The Synergistic Effect of PARP Inhibitors and Immune Checkpoint Inhibitors

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ABSTRACT: Poly (ADP-ribose) polymerase (PARP) inhibitors have demonstrated great promise for treating cancers with homologous recombination (HR) defects, such as germline BRCA1/2 mutation. Further studies suggest that PARP inhibitors (PARPi) can also exhibit efficacy in HR-competent cancers, by amplifying the DNA damage and inducing immunogenic cell death, and PARPi lead to increasing tumor neoantigen, upregulation of interferons and PD-L1, and modulation of the tumor microenvironment, which may facilitate a more profound antitumor immune response. Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 or CTLA-4 have achieved impressive success in the treatment of different malignancies. However, only a subset of populations derive clinical benefit, and the biomarkers and resistance mechanisms are not fully understood. Therefore, given that PARPi could potentiate the therapeutic effect of ICIs, PARPi combined with ICIs are becoming an alternative for patients who cannot benefit from ICI monotherapy. In this review, we focus on the mechanisms and immune role of PARPi and discuss the rationale and clinical studies of this combined regimen.

KEYWORDS: PARP inhibitors, immune checkpoint inhibitors, BRCA, DNA damage response, cancer

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Introduction

Poly (ADP-ribose) polymerase enzymes (PARPs) catalyze the poly ADP-ribosylation (PARylation), with nicotinamide adenine dinucleotide (NAD) serving as a substrate.[1] Of all 17 members in the PARP family, only PARP1, PARP2, and PARP3 are thought to be involved in DNA repair, and PARP1 is the major one. PARP1 participates in both DNA base excision repair (BER)[2] and DNA double-strand break (DSB) repair.[3] PARP inhibitors (PARPi) have been demonstrated to be an effective therapeutic strategy against cancers with defects in DSB repair. In a decade to 2019, various PARPi have been involved in more than 70 clinical trials[4] and approved by the US Food and Drug Administration (FDA), including olaparib,[5] niraparib,[6] rucaparib,[7] and talazoparib.[8] With further development, PARPi are not only used in breast cancer susceptibility gene (BRCA)-mutated patients with prior lines of chemotherapy; in 2018, olaparib was approved for first-line maintenance treatment in BRCA1/2-mutated, newly diagnosed advanced ovarian cancer after a complete response (CR)/partial response (PR) to platinum-based chemotherapy.[9] Cancer types involved in PARPi-associated clinical studies included ovarian cancer, fallopian tube cancer, primary peritoneal cancer, high-grade endometrioid cancer, breast cancer, pancreatic cancer, prostate cancer, and lung cancer.[4]

The commonly recognized biomarker for PARPi is BRCA1/2, and most PARPi are approved by the FDA to be used for patients with BRCA mutation. In addition, some tumors without germline BRCA1/2 mutation exhibit "BRCAness"—a phenotype presenting similar molecular and biological characteristics to BRCA-deficient cancers.[10] For example, patients with high-grade serous ovarian cancer and triple-negative breast cancer (TNBC) have a higher incidence of "BRCAness," and those patients with wild-type BRCA1/2 could still benefit a lot from single-agent treatment,[11] but the overall efficacy in patients with wild-type BRCA was weaker.[12] And patients with germline BRCA1/2 mutation are still challenged by drug resistance and dose-limiting toxicities.[13-15] Therefore, combination therapies based on synergistic effect are worth to be explored. Initial studies about PARPi-related combined therapeutics mostly focused on chemotherapy, radiotherapy, and a few target regimens. With further investigation, PARPi in combination with immunotherapeutics developed from preclinical models to clinical trials.

With the development of immune checkpoint inhibitors (ICIs) and next-generation sequencing, a growing number of medical guidelines for cancer treatment recommend carrying out molecular detection, and biomarkers such as PD-L1 expression, tumor mutation burden (TMB), microsatellite instability (MSI) and Epstein-Barr virus[16-21] help us to select potential beneficiaries. However, patients without driven mutation and positive signatures for ICIs may turn to traditional chemotherapeutics. Although biomarkers for response to

immunotherapy have not been fully studied and are not reliably predictive cancer types, the expression of PD-L1, TMB, and MSI status should be synthetically considered when making clinical strategies. If a patient's disease is unlikely to benefit from immunotherapy as a monotherapy, combined therapy may become a choice. Emerging evidence has shown PARP inhibition can enhance the response of ICIs.[22,23] Poly (ADP-ribose) polymerase inhibitors lead to the accumulation of DNA damage and trigger the interferon pathways.[23,24] Thus, PARPi have the potential to improve response to ICIs by enhancing T-cell–mediated immune response.[24,25]

