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Application of PARP inhibitors combined with immune checkpoint inhibitors in ovarian cancer

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Abstract
The advent of polyadenosine diphosphate ribose polymerase inhibitors (PARPi) has brought about significant changes in the field of ovarian cancer treatment. However, in 2022, Rucaparib, Olaparib, and Niraparib, had their marketing approval revoked for third-line and subsequent therapies due to an increased potential for adverse events. Consequently, the exploration of new treatment modalities remains imperative. Recently, the integration of PARPi with immune checkpoint inhibitors (ICIs) has emerged as a potential remedy option within the context of ovarian cancer. This article offers a comprehensive examination of the mechanisms and applications of PARPi and ICIs in the treatment of ovarian cancer. It synthesizes the existing evidence supporting their combined use and discusses key considerations that merit attention in ongoing development efforts.

Keywords Ovarian cancer, Immune checkpoint inhibitor, PARP inhibitors, Immunotherapy

Background

Ovarian cancer is the third most common cancer among female reproductive system tumors, with the highest mortality rate among gynecological malignancies [1]. Although tumor cytoreductive surgery and platinum-based chemotherapy have witnessed substantial progress in the management of ovarian cancer [2, 3], the recurrence rate in patients with ovarian cancer continues to be notably high [4]. Up to 70% of patients will relapse within 3 years, and the interval between subsequent relapses will become shorter and shorter until platinum resistance [5]. In order to delay and solve platinum resistance, it has become a breakthrough to improve the survival rate of ovarian cancer by finding effective maintenance therapy drugs [6]. Polyadenosine diphosphate ribose polymerase inhibitors (PARPi) are targeted drugs primarily designed for BRCA1/2 gene mutations or homologous recombination deficiency (HRD) in ovarian cancer. Their main mechanism is to kill tumor cells through the "synthetic lethality" effect [7]. The emergence of PARPi therapy,

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particularly in the context of BRCA1/2 mutations, has established a cornerstone for precision treatment in ovarian cancer [8]. Numerous clinical studies have consistently demonstrated that PARPi substantially extend progression-free survival (PFS) among ovarian cancer patients [9–13]. Currently, there are six PARPis approved by the Food and Drug Administration (FDA) for anticancer therapy. They are Olaparib, Rucaparib, Niraparib, Talazoparib, Fuzuloparib, and Pamiparib [14, 15]. Among them, Olaparib, Rucaparib, and Niraparib have obtained approvals from both the FDA and the European Medicines Agency (EMA) for using in epithelial ovarian cancer [16]. In 2022, the FDA withdrew the accelerated approval for certain indications of three PARPi (Rucaparib, Olaparib, and Niraparib) in the advanced treatment of ovarian cancer due to insufficient evidence of clinical benefit in confirmatory trials.

As the follow-up duration in corresponding clinical trials have been extended, the data reveals an elevated risk of mortality among patients who received second- or third-line or third-line maintenance treatment with PARPi compared to those who underwent chemotherapy [17]. This suggests that PARPi treatment did not result in overall survival (OS) benefits for those ovarian cancer patients who received it as a monotherapy in the third line or subsequent lines of treatment [18, 19]. Consequently, finding ways to enhance the survival outcomes for this specific group of patients have become a focal point of attention and research.

Immune checkpoint inhibitors (ICIs) have significantly altered the treatment paradigm for various malignant tumors, leading to substantial improvements in patient survival outcomes [20–24]. Preclinical data indicates that combining ICIs with PARPi could potentially generate synergistic effects, particularly in ovarian cancer patients who may not be suitable candidates for platinum-based retreatment [25–28]. In this article, we will provide an in-depth review of the development and clinical applications of PARPi and ICIs. We will also delve into their combined use in ovarian cancer, with a particular focus on their roles in second-line and subsequent-line treatments. To explore whether this combination can bring hope to ovarian cancer patients.

