Novel clinical potential of poly (ADP-ribose) polymerase inhibitors in triple-negative breast cancer: Mechanistic insights and clinical applications (Review)

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Abstract. Breast cancer is one of the most prevalent malignant tumors worldwide, and triple-negative breast cancer (TNBC) presents a major therapeutic challenge due to the lack of effective targeted treatment options. Poly (ADP-ribose) polymerase (PARP) plays a critical role in DNA damage repair, and its inhibitors have shown significant therapeutic efficacy in patients with TNBC exhibiting breast cancer susceptibility gene (BRCA) mutations. The present review aimed to analyze the molecular mechanisms of cell death induced by DNA damage related to PAR and PARP, thoroughly exploring the role of PARP in regulatory pathways. Additionally, it intended to highlight clinical trials and therapeutic outcomes of PARP inhibitors currently used in TNBC treatment. In particular, the current review delves into the mechanisms of drug resistance, such as BRCA mutation reversion and PARP protein trapping, and examines potential strategies to overcome PARP inhibitor resistance in the future. Ultimately, the present study aims to offer novel perspectives and research directions for further optimizing the application of PARP inhibitors in TNBC therapy.

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Abbreviations: AD, auto-modification domain; ADCs, antibody-drug conjugates; BRCA, breast cancer susceptibility gene; BRCT, BRCA1 C-terminal; CAT, catalytic; CHFR, checkpoint protein with FHA and RING domains; CI, confidence interval; DBD, DNA-binding domain; GDP-M, guanosine diphosphate-mannose; GSDMC, gasdermin-C; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HRD, homologous recombination repair deficiency; HRR, homologous recombination repair; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; QoL, quality of life; SSBs, single-strand breaks; TNBC, triple-negative breast cancer; UFMylation, ubiquitin-fold modifier modification

Key words: poly (ADP-ribose) polymerase, triple-negative breast cancer, DNA damage, breast cancer susceptibility gene mutation, apoptosis, parthanatos, clinical drugs

Contents

1. Introduction

According to data from the 2024 National Cancer Institute and the Centers for Disease Control and Prevention, the age-standardized incidence rate of breast cancer for women during the 2017-2021 period was 131.8 per 100,000 women. Triple-negative breast cancer (TNBC) is a highly heterogeneous subtype of breast cancer with poor prognosis, accounting for 10-20% of all breast cancer cases and having the lowest survival rate (78%) among all subtypes (1). Due to the lack of expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2), TNBC is insensitive to traditional hormone therapy and targeted treatments, leaving chemotherapy as the primary treatment option for TNBC. However, the high rates of recurrence and metastasis in TNBC highlight the urgent need to identify novel therapeutic strategies and molecular targets to improve patient survival (2).

The primary risk factor for breast cancer is a mutation in either of the breast cancer susceptibility genes breast cancer susceptibility gene (BRCA)1 or BRCA2. A considerable proportion of patients with TNBC carry germline BRCA1/2 mutations. Tumors harboring BRCA1/2 mutations are highly dependent on poly (ADP-ribose) polymerase (PARP) proteins, which are essential for repairing single-strand DNA damage through the base excision repair pathway (3). Consequently, PARP inhibitors, due to their unique mechanism of blocking DNA damage repair, are particularly suited for treating tumors with DNA repair deficiencies (4). Over the past decades,

PARP inhibitors have emerged as promising drugs in clinical oncology (5,6).

To date, numerous clinical research articles have been published on PARP inhibitors in the treatment of breast cancer, ovarian cancer and other diseases. At present, there are eight PARP inhibitors, of which only six have been approved for global marketing, excluding Iniparib and Veliparib. These approved drugs include Olaparib (NCT02734004), Rucaparib (NCT02042378), Niraparib (NCT05734911), Talazoparib (NCT04987931), Fuzuloparib (NCT05753826) and Pamiparib (NCT03333915) (7-9), and are used for the treatment of ovarian cancer (such as NCT03333915), pancreatic cancer (such as NCT02677038), breast cancer (such as NCT01074970), prostate cancer (such as NCT03516812) and other solid tumors (10).

It is worth noting that not all PARP inhibitors have achieved highly satisfactory results in the treatment of breast cancer due to the emergence of drug resistance, toxic side effects, such as bone marrow suppression and gastrointestinal discomfort, as well as limitations in the target population (e.g., the efficacy of the drug depends on the BRCA gene mutation status) (11). Clinical research on certain PARP inhibitors is still exploring more suitable dosing regimens and combination therapy strategies (12-15).

Numerous studies have focused on PARP and its inhibitors as therapeutic targets (16-18). However, in the actual clinical treatment of patients with TNBC, the efficacy of PARP inhibitors does not always mirror the promising results observed in experimental models, thus warranting reflection from researchers and clinicians on the outcomes. The main objective of the present study was to explore potential directions for advancing the use of PARP inhibitors in TNBC treatment by integrating feasible therapeutic strategies with the current clinical trial performance of PARP inhibitors in TNBC. The present review focuses on the molecular mechanisms of PARP and its inhibitors, aiming to provide insights into optimizing the use of these agents in future TNBC therapies.

2. Regulatory pathways of PARP in DNA repair

PARPs are a family of DNA repair enzymes that were first identified in the 1960s (19). To date, 17 members of the PARP family have been identified, with PARP-1, PARP-2 and PARP-3 being the most extensively studied. PARP-1 is a protease characterized by highly conserved domains, consisting of three main functional regions: The DNA-binding domain (DBD), the auto-modification domain (AD) and the catalytic (CAT) domain. The DBD is responsible for recognizing and binding to damaged DNA fragments, particularly single-strand breaks (SSBs). Once PARP-1 detects DNA damage, it binds to the damaged site via its DBD and catalyzes the conversion of NAD+ through its CAT, transferring ADP-ribose units from NAD+ to PARP itself or other acceptor proteins, forming PAR chains. This modification, known as poly(ADP-ribosyl)ation (PARylation), rapidly initiates a series of downstream signals, coordinating the protein network involved in DNA repair (20). In this process, the AD, primarily associated with BRCA1 C-terminal (BRCT) regions, plays a key role in facilitating protein-protein interactions and regulating PARP's dissociation from DNA after it recognizes and binds to DNA-damage sites. During DNA repair, PARP identifies and binds to SSBs through its zinc finger domain, which subsequently activates its CAT domain. The CAT domain is responsible for enzymatic activity, including the cleavage of NAD+ and the formation of PAR chains (Fig. 1). This process alters the spatial conformation of PARP, weakening its binding affinity to DNA and allowing it to dissociate from the site of the DNA break (21,22).