DNA Damage Response and PARPi

DNA damage repair

DNA is usually damaged when constantly exposed to endogenous or exogenous assaults, and the detection and repair of DNA damage is called "DNA damage response" (DDR).[26] DNA damage includes DNA single-strand breaks(SSBs) and DSBs. While SSBs are managed mainly by 3 pathways[27,28]—(1) mismatch repair (MMR) mainly repairs mismatched DNA, escaping proofreading during replication; (2) nucleotide excision repair (NER) removes longer stretches of incorrect nucleotides, often resulting from UV/platinum; and (3) BER repairs DNA base lesions—DSBs are mainly repaired by homologous recombination (HR) and nonhomologous end joining (NHEJ). Homologous recombination is an effective repair approach to accurately and efficiently repair the DSB using the sister chromatid as a template,[29] and NHEJ is an error-prone repair pathway that induces DNA rearrangements.[30]

The mechanisms of PARPi

The PARP family consists of 17 members,[31] of which PARP1 is the most abundantly and extensively studied. PARP1 contains 4 domains with particular function: the DNA-binding domain (DBD) at N-terminus, the bipartite nuclear localization signal (NLS) domain, the auto-modification domain (AMD), and the catalytic domain (CD) at C-terminus.[31,32] In response to DNA damage, PARP1 binds to DNA break sites through zinc finger I and II of the DBD, and the CD of PARP1 is activated by reliving the inhibition of α-helical subdomain (HD)[32]; then, PARP1 recruits DDR-related proteins, such as XRCC1, XPA, DNA polymerase β, and DNA ligase III.[33-35] The activated PARP1 cooperates with other PARP enzymes to catalyze NAD^+ to generate the polymer of ADP-ribose covalently on target proteins or itself in a linear or multi-branched way, known as PARylation.[35,36] PARP1 subsequently induces DDR, in which at least 450 proteins are involved,[37] such as ATR/CHEK1/RAD51. While PARP1 contributes to 90% of total PARP activity,[38] PARP2 contributes only 5% to 10%.[39] Besides, PARP1, PARP2, and PARP3 also play an important role in DNA repair,[40,41] whereas PARP4-PARP17 are not thought to be involved in DNA repair.

PARP1 is mainly involved in BER, but it is also critical for HR and NHEJ mechanisms,[3] and BRCA1/2 are involved in the HR pathway.[42] Therapeutic inhibitors of PARP1/2, such as olaparib, bind to the catalytic domain and inhibit the catalytic activity, which leads to the failure of SSB repair. If the replication fork collapses, a DSB might be created, and in tumor cells with HR deficiency such as BRCA1/2 mutation, NHEJ is used for DSB repair, which may determine eventual tumor cell death by increasing genetic instability without deleterious effects on normal cells.[43,44] This is called the "synthetic lethality" effect,[45] and subsequent immune response to dying tumor cells could potentiate antitumor efficacy of ICIs (Figure 1).

In addition to catalytic inhibition, "PARP trapping" is another important mechanism for PARPi. It has been reported that PARPi are more cytotoxic than PARP depletion because of their ability to trap PARP enzymes on damaged DNA by way of a poisonous allosteric effect, and the authors detected PARP-DNA complexes, which interfered with the DNA replication.[46] The capacity to trap PARP varies markedly among different PARPi, with talazoparib ≫ niraparib > olaparib or rucaparib ≫ veliparib, and this capacity may be associated with the extent to which PARPi interacts with the D-loop residues[47-49]

The immunological role of PARPs

Beyond maintaining genomic stability, PARPs play a significant role in both innate and adaptive immune responses. Multiple studies have demonstrated that PARPs are associated with cancer immunity. T cell is the principal part of antitumor immunity, and PARP inhibition significantly influences T cells in the tumor microenvironment (TME). In small cell lung cancer (SCLC),[50] PARPi were reported to induce the activation and function of cytotoxic T lymphocytes via activating the STING/TBK1/IRF3 innate immune pathway and increasing levels of chemokines such as C-X-C motif chemokine ligand 10 (CXCL10) and C-C motif chemokine ligand 5 (CCL5). In ovarian cancer,[51] it was revealed that PARPi could induce the upregulation of PD-L1 expression by promoting phosphorylation of CHK1, and antagonistic PD-L1 could reverse the inhibitory effect of PARPi on $CD8^+$ T cells and had synergistic antitumor effect with PARPi. Moreover, it has been reported that natural killer (NK) cells and macrophages are indispensable for responsiveness to anti–PD-1 immunotherapy.[52] Talazoparib (BMN673) is a PARP1/2 inhibitor, and Huang et al[53] reported that BMN673 significantly increased the number of NK cells and their production of interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) in a murine model of ovarian cancer. Other studies also showed that inhibition of PARP-1/2 maintained NK cell viability and increased tumor cell sensitivity to NK killing in various cancers, including breast, prostate, NSLC, and chronic myeloid leukemia.[54,55] Besides, myeloid-derived suppressor cells (MDSCs) of patients who received PARPi/ICI combination treatment were also demonstrated to influence the efficacy.[56]