Treatment of PARP inhibitors in ovarian cancer

The synthetic lethal mechanism of PARP inhibitors

The human genome changes dynamically. According to statistics, each cell will experience more than 20,000 DNA damage events [29]. Healthy cells can resist the harmful effects of DNA damage through a series of interrelated molecular pathways, namely DNA damage response (DDR). These molecular pathways recognize DNA damage, delay the cell cycle and mediate DNA repair, thus maintaining genome integrity [30]. DNA damage repair includes: (1) DNA mismatch repair, (2) Base excision repair (BER), (3) Nucleotide excision repair, (4) DNA double-strand breaks (DSBs) repair, in which DNA DSBs repair is mediated by non-homologous end joining (NHEJ) and homologous recombination repair (HRR) pathways [31]. In the realm of DNA damage, the most severe forms of damage typically involve single-strand or double-strand breaks [31]. Single-strand DNA damage repair primarily depends on PARP enzymes, of which there are 17 in the human body. Among these enzymes, PARP-1 assumes a predominant role, contributing to approximately 90% of DNA repair processes [32]. DNA double-strand repair encompasses two primary pathways: NHEJ repair and HRR [31]. It is broadly recognized that BRCA proteins play a key role in the HRR pathway, being responsible for responsible for double-strand DNA repair. For normal cell DNA damage - single strand breaks, the cell can rely on PARP proteins for repair through the BER pathway. PARPi refers to small molecule inhibitors capable of triggering cell death by blocking the activity of PARP during DNA damage repair processes [33]. When PARPi acts on normal cells, PARP protein cannot play a role, and the inhibition of BER leads to the shortening of replication forks and the formation of double-strand breaks. At this time, BRCA1/2 can initiate the HRR pathway for cell repair. If the cell has homologous HRD, the double strand break caused by PARPi will not be repaired, and the "synthetic lethality" effect of the two will eventually lead to cell death [34, 35]. Of course, HRR repair is a complex process, and many genes and protein components are involved, including MRE11, RAD50, NBS1, ATM, ATR, etc., and BRCA1/2 are only some of the important components [36]. Mutations or silencing of expression in any gene in the HRR repair pathway will cause defects in the HRR repair pathway, and PARPi may exert anti-tumor activity through synthetic lethal effects. Its primary molecular mechanism involves competitive binding to the catalytic domain's active site of the PARP enzyme using NAD+nicotinamide, which effectively inhibits the activity of the PARP enzyme. It cannot function by forming PAR polymers and recruiting DNA damage repair related proteins [37]. In this scenario, cells with impaired HRR mechanisms cannot effectively mend DNA damage via HRR. This gives rise to a synthetic lethal phenotype, ultimately causing the death of cancer cells. This phenomenon exemplifies the classic synthetic lethal mechanism [38] (Fig. 1).

Safety and tolerability of PARP inhibitors

The clinical application of PARPi is becoming increasingly widespread, not only in the treatment of ovarian cancer but also in other BRCA1/2-related cancers. While their therapeutic effects are significant, their safety and tolerability are also a major concern. The most common