PARP inhibitors have shown promise for treating patients with cancer carrying BRCA1/2 mutations, particularly demonstrating significant clinical efficacy in ovarian and breast cancer (23,24). Based on the strategy of targeting homologous recombination repair deficiency (HRD), PARP inhibitors block DNA repair, leading to cancer cell death and effectively suppressing tumor growth. However, as their clinical applications have expanded, the issue of drug resistance has gradually emerged (25). Overcoming resistance to PARP inhibitors and extend their use to patients without BRCA mutations have become key areas of current research.

Increasing evidence suggests that PARP-1 activation can be triggered by a range of other stimuli, such as protein-protein interactions or changes in redox states. These findings underscore its role as a regulator involved in chromatin remodeling and histone PARylation, or as a transcriptional co-factor in gene expression regulation (26-28).

Furthermore, excessive activation of PARP can be induced by various stressors, including oxidative stress, radiation and chemotherapeutic agents, leading to an energy-depleting form of cell death known as parthanatos, along with apoptosis-inducing factor release and widespread DNA degradation (Fig. 1). Parthanatos has been applied in neuroscience (29,30); however, it remains largely unexplored in oncology. Therefore, there is considerable potential for further investigation in this area.

BRCA-mediated DNA repair effects. In the field of DNA damage repair and breast cancer, particularly TNBC, the key molecular players are most notably *p53* and *BRCA1/2*. Mutations in *p53* can influence the expression of key genes associated with cell proliferation, including MYC proto-oncogene, bHLH transcription factor, C-X-C motif chemokine ligand 1 and cyclin E2, through direct or indirect pathways (31-33). Although TP53 is the most frequently altered gene in breast cancer, *p53* remains in its wild-type form >2/3 of cases. However, in basal-like breast cancer cases, most of which are triple negative, the mutation frequency of *p53* reaches 88% (34). *BRCA1* and *BRCA2* are tumor suppressor genes linked to breast cancer, playing essential roles in homologous recombination repair (HRR). Mutations in *BRCA1* are frequently observed in patients with breast cancer, resulting in defects in DNA repair, abnormal centrosome replication, and impaired cell cycle and spindle checkpoint functions. This has led to the hypothesis that *BRCA1* mutations contribute to tumorigenesis through genomic instability (35). These mutations not only endow cells with malignant potential but also allow the use of targeted therapies.

The concept of synthetic lethality refers to the phenomenon where two different metabolic pathways or gene functions compensate for one another; inhibiting either pathway alone does not result in cell death, but simultaneous inhibition of both leads to cell death, which also applies to tumor cells (36).