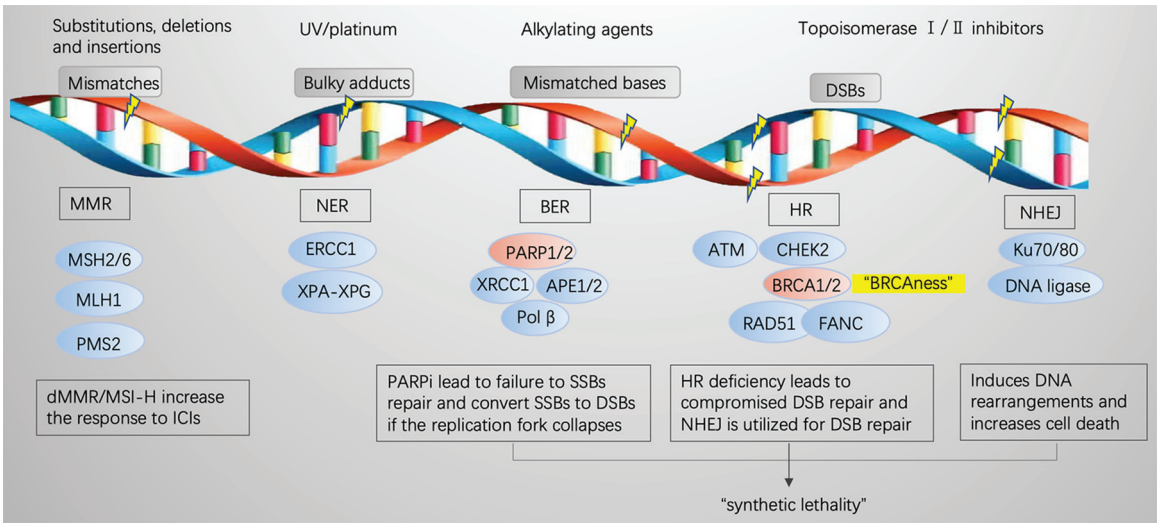

Figure 1. DDR-associated pathways and "synthetic lethality" induced by PARPi.
ATM indicates ataxia telangiectasia-mutated gene; BER, base excision repair; BRCA, breast cancer susceptibility gene; CHEK2, checkpoint kinase 2; DDR, DNA damage response; DSB, double-strand break; HR, homologous recombination; ICI, immune checkpoint inhibitor; MMR, mismatch repair; MSI, microsatellite instability; NER, nucleotide excision repair; NHEJ, nonhomologous end joining; PARPi, poly (ADP-ribose) polymerase inhibitors; SSB, single-strand break.

The effect of PARPi on immune cells was likely due to the immune system's response to dying cancer cells, and this immune response was partly mediated by a series of transcriptional factors and chemokines. The release of IFN-γ by STING/TBK1/IRF3 signaling is a kind of typical immune response induced by PARPi.[51] Nuclear Factor-κB (NF-κB) is a known essential coactivator for PARP-1, and previous literature has shown that PARP-1 could interact with the subunits of NF-κB, format the transcription complex, and ultimately influence NF-κB–dependent gene expression, which was independent of the enzymatic activity of PARP1.[57,58] It was also reported that PARPs regulated a series of cytokines, such as Th1 cytokines (interleukin [IL]-2, IFN-γ), Th2 cytokines (IL-4, IL-5, IL-10), transforming growth factor-β (TGF-β) and the chemokines CXCL10, CCL5, CCL4, and CCL9.[59-62]

The PARP is also involved in a variety of biological processes, including chromatin remodeling, and the regulation of transcription factors and TME.[63] It has been reported that PARPs participated in tumor cell proliferation, epithelial-mesenchymal transition (EMT) (Figure 2E), and apoptosis via coactivating NF-κB, mitogen-activated protein kinases (MAPKs), and TGF-β.[64-66] A previous study has shown that overexpressed PARP-1 enhanced tumor angiogenesis by upregulating the vascular endothelial growth factor (VEGF)[67] (Figure 2F); therefore, PARPi can also inhibit tumor angiogenesis.

Rationale for Combination of PARPi and ICIs

To date, 4 PARPi have been approved by the FDA, mainly for the treatment of several solid cancers with BRCA1/2 mutation. However, the rate of BRCA1/2 mutation is relatively low, which means the population benefiting from PARPi is small. With further study, it was found that sporadic tumors exhibited "BRCAness," a phenotype similar to BRCA1/2 mutation cancers, which resulted in DDR deficiency because of DDR-associated gene mutation or methylation.[68] These mutated genes and downregulated proteins, including ATM, ATR, CHK1, CHK2, BARD1, BRIP1, DSS1, NBS1, PALB2, RAD51, CDK12, members of FANC family, EMSY, PALB2, XRCC2, XRCC3, TP53, or PTEN, may become predictive biomarkers for PARPi treatment,[10,68-70] which lays the foundation for clinical application of PARPi in non-BRCA mutation cancers. Still, combined therapy is needed to improve efficacy. The rationale for PARPi in combination with ICIs mainly involves 4 aspects: tumor neoantigen production, enhanced antigen presentation, increasing tumor-infiltrating lymphocytes (TILs), upregulation of PD-L1, and reprogram of other molecules and immune cells involved in TME (Figure 2).