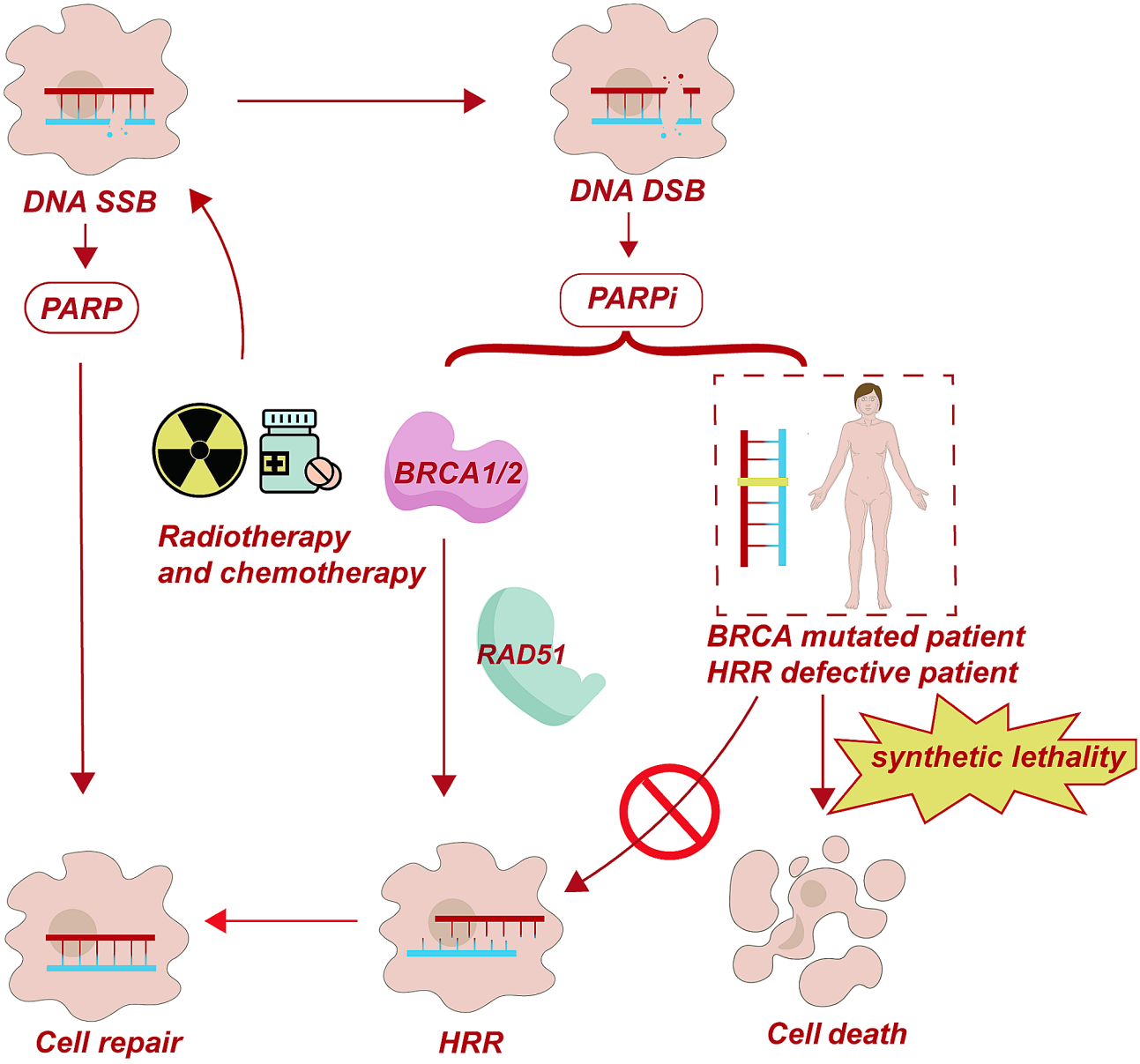

Fig. 1 Mechanism of PARP inhibitors. In cells with normal BRCA1/2 function, the homologous recombination repair (HRR) mechanism can repair DNA double-strand breaks (DSBs) and single-strand breaks (SSBs), preventing cell death. However, in patients with BRCA1/2 mutations, the HRR mechanism fails and cannot repair DNA DSBs. PARP inhibitors (PARPi) block PARP activity, further preventing the repair of SSBs and leading to the accumulation of DSBs. This induces synthetic lethality in patients with BRCA1/2 mutations and HRR deficiency, resulting in tumor cell death

adverse events associated with PARPi include fatigue, nausea, and hematologic toxicity. Some patients also experience gastrointestinal, neurological, and respiratory toxicities [39], with serious side effects such as bone marrow suppression and secondary malignancies. Nearly all patients exposed to PARPi experience adverse events of any grade. Grade 1–2 toxicities are common in approximately two-thirds of patients, with similar incidence rates across all PARPi [40]. Grade 1–2 toxicities generally require monitoring while continuing treatment or pausing treatment for up to 28 days, but Grade 3 or higher toxicities should be carefully considered, with dose reduction or discontinuation of treatment if necessary [41].