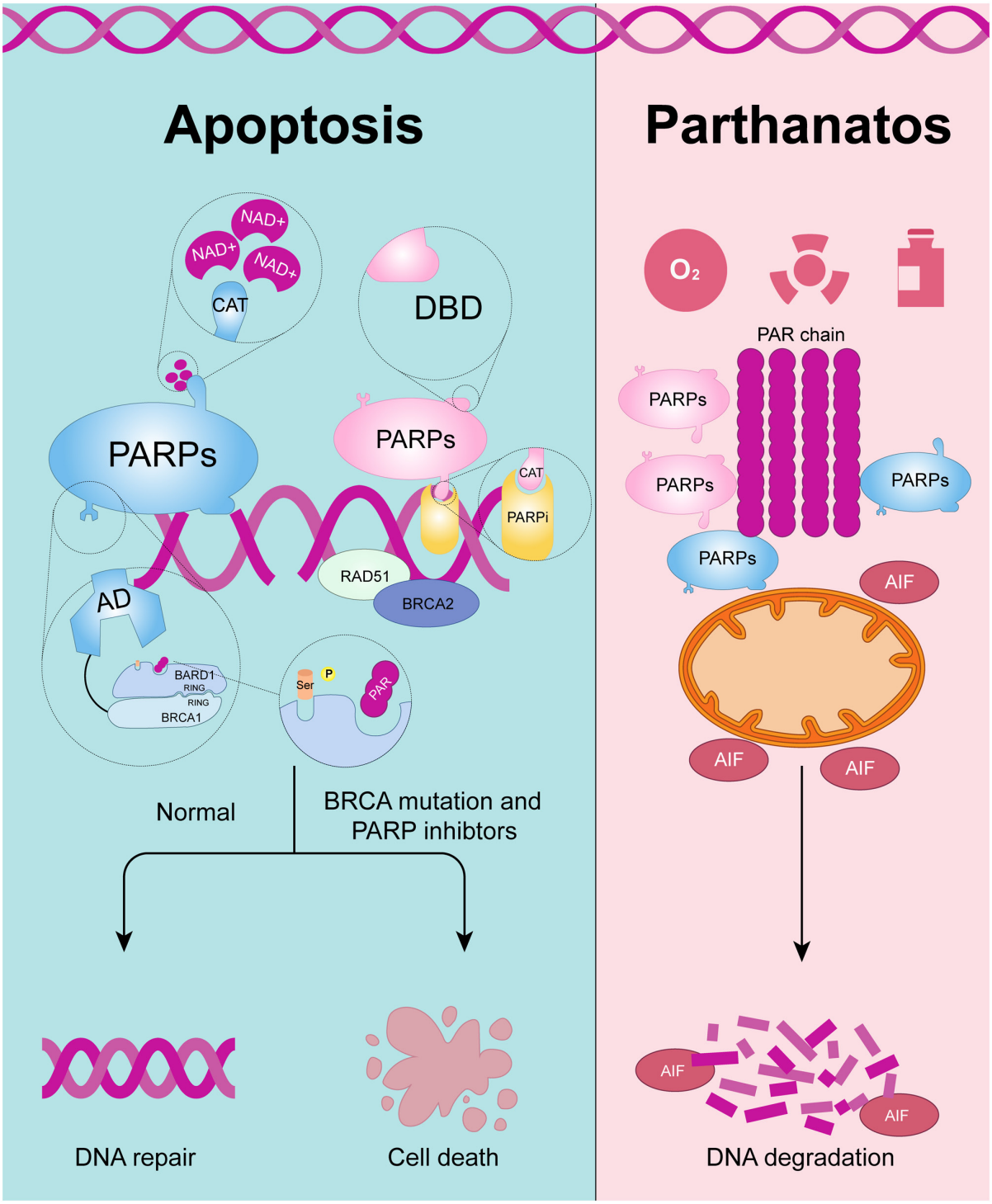

Figure 1. PARP molecule-associated modes of cell death. In apoptosis, according to the study by Rouleau-Turcotte and Pascal (22), the domains of PARP consist of zinc fingers, and CAT, BRCT and WGR (Trp-Gly-Arg) domains. Based on functional classification, the domains can be broadly categorized into three types: i) AD, which primarily involves the BRCT structure and is responsible for protein-protein interactions; ii) DBD, which is responsible for the binding of PARP molecules to DNA; and iii) CAT, which is responsible for the cleavage of NAD+ and the polymerization of ADP-ribose. In parthanatos, excessive oxidative stress, radiation or drug stimulation can induce cells to consume large quantities of NAD and ATP to repair damaged DNA. However, the excessively synthesized PAR polymers can translocate from the nucleus to the mitochondria as signaling molecules, inducing the release of AIF from mitochondria. AIF then translocates to the nucleus, leading to large-scale DNA fragmentation and chromatin condensation. The chart was generated using Adobe Illustrator CC 2018, version 2018.0.0; Adobe Systems. PARP, poly (ADP-ribose) polymerase; CAT, catalytic; BRCT, BRCA1 C-terminal; BRCA, breast cancer susceptibility gene; AD, automodification domain; DBD, DNA-binding domain; AIF, apoptosis-inducing factor.

Mutations in the *p53* and *BRCA1/2* genes in patients disable one of the primary DNA repair pathways, and further inhibition of the DNA repair function of PARP leads to pronounced cell death (37). This theory has been validated in numerous experiments. For instance, Bryant *et al* (38) demonstrated that *BRCA2* deficiency (either BRCA2$^{+/-}$ or BRCA2$^{-/-}$) resulted in HRR defects, and mice with BRCA2 mutations showed a high sensitivity to PARP inhibitors, which induced replication fork

collapse and selectively killed the defective cells, while cells with normal BRCA function remained largely unaffected. Farmer *et al* (39) elucidated the mechanism involving the interaction between BRCA2 and RAD51, highlighting that the rapid recruitment of RAD51 to DNA damage sites was fundamental to the HRR pathway. While PARP1 does not play a direct role in HRR, its absence increases the need for an efficient HRR pathway, possibly due to the conversion of unrepaired SSBs into double-strand breaks. Normally, BRCA2 recruits RAD51 to these sites for HRR, but without functional BRCA2, HRR does not occur (39).

BRCA1-associated ring domain 1 (BARD1) is a protein that forms a heterodimer with BRCA1 and plays a crucial role in DNA damage repair. Regarding the mechanism by which BRCA molecules are recruited to DNA damage sites, the role of BARD1 has been widely recognized. BARD1, the primary partner of BRCA1, contains tandem BRCT motifs. The heterodimer of BARD1 and *BRCA1* is targeted to sites of DNA damage mainly through their ring-like structures, while the BRCT domains, which recognize phosphorylated serine motifs, influence the translocation of the dimer at DNA sites (40,41). Additionally, the interaction between BRCT and PAR occurs through the binding of each ADP-ribose unit in PAR, thereby ensuring the adequate progression of HRR (42,43).

Protein ubiquitination. Protein ubiquitination not only plays a key role in protein degradation but also has crucial functions in DNA damage repair and maintaining genomic stability. A study has shown that checkpoint protein with FHA and RING domains (CHFR), through its interaction with PARP1, regulates the crosstalk between PARylation and ubiquitination. PARP1 recruits downstream DNA repair factors via PAR modification, while CHFR may regulate the ubiquitination of PAR and repair proteins, thereby modulating the duration and intensity of PARP1 activity during the DNA damage repair process (44). This coordinated regulation is critical to ensure the accuracy and timeliness of DNA damage repair, and it may also confer sensitivity to PARP inhibitors in TNBC cells (45). Furthermore, a diverse range of ubiquitin ligases have been identified, including deltex E3 ubiquitin ligase (DTX), ring finger protein 8(RNF8) and mediator of DNA damage checkpoint 1(MDC1) (46-49). The combined use of drugs targeting ubiquitin ligases exacerbates the accumulation of DNA damage, leading to unrepaired DNA breaks in cancer cells, ultimately triggering cell death.

Epigenetic modifications. Epigenetic modifications refer to alterations in gene expression that do not involve changes to the DNA sequence itself. Common epigenetic modifications include DNA methylation and histone modifications (such as acetylation, methylation and phosphorylation), which regulate gene expression by altering chromatin structure (50). One of the central mechanisms of epigenetic regulation involves modifying chromatin conformation to control gene accessibility. PARP-1 and other members of the PARP family modulate chromatin plasticity through the PARylation of histones (51,52). For example, previous research has shown that histones such as H2A at K13, H2B at K30, H3 at K27 and K37, and H4 at K16 can serve as ADP-ribose acceptor sites (53). The PARylation of H2 introduces a considerable negative charge around chromatin proteins, leading to chromatin decondensation, thereby facilitating the access of DNA repair factors to sites of damage (54). Zhou *et al* (55) treated trophoblast stem cells with a DNA-modifying agent in PAR glycohydrolase-deficient cells and found that excessive PARylation of histones, due to inhibition of PAR chain hydrolysis, increased the sensitivity of the cells to DNA damage-induced cell death.

Activation of PARP-1 can also alter chromatin structure by recruiting chromatin remodeling complexes such as the Switch/sucrose non-fermentable complex, which plays a critical role in regulating chromatin structure and gene expression by altering chromatin accessibility (56). However, in tumor cells, this can more easily induce synthetic lethality (57). It is worth noting that PARylation can activate gene expression but can also regulate gene silencing through chromatin compaction. For instance, SIRT1, a deacetylase that promotes cell survival, competes with PARP-1 as both rely on NAD+ as a substrate. Overactivation of PARP-1 can reduce SIRT1 activity, thereby contributing to gene silencing (58). Previous research has suggested that certain viruses can exploit PARP-1 to modify viral episomes or host genes, aiding long-term viral infections of DNA viruses, which can lead to tumorigenesis (59).