Neoantigen formation, TMB, and increased immunogenicity

The accumulated DNA damage by PARP inhibition fails to be repaired and results in tumor cell death, and dead tumor cells will release tumor neoantigen and increase immunogenicity, which lays the foundation for combination of PARPi with ICIs. DNA damage response–associated frameshift mutations contribute to neoantigen repertoire, and mismatch repair–deficient tumors are found to be sensitive to ICIs, regardless of the cancer types, which attributes to its large proportion of mutant neoantigens.[21] Tumor mutation burden is regarded as a surrogate of neoantigen burden, which heralds the ICI therapeutic response, and in many malignancies, including non–small cell lung carcinoma (NSCLC) and melanoma, TMB was reported to be correlated with clinical response and survival.[71,72] DNA damage response deficiency, including BRCA1/2, was found to be associated with higher tumor mutational load and predicted neoantigen in cancers such as ovarian cancer and NSCLC.[72,73]

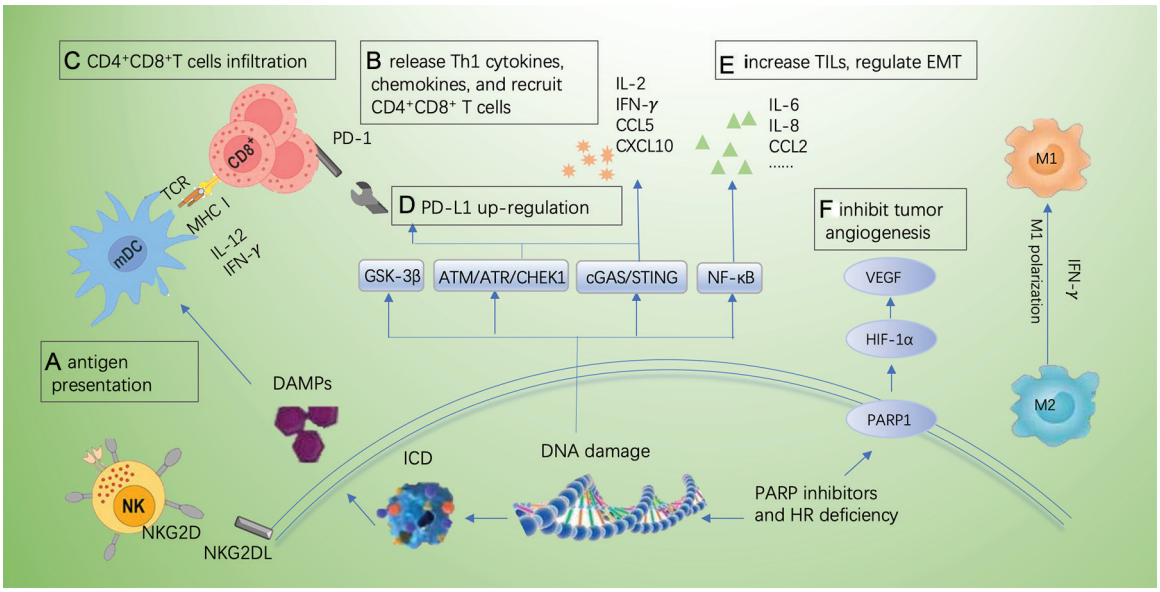

Figure 2. The mechanisms involved in DDR and checkpoint immunotherapies. (A) PARPi promote antigen presentation by ICD owing to the failure of DNA repair; (B) PARPi upregulate the release of Th1 cytokines and recruit $CD4^+CD8^+$ T cells via CCL5 and CXCL10; (C) PARPi promote T-cell infiltration; (D) PARPi increase PD-L1 expression by GSK-3β, ATM-ATR-CHK1, and cGAS-STING pathway; (E) PARPi regulate EMT; and (F) PARPi inhibit tumor angiogenesis by modulating PARP1/HIF1-α/VEGF signals.

ATM indicates ataxia telangiectasia-mutated gene; ATR, ataxia telangiectasia and Rad3 related; CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; cGAS, cyclic GMP-AMP synthase; CHEK1, checkpoint kinase 1; CXCL10, C-X-C motif chemokine ligand 10; DAMP, damage-associated molecular pattern; DDR, DNA damage response; EMT, epithelial-mesenchymal transition; GSK-3β, glycogen synthase kinase-3β; HIF-1α, hypoxia-inducible factor-1 α; HR, homologous recombination; ICD, immunogenic cell death; IL, interleukin; INF-g, interferon-γ; MHC I, major histocompatibility complex class I; NF-κB, nuclear factor-kB; NKG2D(L), natural killer cells group 2D (ligand); PARPi, poly (ADP-ribose) polymerase inhibitors; SSB, single-strand breaks; PD-L1, programmed-death ligand 1; STING, stimulator of interferon genes; TILs, tumor-infiltrating lymphocytes; VEGF, vascular endothelial growth factor; TCR, T cell receptor; mDC, myeloid dendritic cells.