Application of PARP inhibitors in ovarian cancer

Building upon the understanding of the PARP mechanism, a multitude of PARPi have been developed, primarily with a focus on cancer patients who possess BRCA1/2 mutations [42]. The prevalence of certain ovarian cancers is linked to mutations in the BRCA gene, which serves a critical function in DNA double-strand repair. Consequently, PARPi have gained extensive utilization in the management of ovarian cancer [43].

In 2009, PARPi's first human clinical trial conducted a clinical evaluation of Olaparib, confirming for the first time the synthetic lethal interaction between PARPi and BRCA1/BRCA2 mutations [8, 44]. In the following ten years, relevant clinical research has been carried out in breast cancer, ovarian cancer, prostate cancer, gastric cancer, pancreatic cancer and other cancers [45, 46]. Olaparib, Rucaparib, and Niraparib have garnered approval from both the FDA and the EMA for their application in treating epithelial ovarian cancer [16]. Olaparib holds the distinction of being the inaugural PARPi to undergo extensive research and remains the most thoroughly evaluated to date. In April 2014, the European Commission granted the marketing license for Olaparib as the first treatment drug for platinum sensitive recurrent BRCA mutations in advanced serous epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer in adult patients with complete or partial response to platinum chemotherapy (AstraZeneca press release 18 December 2014). Subsequently, Rucaparib was approved in 2016, followed by Niraparib in 2017 [47].

In 2018, the SOLO-1 trial, which investigated Olaparib as a first-line maintenance treatment for primary ovarian cancer, reached the significant milestone of completing its five-year follow-up. Building upon this development, the FDA has now granted approval for Olaparib as a first-line maintenance treatment specifically for high-grade serous ovarian cancer (HGSC) with BRCA1/2 mutations in either embryonic or somatic cell lines [48]. In 2022, the SOLO-1 study's seven-year follow-up data was unveiled, marking the most extended follow-up period to date for first-line maintenance therapy employing PARPi. This outcome reaffirms the long-term survival benefits associated with Olaparib maintenance therapy for patients with BRCA mutations [49]. The PRIMA trial, Study 19 trial, and PRIME trial (Table 1)have once more underscored the substantial effectiveness of single-agent PARPi in the maintenance treatment of ovarian cancer [9, 50]. In light of the aforementioned research findings, the use of specific PARPi is strongly recommended for first-line maintenance therapy in appropriate cases. Study 19 trial provided initial evidence suggesting that Olaparib could offer benefits to patients experiencing platinum-sensitive relapses [13]. The SOLO-2 study marked the inaugural confirmation that Olaparib maintenance treatment can significantly enhance OS in patients with gBRCA mutation [51]. The OPINION study further substantiated the effectiveness of Olaparib in the maintenance treatment of platinum-sensitive relapses in patients without gBRCA mutations [52]. The L-MOCA study demonstrated that Olaparib maintenance treatment could bring significant benefits to Asian platinum-sensitive relapse patients, irrespective of their BRCA mutation status [12]. The OReO study and NORA study further validated the substantial effectiveness of PARPi monotherapy in second-line maintenance therapy for ovarian cancer [11, 53]. Building on the research mentioned, PARPi have been established as the standard treatment for maintenance therapy in platinum-sensitive relapse cases. In real world studies, ovarian cancer patients newly diagnosed with the condition received PARPi maintenance therapy in natural clinical settings. These studies demonstrated significant PFS benefits when compared to patients who did not receive PARPi maintenance therapy [54, 55] (Table 1).

However, in 2022, due to the potential increased risk of death in the quality of Olaparib, Niraparib, and Rucaparib [17, 18, 56], as a result of the FDA's review, the indications for advanced treatment of ovarian cancer using these medications were revoked [57]. This has led to a rising clinical demand for the treatment of late-stage ovarian cancer.