Long non-coding RNAs (lncRNAs) are also involved in the epigenetic regulation of gene expression by interacting with epigenetic regulatory protein complexes, such as histone-modifying enzymes and DNA methyltransferases, and are closely associated with apoptosis, autophagy and transformation. Increasing evidence has revealed their role in promoting tumor initiation, invasion and malignancy (60-62). A PAR-related study has reported that a human lncRNA-encoded micropeptide called PACMP not only inhibits the ubiquitination of C-terminal binding protein-interacting protein by blocking its interaction with *KLHL15* but also directly binds to DNA damage-induced PAR chains, thus enhancing PARP1-dependent PARylation. Targeting lnc15.2/PACMP has shown reversal of resistance to several chemotherapy drugs, including PARP inhibitors, ataxia telangiectasia and Rad3-related inhibitors and cyclin-dependent kinase-4/6 inhibitors (63). However, there is limited research on targeted therapy of lncRNAs related to breast cancer in combination with PARP inhibitors, thus offering a broad scope for exploration in the future.

3. PARP-related therapeutic strategies

Both the inhibition and activation of PARP can induce cell death, with the former primarily attributed to apoptosis caused by DNA damage within a controllable range for the cell, while the latter triggers energy depletion and widespread degradation of genetic material by exhausting the precursors of PAR, such as NAD+ and ATP (64).

For TNBC, the mainstream treatment still focuses on PARP inhibitors, mainly in combination with other clinical chemotherapy agents. For example, combining PARP inhibitors with DNA cross-linking agents such as carboplatin and cisplatin exacerbates DNA damage, while combining them with microtubule inhibitors such as paclitaxel increases replication stress in tumor cells. Additionally, targeting signaling pathways such

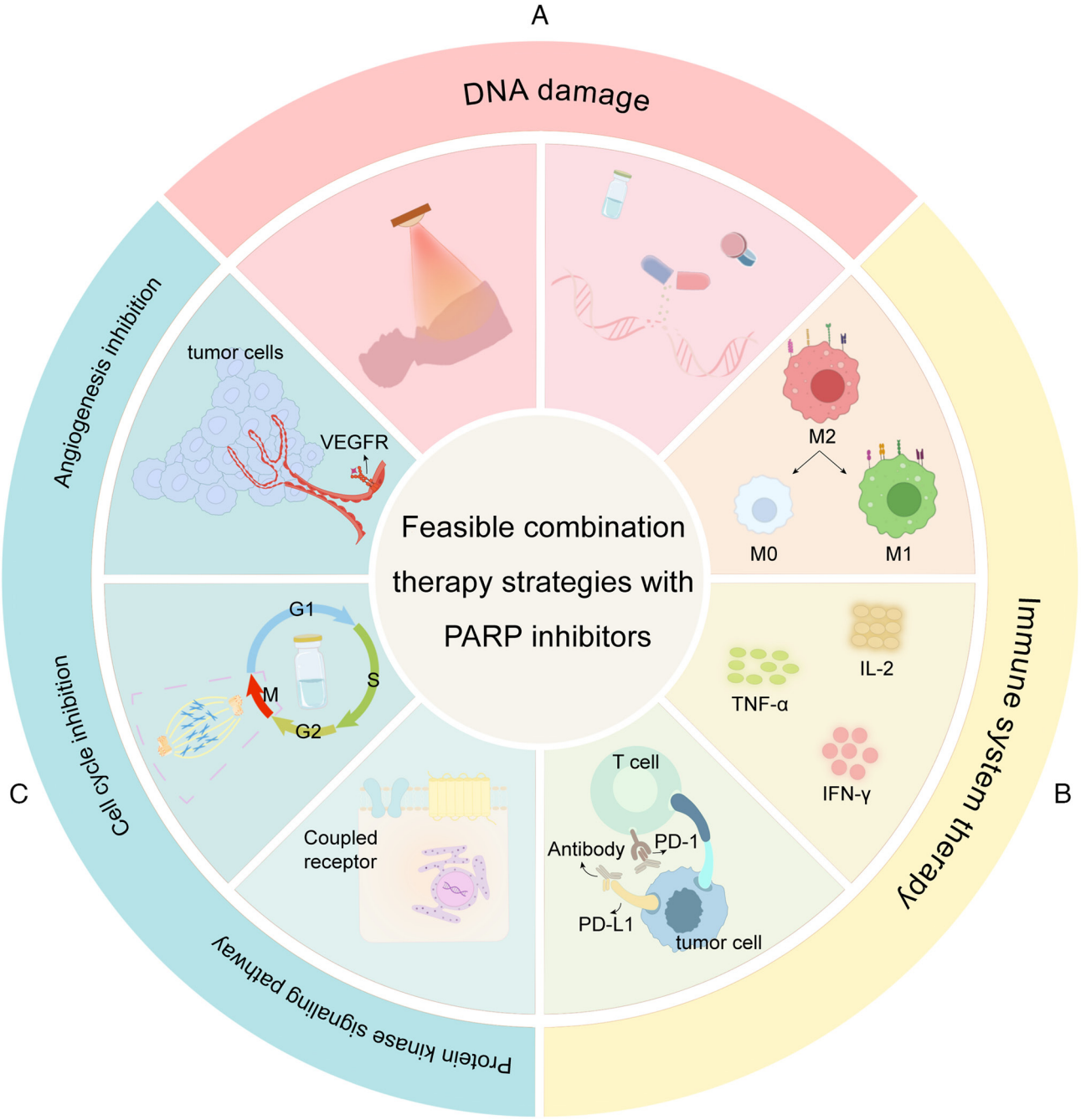

Figure 2. Feasible combination therapy strategies with PARP inhibitors. Class A (red): Classical cancer treatment methods, including radiotherapy and chemotherapy, which kill tumor cells by inhibiting DNA replication or promoting DNA strand breaks. Common drugs include DNA cross-linking agents (such as platinum-based drugs) and thymidine analogs (such as gemcitabine). Although these methods are effective, they cause notable damage to normal cells. Class B (yellow): Immunotherapy, which restores T cell-mediated killing of tumor cells through immune checkpoint inhibitors (such as anti-PD-1/PD-L1 antibodies). Additionally, tumor vaccines or immune modulators (such as IL-2, TNF-α and IFN-γ) can promote antitumor immune responses. Another strategy involves reducing M2-type immunosuppressive macrophages and enhancing the activity of M1-type macrophages. Class C (blue): Other types of therapies, including: i) Angiogenesis inhibition (for example cediranib and apatinib targeting VEGFR), which limits tumor nutrient supply by reducing blood vessel formation; ii) cell cycle inhibition (for example microtubule inhibitor paclitaxel); and iii) protein kinase signaling pathway regulation (for example PI3K/AKT/mTOR inhibitors such as alpelisib and buparlisib). The efficacy of these strategies is being further evaluated in combination with PARP inhibitors. The chart was generated using Adobe Illustrator CC 2018, version 2018.0.0; Adobe Systems. PARP, poly (ADP-ribose) polymerase; VEGFR, vascular endothelial growth factor receptor; PD-L1, programmed cell death ligand 1; PD-1, programmed cell death protein 1.