Therefore, PARPi may facilitate a more profound antitumor immune response and synergize with ICIs by inducing DNA damage and neoantigen, which can increase immunogenicity.

Enhanced antigen presentation

Besides, neoantigen presentation by major histocompatibility complex class I (MHC I) is requisite for cytotoxic T-cell activation, which is accomplished by antigen-presenting cells (APCs), such as dendritic cells (DCs), monocytes/macrophages, and B lymphocytes. It was reported that DDR induced the expression of MHC I and antigen presenting,[74] and PARP inhibition could upregulate MHC I.[75] The PARPi lead to DDR and immunogenic cell death (ICD), thus inducing damage-associated molecular patterns (DAMPs) to promote recruiting APCs.[76] Immune checkpoint inhibitors function to inhibit tumor growth by restoring and enhancing T-cell activation, and T-cell-DC crosstalk involving the cytokines IFN-γ and IL-12 is essential for improved ICI response.[77,78] The PARPi have the ability to increase IFN-γ release via stimulator of interferon genes (STING) pathway,[22,23] thus enhancing T-cell-DC crosstalk to promote antigen presentation.

Increasing TILs

T lymphocytes can be stimulated and recruited to tumors by tumor-specific neoantigens, and recent preclinical studies indicate that different PARPi can significantly increase the infiltration of $CD4^+$ T cells and $CD8^+$ T cells by activating the STING pathway in BRCA-deficient models.[22,24,53] Increasing evidence suggests that the distribution, density, and phenotype of TILs influence the efficacy of ICI.[79] Strickland et al[73] demonstrated that BRCA1/2-mutated high-grade serous ovarian cancers exhibited significantly increased $CD3^+$ and $CD8^+$ TILs, compared with HR-proficient tumors, and the number of TILs was independently associated with patients' survival outcome. Therefore, combined therapy of ICI and PARPi may extend durable responses for HR-deficient tumors.

Upregulation of PD-L1 and influence on other factors in TME

Although PD-L1 remains an imperfect biomarker owing to drug types, cancer types, cut-off value, and antibody for PD-L1 assay, many studies suggest PD-L1 is a biomarker for ICI response or overall survival (OS),[17,80,81] and PD-L1 detection using immunohistochemistry has been widely used in clinical practice. Increasing evidence showed PARPi could increase the expression of PD-L1. The PARPi increase the DNA damage, and the stimulation of cytoplasmic DNA can result in the activation of cyclic GMP-AMP synthase (cGAS), and then cGAS catalyzes the generation of cyclic dinucleotide and promotes the activation of the STING pathway.[82] Active STING upregulates the generation of type I IFNs mainly by initiating the downstream TBK1-IRF3-type I IFN pathway and NF-κB pathway.[83] Type I IFN induces the activation of an antitumor

immune response and increased PD-L1 expression. Therefore, PARPi could determine an increase in DNA damage and upregulate the PD-L1 expression by cGAS-STING pathway. In addition, PARPi-induced DSB could upregulate PD-L1 expression by ATM-ATR-CHK1 pathway.[84] Preclinical studies also showed that PARP inhibition could upregulate PD-L1 by inactivating GSK-3β, and that PD-L1 upregulation may be a resistance mechanism of PARPi, and subsequent blockade of PD-L1 resensitized PARPi-treated cells to T-cell killing.[85] Thus, PARPi-induced upregulation of PD-L1 expression may provide a theorical explanation for PARPi to combine with anti–PD-1/PD-L1 blockades.

The PARP inhibition extends durable ICI response by influencing the integral TME, including the regulation of NK cells, a series of cytokines and chemokines, angiogenesis, and oxidative stress. Olaparib was proved to improve the killing activity of NK cells,[55] and NK-DC axis defined ICI response.[52] The knockout of PARPi and PARP-1 was also found to impair angiogenesis and abrogate migration of tumor cells by modulating PARP1/HIF1-α/VEGF signals.[86] Given the effect of PARPi on the proliferation, apoptosis, and migration of TILs, it is promising to combine it with ICIs.

Studies about PARPi combined with checkpoint blockades

Preclinical studies suggest that PARPi, including olaparib, niraparib, rucaparib, and talazoparib, synergize with PD-1/PD-L1 blockade regardless of the BRCA status,[22,23,85,87] and it has been reported that veliparib, a PARP inhibitor, can enhance the therapeutic efficacy of CTLA-4 blockade and contribute to tumor clearance and long-term survival in BRCA$^{-/-}$ mouse models.[88] Based on the above promising data from preclinical studies, a series of clinical trials are currently underway (Table 1).