The combination of PARPi and ICIs in ovarian cancer

ICIs treatment in ovarian cancer

The immune system plays a pivotal role in both restraining and facilitating cancer development by actively engaging in various phases of the body's response to cancer [58]. Current immunotherapy for cancer is mainly divided into oncolytic virus therapy, cancer vaccines, cytokine therapy, adoptive cell, and ICIs [59]. Recent studies have confirmed that targeting immune checkpoint pathways has significant clinical efficiency [60]. Over the past few decades, significant breakthroughs have been made in the exploration of the treatment of tumor ICIs. Interventions aimed at programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) have achieved broad acceptance for treating solid tumors [61, 62] (Fig. 2). PD-1 is a co-inhibitory receptor that exhibits widespread expression on T cells, natural killer (NK) cells, and B cells [63–65]. Indeed, PD-1 has two ligands: PD-L1 and PD-L2 [66]. Interaction between PD-1 and PD-L1 can suppress T cell proliferation, dampen T cell activation, and contribute to the prevalence of a tumor microenvironment characterized by helper T cell 2 (Th2) cytokines, which tends to favor tumor growth and development. Hence, inhibiting the interaction between PD-L1 and PD-1 can rejuvenate cytotoxic T lymphocyte (CTL) function, which had been compromised, and reestablish the capacity to eliminate cancer cells [67]. CTLA-4 and PD-1 have distinct roles in modulating T cell immunity. CTLA-4, a member of the CD28 immunoglobulin subfamily, serves as an inhibitory receptor primarily expressed by T cells. Its ligands, CD80 and CD86, are typically present on the surface of antigen-presenting cells. These ligands can interact with CD28,

Table 1 Clinical trials of PARP inhibitors in ovarian cancer

Phase	NCT number/name	Drug	Aim	Study Design and outcome	Adverse Events		Start and end dates	Reference
					All-Cause Mortality	Serious Adverse Events		
First-line maintenance therapy								
III	NCT01844986/SOLO-1	Olaparib	Evaluate the Olaparib maintenance monotherapy in BRCA mutated advanced (FIGO stage III-IV) ovarian cancer following first line platinum based chemotherapy	mPFS: Olaparib: 56 m, Placebo: 13.8 m	Olaparib: 55/260 (21.15%), Placebo: 27/131 (20.61%)	Olaparib: 54/260 (20.77%), Placebo: 16/130 (12.31%)	2013-	[48]
III	NCT02655016/PRIMA	Niraparib	Evaluate efficacy of Niraparib as maintenance treatment in participants with Stage III or IV ovarian cancer following response on front-line platinum-based chemotherapy	mPFS: Niraparib: 13.8 m, Placebo: 8.2 m; mOS: Niraparib: 30.3 m, Placebo: 25.0 m	Niraparib: 48/484 (9.92%), Placebo: 31/244 (12.70%)	Niraparib: 156/484 (32.23%), Placebo: 32/244 (13.11%)	2016-	[9]
III	NCT03709316/PRIME	Niraparib	Evaluate efficacy and safety of Niraparib for maintenance	mPFS: Niraparib: 24.8 m, Placebo: 8.3 m;	-	Niraparib: 48/255 (18.8%), Placebo: 11/129 (8.5%)	2018–2023	[56]
Second- line maintenance therapy								
II	NCT00753545/Study 19	Olaparib	Evaluate if Olaparib is effective and well tolerated in maintaining the improvement in your cancer after previous platinum-based chemotherapy	mPFS: Olaparib: 8.4 m, Placebo: 4.8 m; mOS: Olaparib: 29.8 m, Placebo: 27.8 m; ORR: Olaparib: 12.3%, Placebo: 4.2%	-	Olaparib: 31/136 (22.79%), Placebo: 11/128 (8.59)	2008–2023	[13]
III	NCT01874353/SOLO-2	Olaparib	Evaluate the efficacy of Olaparib maintenance monotherapy in relapsed HGSOC patients or high grade endometrioid cancer with BRCA mutations who have responded following platinum based chemotherapy.	mPFS: Olaparib: 19.1 m, Placebo: 5.5 m; mOS: Olaparib: 51.7 m, Placebo: 38.8 m	Olaparib: 116/196 (59.18%), Placebo: 65/99 (65.66%)	Olaparib: 31/136 (22.79%), Placebo: 11/128 (8.59%)	2013-	[51]
III	NCT03106987/OReO	Olaparib	Evaluate the efficacy and tolerability of Olaparib retreatment, versus matching placebo, in non-mucinous epithelial ovarian cancer patients	mPFS: BRCA1/2 + (Olaparib: 4.3 m, Placebo: 2.8 m), BRCA1/2- (Olaparib: 5.3 m, Placebo: 2.8 m; mOS: BRCA1/2 +(Olaparib: 20.1 m, Placebo: 20.9 m), BRCA1/2- (Olaparib: 23.2 m, Placebo: 30.2 m)	BRCA1/2 +: Olaparib: 39/74 (52.70%), Placebo :22/38 (57.89%); BRCA1/2 -: Olaparib: 15/72 (20.83%), Placebo: 8/36 (22.22%)	BRCA1/2 + : Olaparib: 5/74 (6.76%), Placebo: 0/38 (0.00%); BRCA1/2 -: Olaparib: 11/72 (15.28%), Placebo: 2/36 (5.56%)	2017–2022	[57]
III	NCT03705156/NORA	Niraparib	Evaluate the efficacy and safety of Niraparib for maintenance treatment in patients with platinum-sensitive relapsed ovarian cancer	mPFS: Niraparib: 18.3 m, Placebo: 5.4 m;	-	Niraparib: 23 /177 (13.0%), Placebo: 4 /88 (4.5%)	2017-	[53]
III	NCT03534453/L-MOCA	Olaparib	Evaluate the clinical efficacy and safety of Olaparib maintenance monotherapy	mPFS: Olaparib: 16.1 m	-	57/224 (25.4%)	2018-	[12]