as PI3K/Akt inhibition or anti-angiogenesis agents can further prevent tumor growth and metastasis (Fig. 2) (65).

There is a close association between immunotherapy and PARP inhibitors. From a metabolomics perspective, Ding *et al* (66) reported that guanosine diphosphate-mannose (GDP-M), a metabolite, accumulates in cells and reduces the interaction between BRCA2 and ubiquitin-specific peptidase 21. This promotes the ubiquitin-mediated degradation of BRCA2, thereby inhibiting HRR. Furthermore, the authors found that the combination of GDP-M and DNA-damaging agents activates STING-dependent antitumor immunity in immunocompetent mouse models. Using whole-genome

clustered regularly interspaced short palindromic repeats screening, Zhong *et al* (67) identified PARP1 as a restriction factor for herpes simplex virus 1 replication. By combining their custom-designed oncolytic virus with a PARP inhibitor, the authors were able to render TNBC highly sensitive to immune checkpoint inhibitors. Seaweed polysaccharides have been recommended as anticancer supplements and for boosting human health. Chen *et al* (68) observed that oligo-fucoidan combined with Olaparib more effectively inhibited the formation of TNBC stem cell mammospheres, while also suppressing the oncogenic IL-6/phosphorylated EGFR/PD-L1 pathway. This combination promoted the repolarization of M2 macrophages into M0-like and M1-like macrophages, thereby inducing immune activation. In the same study, this effect has been confirmed in mice, where oral administration of oligo-fucoidan alongside Olaparib inhibited postoperative TNBC recurrence and metastasis (68).

4. PARP-related inhibitors in clinical trials

Before evaluating the clinical efficacy of PARP inhibitors, it is essential to understand their mechanisms of action. The catalytic function of PARP enzymes stems from the CAT domain, which includes a binding site for NAD+. PARP inhibitors competitively bind to the catalytic active site of PARP, thereby blocking the entry of NAD+. Simultaneously, when PARP inhibitors bind to the catalytic site, PARP is unable to complete PARylation and dissociates from DNA damage sites. This trapping effect prevents other DNA repair factors from reaching the damage site, further exacerbating DNA damage. Therefore, the efficacy of a PARP inhibitor largely depends on its binding strength to the CAT domain and its ability to trap PARP at DNA damage sites (22,69).

Over the past two decades, numerous PARP inhibitors have entered clinical trials. These drugs include Iniparib (NCT01173497) (70) and Veliparib (NCT02163694) (71) Olaparib (NCT02734004) (72), Rucaparib (NCT02042378) (73), Niraparib (NCT05734911) (74), Talazoparib (NCT04987931) (75), Fuzuloparib (NCT05753826, Recruiting) and Pamiparib (NCT03333915) (76). Understanding their efficacy in these trials provides valuable insights for developing effective clinical treatment strategies for patients in the future.

Iniparib. Iniparib (chemical name: BSI-201) was initially considered one of the promising candidate drugs in the category of PARP inhibitors. In 2011, it entered phase II clinical trials and demonstrated significant efficacy in treating TNBC (clinical trial no. NCT00540358) (77). However, subsequent phase III randomized controlled trials (clinical trial no. NCT00938652) (78) delivered disappointing results. In the trial, 261 patients treated with the combination of gemcitabine + carboplatin + Iniparib were compared with 258 patients receiving gemcitabine + carboplatin alone, and no statistically significant difference was observed in overall survival (OS) [hazard ratio (HR)=0.88; 95% confidence interval (CI), 0.69-1.12; P=0.28] or progression-free survival (PFS) (HR=0.79; 95% CI, 0.65-0.98; P=0.027). These results indicated that the potential benefits of Iniparib required further evaluation (78).

Subsequent analysis of these results, which was conducted by Mateo *et al* (79), suggested that Iniparib is not a true PARP inhibitor. The authors also proposed a framework for identifying potential 'pitfalls' in anticancer drug development. In fact, Liu *et al* (80) pointed out that the primary mechanism of action of Iniparib may be through non-selectively modifying cysteine-containing proteins in tumor cells. This modifying effect does not rely on the catalytic mechanism of PARP. Instead, it affects the survival and proliferation of tumor cells through other pathways.

Olaparib. Olaparib (chemical name: AZD2281), developed by AstraZeneca, is the first widely used PARP inhibitor in clinical settings. Its earliest clinical trials began in 2005, focusing on breast and ovarian cancer cases with BRCA1/2 mutations, and it also showed efficacy in HER2-negative metastatic breast cancer (81). In 2009, the results of a phase I clinical trial (clinical trial no. NCT00516373) demonstrated the effectiveness of Olaparib in BRCA-mutated ovarian and breast cancer (23). Subsequently, a phase II, multicenter, open-label, non-randomized study (clinical trial no. NCT00679783) was conducted to evaluate Olaparib treatment in women with ovarian cancer and TNBC. The results showed that 18 out of 64 patients with ovarian cancer had a confirmed objective response, while no responses were observed in any of the 26 patients with TNBC (15). Similarly, a multicenter phase II clinical study in 2015 reported the therapeutic response in germline BRCA1/2-mutated tumors, with a relatively low response rate of 12.9% (8/62; 95% CI, 5.7-23.9) in breast cancer. Additionally, 47% of the patients experienced stable disease for >8 weeks (95% CI, 34.0-59.9) (82).