The first reported clinical study about the combined therapy of PARPi and checkpoint blockade is TOPACIO trial (NCT02657889). In this study, researchers analyzed the efficacy and safety of niraparib in combination with pembrolizumab in the treatment of recurrent ovarian carcinoma and TNBC. Totally, 62 patients were enrolled in ovarian cancer cohort and 60 patients were evaluable, and the integrated objective response rate (ORR) was 18% and the disease control rate (DCR) was 65%. Further analysis showed the ORRs of tumor PD-L1 expression, BRCA or HR status, and other biomarker-based subgroups were similar.[89] In the TNBC cohort, 47 of 55 patients were evaluable, and the ORR and DCR were 21% and 49%, respectively. Different from the ovarian cancer cohort, patients with BRCA mutation significantly benefited more compared with those without, with a better ORR of 47% versus 11%, DCR of 80% versus 33%, and median progression-free survival (mPFS) of 8.3 months versus 2.1 months.[90] Different data from several clinical studies about ovarian cancers suggested PARPi/PD-1 or PD-L1 combinations[89,94] contributed to similar ORR with PARPi treatment in the same settings.[95]

Besides, olaparib/durvalumab combination also showed excellent efficacy in mCRPC,[96] 9 of 17 patients (53%) demonstrated a prostate-specific antigen (PSA) response (⩾50% declination), and patients with DDR defects acquired better mPFS of 16.1 months, whereas mPFS of those without was 4.8 months. These data compare favorably with those of monotherapy, despite results from different trials; pembrolizumab monotherapy showed a 6% PSA response rate,[97] whereas olaparib led to a 22% PSA response rate, an ORR of 33%, and a mPFS of 9.8 months in DDR-deficient patients and 2.1 months in DDR-proficient patients.[98] In platinum-resistant/refractory SCLC, the olaparib/durvalumab combination displayed a clinical benefit in 4 (21.1%) of 19 patients, including 2 patients with PR or CR and 2 patients with prolonged stable disease for more than 8 months, and the 2 with CRs showed an inflamed phenotype in pretreated tumors.[56] The details are shown in Table 2.

About safety, the most common adverse effects (AEs) included hematologic-related toxicities, such as anemia, lymphopenia, leukopenia, thrombocytopenia, fatigue, nausea, and constipation, and immune-related adverse effects (irAEs).[56,89,90,96] According to available safety data from clinical trials about PARPi (niraparib) combined with anti–PD-1/PD-L1 (pembrolizumab), the incidences of irAEs of any grade and severe grade were 15% to 19% and 4% to 6%, respectively,[89,90] and these data were similar to those observed with PD-1/PD-L1 monotherapy, which showed that in 18.5% and 5.1% of patients any grade and severe-grade irAEs occurred.[105] And for olaparib/durvalumab combination, the incidences of all grade and grade 3+ irAEs were 23.5% to 25.0% and 11.8%, respectively,[56,96] and the incidences were lower than those reported in durvalumab monotherapy, which were 53.8% and 21.5% of any grade and grade 3+ irAEs.[106] Although many clinical trials reported the maximum tolerated dose and demonstrated that the toxicity of these combinations was acceptable, the combination of BGB-A317/BGB-290 was reported to show an increased rate of autoimmune hepatitis and elevated aspartate transaminase/alanine transaminase[91]; this hepatic toxicity of PARPi/ICI combinations may vary according to the agents used in different combination settings.

Conclusions and Perspectives

The PARPi have exhibited remarkable antitumor efficacy in BRCA1/2 mutant solid tumors, mainly through catalytic inhibition-induced synthetic lethality and PARP trapping.[45,46] In tumors, emerging evidence has suggested that PARPi modify the immune context. Given the immune role of PARPi, especially the recruitment and priming of CD4$^+$/CD8$^+$ T cells through neoantigen production and releasing cytokines and chemokines, such as CCL5 and CXCL10,[23,61] the PARPi/ICI combination may have potential to extend benefit populations and broaden durable responses of both PARPi and immune checkpoint blockades. Preclinical studies show that PARPi/ICI combinations synergize via STING-associated signal

Table 1. Clinical studies about PARPi/ICIs.

