorithm optimizes molecular interactions [221, 222]. Together, these technologies enabled de novo creation of PARPi-binding proteins (PiB) with sub-nanomolar affinity. By analyzing data from BRCA-mutant cancers (including single-cell profiles and patient treatment histories), AI systems can forecast resistance development with 85% accuracy. These models guide the engineering of "PARPi-capturing" proteins, whose drug-binding strength is enhanced by simulating key molecular interactions like the Q54-D58-N131 network [221]. In lab tests, such AI-designed proteins restored PARPi sensitivity in resistant cells, cutting the required drug dose by 78% [221]. Meanwhile, AI accelerates personalized treatment by predicting optimal drug concentrations for individual patients. Advanced models calculate drug-protein binding efficiency with near-atomic precision, enabling tailored dosing strategies. By combining computational predictions with experimental validation, AI is proving indispensable to overcoming resistance and improving PARPi therapies.

By pursuing these multifaceted research directions and integrating insights from basic science, translational research, and clinical observations, we can develop more effective strategies to overcome PARPi resistance and improve patient outcomes. Furthermore, understanding the mechanisms of PARPi resistance may provide valuable insights into cancer biology and DNA repair pathways, potentially leading to novel therapeutic approaches beyond PARPi. As we unravel the complexities of PARPi resistance, a collaborative, interdisciplinary approach will be essential to translate these findings into meaningful clinical advancements.

Abbreviations

2-DG	2-Deoxyglucose
3-BrPA	3-Bromopyruvate
53BP1	P53-binding protein 1
ABC	ATP-binding cassette
AML	Acute myeloid leukemia
AR	Androgen receptor
ARSI	Androgen receptor signaling inhibitors
ATLL	Adult T-cell leukemia/lymphoma
BER	Base Excision Repair
BETi	BET inhibitors
CDKi	CDK inhibitors
cfDNA	Cell-free DNA
CHK1i	CHK1 inhibitors
CST	CTC1-STN1-TEN1
D-2HG	D-2-hydroxyglutarate
DDR	DNA Damage Response
DSBs	Double-strand breaks
ECM	Extracellular matrix
FAO	Fatty acid oxidation
HDACi	HDAC inhibitors
HR	Homologous Recombination
HRD	Homologous recombination deficiency
HRR	Homologous recombination repair
ICIs	Immune checkpoint inhibitors
IDH	Isocitrate dehydrogenase
IFN-I	Type I interferon
IR	Ionizing radiation
LOH	Loss of heterozygosity
LST	Large-scale transitions
mCRPC	Metastatic castration-resistant prostate cancer
MDS	Myelodysplastic syndromes
meRAD51 C	RAD51C promoter methylation
MMR	Mismatch Repair
MMEJ	Microhomology-mediated end joining
MSI-H	Microsatellite instability-high
NAMPT	Nicotinamide phosphoribosyltransferase
NAPRT1	Nicotinate phosphoribosyltransferase
NHEJ	Non-Homologous End Joining
NSCLC	Non-small cell lung cancer
PARP	Poly (ADP-ribose) polymerase
PARPi	PARP inhibitors
PDX	Patient-derived xenograft
PiB	PARPi-binding proteins
SLFN11	Schlafen-11
SSBs	Single-strand breaks
TAFs	Tumor-associated fibroblasts
TAI	Telomeric allelic imbalance
TIM	TIMELESS
TMB	Tumor mutational burden
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
TRCs	Transcription-replication conflicts
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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Authors' contributions
Conceptualization and design: H.T., C.N., X.L., and Z.G.; Literature search: H.Z. and P.C.; Data interpretation: Y.Z. and H.Z.; Writing: Y.Z., H.Z., P.C., J.T. and S.Y.; Reviewing and editing: C.N., H.T., X.L., and Z.G. All authors read and approve the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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