Whether used as a monotherapy or in combination with other drugs, the majority of the early clinical studies reported that ≥50% of patients experienced grade ≥3 adverse events (82-86). Previous studies have also evaluated the safety and tolerability of combining Olaparib with radiotherapy. For instance, Loap *et al* (87-89) conducted the long-term RADIOPARP phase I trial in 24 patients with TNBC who exhibited residual disease after neoadjuvant chemotherapy. These patients were treated with four different doses of Olaparib (50, 100, 150 and 200 mg, twice daily). Initially, no dose-limiting toxicities were observed, and after 1 year of follow-up, no treatment-related grade ≥3 toxicities were noted. Additionally, the 3-year OS and event-free survival rates were 83% (95% CI, 70-100%) and 65% (95% CI, 48-88%), respectively.

In recent years, the majority of clinical trials involving Olaparib have progressed to phase II or III (Table I). Based on the trial endpoints, it can be observed that Olaparib has improved pathological complete response and OS in patients, although the improvements are not always statistically significant. Additionally, certain studies have not only focused on efficacy but also on quality of life (QoL). For example, a patient-reported outcomes study indicated that patients receiving Olaparib experienced statistically significantly higher levels of fatigue at 6 and 12 months during the treatment and follow-up periods compared to those receiving placebo. However, this did not reach the predetermined clinical significance threshold of a 3-point difference. At 18 and 24 months, the Olaparib and placebo scores were similar (90). In conclusion, the importance of these clinical studies lies in

Table I. Clinical studies on Olaparib treatment for breast cancer with germline BRCA mutations published in the last 5 years.

First author, year	Trial phase	Treatment regimen	Endpoint events	Results	(Refs.)
Domchek *et al*, 2020	Phase I/II	Olaparib + durvalumab	12-week disease control rate	80%	(72)
Tutt *et al*, 2021	Phase III	Olaparib vs. placebo	3-year invasive disease-free survival	85.9% (Olaparib) vs. 77.1% (placebo)	(122)
Gelmon *et al*, 2021	Phase IIIb	Olaparib	PFS	8.11 months (95% CI, 6.93-8.67)	(123)
Pusztai *et al*, 2021	Phase II[a]	Olaparib + durvalumab	pCR	HER2-negative (20-37%), HRE-positive/HER2-negative (14-28%), TNBC (27-47%)	(124)
Batalini *et al*, 2022	Phase Ib[a]	Olaparib + Alpelisib	ORR	18% (59% of patients exhibited disease control)	(125)
Geyer *et al*, 2022	Phase III	Olaparib vs. placebo	4-year OS	89.8% (Olaparib) vs. 86.4% (placebo)	(126)
Loap *et al*, 2022	Phase I	Olaparib + radiotherapy	OS; EFS	3-year OS, 83%; EFS, 65% (2-year follow-up)	(89)
Robson *et al*, 2023	Phase III	Olaparib vs. TPC	OS	Median OS: 19.3 months (Olaparib) vs. 17.1 months (TPC)	(127)
Yamauchi *et al*, 2023	Phase III	Olaparib vs. placebo	IDFS; DDFS; OS	HR for IDFS, 0.5 (95% CI, 0.18-1.24); HR for DDFS, 0.41 (95% CI, 0.11-1.16);HR for OS, 0.62 (95% CI, 0.13-2.36)	(128)
Senkus *et al*, 2023	Phase III	Olaparib vs. TPC	PFS; OS	Median PFS, 8.0 months (Olaparib) vs. 3.8 months (TPC); median OS, 18.9 months (Olaparib) vs. 15.5 months (TPC)	(129)
Ring *et al*, 2023	Phase II[a]	Olaparib + Ceralasertib	ORR	ORR, 17.1% (12/70 patients; 95% CI, 10.4-25.5)	(130)
Balmana *et al*, 2024	Phase IIIb	Olaparib	PFS; OS	Median PFS, 8.18 months; median OS, 24.94 months	(131)
Tan *et al*, 2024	Phase II[a]	Olaparib ± Durvalumab	PFS; CBR	Median PFS, 4.0 months (Olaparib) vs. 6.1 months (combination); CBR, 44% (95% CI, 23-66%, Olaparib) vs. 36% (95% CI, 17-59%, combination)	(132)
Ganz *et al*, 2024	Phase III	Olaparib vs. placebo	Fatigue severity and quality of life	Fatigue severity was statistically higher for Olaparib at 6 and 12 months but not clinically significant	(90)

Table I. Continued.

First author, year	Trial phase	Treatment regimen	Endpoint events	Results	(Refs.)
Abraham *et al*, 2024	Phase II/III[a] (BRCA wild- type)	Olaparib ± Carboplatin-Paclitaxel	pCR; EFS; OS	pCR, 51% (Olaparib arm) vs. 52% (control arm); EFS, 80% (Olaparib arm) vs. 79% (control arm) at 36 months; OS, 90% (Olaparib arm) vs. 87.2% (control arm)	(133)

[a]Trials including TNBC in the post-trial period. HRE, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; PFS, progression-free survival; pCR, pathological complete response; ORR, objective response rate; IDFS, invasive disease-free survival; DDFS, distant disease-free survival; EFS, event-free survival; TPC, treatment of physician's choice; CBR, clinical benefit rate; HR, hazard ratio; CI, confidence interval; OS, overall survival.

helping physicians make more precise decisions about treatment options by considering both QoL and efficacy, ensuring that therapeutic effectiveness is maximized while minimizing the burden on the QoL of patients.

Rucaparib. The earliest clinical study on Rucaparib (chemical name: AG-014699) was reported in 2008, when Plummer *et al* (91) evaluated the safety, efficacy, pharmacokinetics and pharmacodynamics of AG-014699 in combination with temozolomide in adult patients with advanced malignant tumors. The study observed encouraging evidence of activity. In 2016, clinical research focusing on breast cancer-related treatments indicated that Rucaparib was well tolerated at doses ≤480 mg/day and was a potent PARP inhibitor, providing sustained inhibition for ≥24 h after a single dose, although specific efficacy data for patients with breast cancer were not provided (92).