CLINICALTRIALS.GOV IDENTIFIER	COMBINATION	PHASE	CANCER TYPE	REFERENCES
NCT02657889	Niraparib + pembrolizumab	I/II	Basket study in TNBC and ovarian cancer	Konstantinopoulos et al,[89] Vinayak et al[90]
NCT02849496	Veliparib + atezolizumab	II	HR-deficient and HER-2–negative TNBC	N/A
NCT03101280	Rucaparib + atezolizumab	I	BRCA+ ovarian cancer and TNBC	N/A
NCT03598270	Niraparib + atezolizumab	III	Maintenance treatment of recurrent ovarian cancer	N/A
NCT03522246	Rucaparib + nivolumab	III	Front-line ovarian cancer	N/A
NCT03642132	Talazoparib + avelumab	III	Front-line ovarian cancer	N/A
NCT03602859	Niraparib + TSR-042	III	Front-line ovarian cancer	N/A
NCT03307785	Niraparib + TSR-042	I/II	Solid tumors	N/A
NCT03565991	Talazoparib + avelumab	II	BRCA/ATM-mutant solid tumors	N/A
NCT03330405	Talazoparib + avelumab	II	Basket study in ovarian cancer, HER2-breast cancer, mCRPC, bladder cancer, and NSCLC	N/A
NCT02660034	Pamiparib + tislelizumab	I	Basket study in TNBC, ovarian cancer, mCRPC, SCLC, bladder cancer, HER2-gastric cancer, pancreatic cancer, and other solid tumors	Friedlander et al[91]
NCT02734004	Olaparib + durvalumab	II	Basket study in germline BRCA-mutant ovarian, HER2-breast cancer, gastric cancer, and relapsed SCLC	Krebs et al[92]
NCT02484404	Olaparib + durvalumab	II	Basket study in ovarian cancer, TNBC, NSCLC, SCLC, mCRPC, and microsatellite stable colorectal cancer	Thomas et al,[56] Karzai et al[93]
NCT03572478	Rucaparib + nivolumab	I/IIa	Prostate/endometrial cancers	N/A
NCT03338790	Rucaparib + nivolumab	II	Umbrella study in mCRPC	N/A
NCT02861573	Olaparib + pembrolizumab	I	Umbrella study in mCRPC	N/A
NCT02546661	Olaparib + durvalumab	Ib	Umbrella study in HR-deficient muscle invasive bladder cancer	N/A
NCT03459846	Olaparib + durvalumab	II	Cisplatin-ineligible bladder cancer	N/A
NCT03534492	Olaparib + durvalumab	II	Study before surgery of resectable urothelial bladder cancer	N/A
NCT03334617	Olaparib + durvalumab	II	Umbrella study in patients with NSCLC who have progressed on anti–PD-1/PD-L1	N/A
NCT03308942	Niraparib + PD-1 inhibitor	II	NSCLC	N/A

Abbreviations: ATM, ataxia telangiectasia mutated gene; BRCA, breast cancer susceptibility gene; HER-2, human epidermal growth factor receptor-2; HR, homologous recombination; ICI, immune checkpoint inhibitor; mCRPC, metastatic castration-resistant prostate cancer; NSCLC, non–small cell lung cancer; PARPi, poly (ADP-ribose) polymerase inhibitors; PD-1, programmed cell death 1; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

pathways,[22,23] which are responsible for releasing INF-γ, recruiting $CD8^+$ T cells, and upregulating the expression of PD-L1.[24,107] And both preclinical studies and clinical trials demonstrate that PARPi in combination with ICIs improve antitumor efficacy compared with single regimen. Still, there are several questions to be explored and answered. How to choose the potential benefit patients? How to choose the different drug combinations? What is the timing to apply this combination?

Table 2. Efficacy comparison of PARPi/ICI combination therapy with single agents.

CANCER	CLINICAL TRIALS	DRUGS	ORR, %	DCR, %	MPFS, MO	MOS, MO	REFERENCES
TNBC	NCT02657889	Niraparib + pembrolizumab	Total: 21 BRCA+: 47 BRCA–: 11 PD-L1+: 32 PD-L1–: 8	Total: 49 BRCA+: 80 BRCA–: 33	Total: 2.3 BRCA+: 8.3 BRCA–: 2.1	NA	Vinayak et al[90]
	NCT01848834	Pembrolizumab	18.5	25.9	1.9	11.2	Nanda et al[99]
	NCT02447003	Pembrolizumab	PD-L1+: 5.3 PD-L1–: 5.7	PD-L1+: 7.6 PD-L1–: 9.5	2.0	9.0	Adams et al[100]
	NCT00749502	Niraparib	BRCA+: 5	NA	NA	NA	Sandhu et al[15]
Ovarian cancer	NCT02657889	Niraparib + pembrolizumab	Total: 18 BRCA+: 18 BRCA–: 19 PD-L1+: 21 PD-L1–: 10	65	3.4	NA	Konstantinopoulos et al[89]
	NCT02674061	Pembrolizumab	9.9	37.4	2.1	17.6	Cohort B[101]
	NCT02054806	Pembrolizumab	11.5	NA	1.9	13.1	Varga et al[102]
SCLC	NCT02484404	Olaparib + durvalumab	10.5	NA	1.8	4.1	Thomas et al[56]
	NCT02734004	Olaparib + durvalumab	11	29	NA	NA	Krebs et al[92]
	NCT02054806 NCT02628067	Pembrolizumab	19.3	37.4	2.0	7.7	Chung et al[103]
	NCT01928394	Nivolumab	10	32	NA	4.4	Antonia et al[104]
mCRPC	NCT02484404	Olaparib + durvalumab	23.5	70.6	16.1	NA	Karzai et al[96]
	NCT02787005	Pembrolizumab	5	10	2.1	9.6	Antonarakis et al[97]

Abbreviations: BRCA, breast cancer susceptibility gene; DCR, disease control rate; ICI, immune checkpoint inhibitor; mCRPC, metastatic castration-resistant prostate cancer; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; PARPi, poly (ADP-ribose) polymerase inhibitors; PD-L1, programmed cell death ligand 1; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

With the development of precision medicine, biomarker-guided treatment is urgently needed. It is significant to choose the patients who are likely to benefit from the combinations. Because DDR defects, especially BRCA mutation, are related to high response to PARP inhibition, detection of DDR defects is important for guiding therapeutic decisions. However, different DDR gene mutations may have distinct effects on immunogenicity. More mutated genes of different DDR pathways may be more likely to result in DDR dysfunction, and heterozygous or homozygous mutation, and germline or somatic mutation have different influences on tumor development and susceptibility to PARP inhibition. It has been demonstrated that loss of heterozygosity (LOH) led to biallelic BRCA inactivation,[108] so we should pay attention to distinguish the gene mutation numbers and forms. Besides, many other mutations were reported to be associated with PARPi and/or PD-1/PD-L1 blockades, such as ATM, ATR, POLE, POLD1, CHECK1/2, WEEK1, JAK2, ATK11, and MMR-related genes.[79] It is also reported that the expression of PD-L1 and TILs are somehow related to the efficacy of PARPi/PD-1 or PD-L1 therapeutics, in which PARPi may play a vital role to modulate the tumor immune microenvironment, especially to regulate the expression of PD-L1 through STING-associated signal pathways. Therefore, dynamic detection and analysis of tumor-related immune cells, PD-L1 expression, gene mutation, and TMB with pretreatment and posttreatment samples is a significant step to seek the appropriate biomarker. Nevertheless, it is a long way to go to find the precise biomarker.

The question of the optimal combination and drug dose is not easy to answer. To date, available clinical data only focus on PD-1/PD-L1 blockade in combination with PARPi therapies. A previous animal study indicated that the combination of veliparib with anti–CTLA-4 blockade enhanced tumor clearance and improved long-term survival in BRCA1-deficient mouse models; however, the combination with anti–PD-1/PD-L1 failed to improve survival in this study.[88] These different results may be due to the higher drug activity of CTLA-4 antibody compared with PD-1/PD-L1 blockades under the immune context of BR5 mouse ovarian cancer model and may because of the activation of new $CD8^+$ T cells, but not reversal of exhausted

T cells, promote the selective efficacy of CTLA-4 antibody. Another preclinical study conducted in BRCA1-mutant, but not BRCA wild-type, syngeneic models showed the combination led to better tumor shrinkage and improved survival compared with single-agent treatment,[87] and this might be explained by the different immune context of different mouse models, such as TILs, and another reason that might lead to these contrast results was that the activity of different PARPi varies because of different capacity of PARP trapping and immune modulation. Current clinical trials about PARPi/ICI combination mainly focus on anti–PD-1/PD-L1 blockades, such as pembrolizumab, nivolumab, and durvalumab; anti–CTLA-4 blockade has not been studied. Therefore, randomized controlled trials (RCT) are necessary to further compare and explain the efficacy of combinations and single agent in different cancer types. Besides, the drug dose of different combinations has not reached a consensus. Taking clinical experience and limited data from literature, it may become a choice to deliver PARPi in a pulsatile way or by decreasing PARPi administration, and enzyme-linked immunosorbent assay can be used as a biomarker assay to measure PARP activity.[109] Overall, it is essential to explore different agents and their dose combinations to find an optimal balance between the efficacy and safety.

It is a question worthy to explore when to apply this combined therapy. The ICI monotherapy only has a small number of benefit population, and it usually takes effect slowly; even some patients may experience "hyper-progressive disease" which means the faster growth of tumor. Given the ability of PARPi to promote inflammation and immune priming, it is a potential choice to combine PARPi for PD-1/PD-L1 blockade-resistant settings, and there has been a related clinical trial focusing on patients with NSCLC who progressed on anti–PD-1/PD-L1 containing therapy. Besides, PD-L1 upregulation is one of the resistance mechanisms for PARPi,[84,85] so it can be addressed through the combination of PARPi and ICI. Under the different immune contexture and mutation milieu, we should consider personalized treatment plans.

Finally, the multiple links between PARPi and tumor immune response suggest PARPi/ICI combinations have potential to improve cancer patient responses, and clinical trials investigating this combination showed preliminary promising results; still, it is a long way to go to further explore the precision biomarker and choose potential benefit patients. Greater clarity of the above key questions will bring new insights to better develop PARPi and immunotherapeutic agents to guide clinical treatment.

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Author Contributions

All authors contributed to study design. ZW, HT and SZ collected the literature. ZW and PC collected the data of clinical trials and drew the figures. ZW and YH conceived the discussion part. ZW drafted the manuscript, and the other authors revised the manuscript. All authors have read and approved the final manuscript.

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