Another phase II clinical trial in patients with TNBC found that Rucaparib significantly reduced circulating tumor DNA levels in homologous recombination repair-deficient cancer and induced the expression of interferon response genes, suggesting that Rucaparib may enhance antitumor effects not only through inhibition of DNA repair pathways but also by triggering DNA damage-induced immune responses (93). In another study, Kristeleit *et al* (94) evaluated the combination of Rucaparib with the immune checkpoint inhibitor Atezolizumab in advanced gynecological cancer or TNBC. Patients with higher PD-L1 levels and BRCA mutations prior to treatment were more likely to experience adverse reactions such as gastrointestinal symptoms, elevated levels of liver enzymes or anemia. Markers of DNA damage repair (such as *RAD51 foci*) and apoptosis markers were also reduced. This suggests that there may be a synergistic effect between the immune response and PARP inhibitors. Rucaparib may enhance tumor antigen production by promoting DNA damage, thereby activating the immune system.

Niraparib. Niraparib (chemical name: MK-4827) is an oral, potent and selective inhibitor of PARP-1 and PARP-2, capable of inducing functional loss in BRCA and phosphatase and tensin homolog. In 2013, Sandhu *et al* (95) clinically evaluated its safety and tolerability, establishing 300 mg/day as the maximum tolerated dose. The oral bioavailability of Niraparib in humans was measured at 72.7% (96). In the multi-country, phase III Niraparib in Patients with Platinum-Sensitive Recurrent Ovarian Cancer trial (NCT01847274) conducted in adult patients with platinum-sensitive recurrent ovarian cancer (97), Niraparib significantly prolonged the median PFS, regardless of the presence of germline BRCA mutations or HRD, highlighting its distinct advantage (98).

Although clinical research on the treatment of TNBC with Niraparib remains limited, a combination therapy study involving Niraparib (MK-4827) and fractionated radiotherapy in the MDA-MB-231 TNBC cell line has demonstrated promising results. Regardless of p53 status, MK-4827 reduced tumor PAR levels within 1 h of administration, with the effect lasting ≤24 h (99). These findings provide a foundation for future research in this area.

Talazoparib. Talazoparib (chemical name: BMN673), developed by BioMarin Pharmaceutical Inc., is a second-generation PARP inhibitor. Previous research has shown that BMN673 exhibits selective cytotoxicity against tumor cells and induces DNA repair biomarkers at notably lower concentrations compared to first-generation PARP1/2 inhibitors such as Olaparib, Rucaparib and Veliparib (PARP1 half-maximal inhibitory concentration, 0.57 nmol/l) (100). In a 2017 phase I clinical trial (clinical trial no. NCT01286987), Talazoparib demonstrated notable antitumor activity and safety as a monotherapy, with 7 out of 14 patients with BRCA-mutated breast cancer showing confirmed responses, resulting in a response rate of 50%. Grade 3-4 adverse events included anemia (17 out of 71 patients; 24%) and thrombocytopenia (13 out of 71 patients; 18%) (12).

Talazoparib has been widely applied in clinical treatments for breast cancer, primarily as a monotherapy to assess efficacy (Table II). For instance, a phase II single-arm, open-label study (clinical trial no. NCT03499353) evaluated the efficacy of Talazoparib as a neoadjuvant therapy in patients with TNBC, and achieved a pathological complete response rate of 45.8% (95% CI, 29.4-63.2%) in the evaluable population, demonstrating considerable activity (101).

Table II. Clinical studies on Talazoparib treatment for breast cancer with germline BRCA mutations.

First author, year	Trial phase	Treatment regimen	Endpoint events	Results	(Refs.)
Litton *et al*, 2018	Phase III	Talazoparib vs. standard therapy	PFS; ORR	PFS, 8.6 months (Talazoparib) vs. 5.6 months (standard therapy), ORR, 62.6 vs. 27.2% (odds ratio, 5.0)	(134)
Ettl *et al*, 2018	Phase III	Talazoparib vs. PCT	GHS/QoL; TTD	GHS/QoL improvement, Talazoparib (HR, 0.38); Median TTD, 24.3 vs. 6.3 months (Talazoparib vs.) PCT	(135)
Litton *et al*, 2020	Phase II[a]	Talazoparib	RCB	RCB 0/I, 63%; RCB 0, 53%	(136)
Litton *et al*, 2020	Phase III	Talazoparib vs. chemotherapy	OS	HR for OS, 0.848 (95% CI, 0.670-1.073); median OS, 19.3 months (Talazoparib) vs. 19.5 months (chemotherapy)	(137)
Litton *et al*, 2023	Phase II[a]	Talazoparib	pCR; RCB	pCR, 45.8%; RCB 0/I, 45.8-50.8%	(101)
Bardia *et al*, 2024	Phase Ib[a]	Talazoparib + Sacituzumab govitecan	PFS; DLT	Sequential SG/TZP: PFS, 7.6 months; Concurrent SG/TZP: PFS, 2.3 months with severe DLTs	(13)

[a]Trials including TNBC in the post-trial period. PFS, progression-free survival; ORR, objective response rate; PCT, treatment of physician's choice; TTD, time to deterioration; RCB, residual cancer burden; pCR, pathological complete response; DLT, dose-limiting toxicity; OS, overall survival; GHS/QoL, global health status/quality of life.

It is important to note that, when combining Talazoparib with other potent anticancer drugs, careful attention must be paid to dosing and administration sequence. Previous research has indicated a potential synergistic effect between antibody-drug conjugates (ADCs) and PARP inhibitors. ADCs can effectively increase DNA damage in tumor cells, and subsequent use of PARP inhibitors can further block DNA repair, leading to cancer cell apoptosis (102). However, simultaneous administration in clinical settings has shown significant toxicity, particularly myelosuppression. Sequential administration, however, creates a time window that allows PARP inhibitors to act more effectively within tumor cells without increasing toxicity (13).

Other PARP inhibitors. Veliparib, a PARP inhibitor, has been evaluated in combination with other drugs in clinical trials for various cancer types. In the treatment of TNBC, its combination with cisplatin or carboplatin has shown good tolerability and response rates (14). In addition to its use in classic gynecological tumors such as breast and ovarian cancer, Veliparib has also been investigated in the treatment of non-small cell lung cancer, pancreatic cancer, prostate cancer and acute myeloid leukemia (103-106). Although Veliparib has not yet received broad clinical approval, its extensive research and application in various cancer types provides promising insights for future therapeutic strategies.

Recently developed in China, Fuzuloparib and Pamiparib are novel PARP inhibitors. In a phase I clinical trial (clinical trial no. NCT03945604) of Fuzuloparib for patients with recurrent or metastatic TNBC, 29 patients received camrelizumab (200 mg, every 2 weeks), Apatinib (375 or 500 mg, daily) and Fuzuloparib (starting dose of 100 mg, twice daily). In total, 2 patients (6.9%; 95% CI, 0.9-22.8) had an objective response, while the disease control rate was 62.1% (95% CI, 42.3-79.3). The median PFS was 5.2 months (95% CI, 3.6-7.3), while the 12-month OS rate was 64.2% (95% CI, 19.0-88.8), indicating controllable safety and preliminary antitumor activity (107). Similarly, another phase I trial (clinical trial no. NCT03075462) confirmed the acceptable safety of Fuzuloparib combined with Apatinib in patients with advanced ovarian cancer or TNBC (108).

In addition, Pamiparib in combination with the immune checkpoint inhibitor Tislelizumab demonstrated efficacy in

a dose-escalation study for treating various advanced solid tumors (109). In monotherapy for patients with non-mucinous high-grade ovarian cancer and TNBC in China, the most common adverse effects were fatigue, nausea and hemoglobin reduction. Among all patients with TNBC who were evaluable under the Response Evaluation Criteria in Solid Tumors criteria (n=5), disease progression was reported, indicating the need for further evidence to support its efficacy in breast cancer (76).

5. Overcoming resistance and research directions

Although PARP inhibitors have shown significant efficacy in cancer cases with BRCA mutations, resistance remains one of the most challenging clinical issues. Resistance can arise through various mechanisms, and previous studies have uncovered some key pathways. For example, certain resistant cancer cells can overcome the effects of PARP inhibitors by reversing BRCA gene mutations or restoring BRCA1/2 function (11,110). Additionally, PARP inhibitors act not only by inhibiting PARP activity but also by inducing PARP trapping, which increases DNA damage. Resistant cancer cells can reduce PARP trapping by altering the expression or function of PARP-related proteins, thereby diminishing the efficacy of PARP inhibitors (111). Moreover, cancer cells may repair DNA through alternative pathways, using different enzymes or repair mechanisms. For instance, tankyrase, which has a catalytic activity similar to PARP, regulates other proteins through ADP-ribosylation. This suggests that tankyrase may serve as an alternative mechanism during PARP inhibitor therapy, and several studies have summarized its importance in cancer treatment (112-114). It is also noteworthy that upregulation of the *ABCB1* gene, which encodes the P-glycoprotein efflux pump, may contribute to drug efflux and resistance to PARP inhibitors (115).

As a result, numerous studies have evaluated the efficacy of PARP inhibitors in tumors without BRCA mutations, expanding their potential application beyond BRCA-mutated tumors. HRD testing tools have been developed to assess genomic instability (for example, copy number alterations, gene rearrangements and microsatellite instability) in tumors. This enables the identification of HRD-positive patients who are more likely to benefit from PARP therapy (116). Gasdermin-C (GSDMC) is a member of the gasdermin family protein, which contains a gasdermin domain, and GSDMC/caspase-8 are key molecules in pyroptosis. Wang *et al* (117) found that treatment with PARP inhibitors triggered GSDMC/caspase-8-mediated pyroptosis in cancer cells. Additionally, GSDMC-mediated pyroptosis increased the population of memory $CD8^+$ T cells in the lymph nodes, spleen and tumors, thereby promoting the infiltration of cytotoxic $CD8^+$ T cells into the tumor microenvironment. Notably, this process was independent of BRCA mutations.

Furthermore, the efficacy of PARP inhibitors in non-BRCA-mutated tumors has being explored. For instance, a phase II trial evaluating Olaparib in patients with advanced TNBC or high-grade serous and/or undifferentiated ovarian cancer without BRCA1 or BRCA2 mutations found that, among 63 patients with ovarian cancer, the objective response rate was 41% in the mutation group (n=17) and 24% in the non-mutation group (n=46). No responses were reported in any of the 26 patients with breast cancer (15). Another similar study also explored the use of PARP inhibitors in patients with BRCA wild-type TNBC (118).

Replication fork stability can endow BRCA-deficient cells with resistance. A defect in PTIP, a paired box transcription activation domain interaction protein, does not restore homologous recombination but inhibits the recruitment of the MRE11 nuclease to stalled replication forks. This, in turn, protects nascent DNA strands from extensive degradation (119). Tan and Xu (120) found that ubiquitin-fold modifier modification (UFMylation) played a critical role in replication fork dynamics in BRCA1-deficient cells, where PTIP UFMylation promoted the resection of nascent DNA, conferring resistance to BRCA1-deficient cells. Furthermore, Tian *et al* (121) demonstrated that, during replication stress, *UFL1*, a UFM1-specific E3 ligase, localized to stalled forks and catalyzed PTIP UFMylation, thus providing a mechanism for UFMylation in PTIP regulation. These studies offer potential avenues for overcoming resistance to PARP inhibitors in patients with BRCA-deficient TNBC.

In conclusion, identifying more precise molecular biomarkers, optimizing drug sequencing and dosing in resistant patients, and improving the use of PARP-related cell death mechanisms (such as energy depletion) are potential strategies for the future treatment of breast cancer, particularly TNBC.

6. Conclusions

The present review focuses on the role of PARP inhibitors in the treatment of TNBC, particularly highlighting their efficacy in BRCA mutation-associated tumors. By analyzing key mechanisms of DNA damage repair, it was observed that, in multiple clinical trials, PARP inhibitors have demonstrated not only strong efficacy in BRCA-mutated TNBC but also potential in non-BRCA-mutated tumors. Despite the notable efficacy of PARP inhibitors in patients with BRCA-mutated TNBC, the emergence of resistance remains a major challenge in clinical applications, and identifying additional biomarkers to combat this resistance requires further exploration.

Future research should focus on overcoming resistance to PARP inhibitors through combination therapy strategies while refining patient selection by integrating genomic data and biomarker analysis. This should help ensure optimal efficacy with the most appropriate dosing for the suitable patients. Additionally, further investigation of combination treatment regimens and sequencing should provide improved survival benefits to patients.

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Authors' contributions

YH and LW contributed to the study conception and design. YH proposed the concept of the study and drafted for the article, and performed literature search and data analysis. LW determined the writing framework of the article, put forward valuable revision suggestions for the first draft and also provided assistance in the detailed revisions of the article. Both authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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