Table 1 (continued)

Phase	NCT number/name	Drug	Aim	Study Design and outcome	Adverse Events		Start and end dates	Reference
					All-Cause Mortality	Serious Adverse Events		
IV	NCT03752216/NiQoLe	Niraparib	Evaluate tolerability of Niraparib and the management by the physicians of the side-effects in real life in France.	Waiting for publication	-	-	2019–2022	[11]
Later-line treatment								
III	NCT01847274/NOVA	Niraparib	Evaluate efficacy of Niraparib as maintenance therapy in patients who have platinum sensitive ovarian cancer	mPFS: gBRCA (Niraparib: 21 m, Placebo: 5.5 m), non-gBRCAmut HRD + (Niraparib: 12.9 m, Placebo: 3.8 m), Non-gBRCA HRD- (Niraparib: 9.3 m, Placebo: 3.9 m); mOS: gBRCA: (Niraparib: 40.9 m, Placebo: 38.1 m), non-gBRCA (Niraparib: 31.0 m, Placebo: 34.8 m)	gBRCA: Niraparib:72/136 (52.94%), Placebo:29/65 (44.62%), non-gBRCA : Niraparib: 146/231 (63.20%), Placebo: 68/114 (59.65%)	gBRCA: Niraparib: 51/136 (37.50%), Placebo: 9/65 (13.85%); non-gBRCA ; Niraparib: 76/23 (32.90%), Placebo: 20/114 (17.54%)	2013–2021	[58]
III	NCT02282020/SOLO3	Olaparib	Comparison of Olaparib vs. physician's in patients with gBRCA mutated platinum sensitive ovarian cancer patients	mPFS: Olaparib: 13.4 m, Chemotherapy: 9.2 m; mOS: Olaparib: 34.9 m, Chemotherapy: 32.9 m	Olaparib: 116/178 (65.17%), Chemotherapy: 46/88 (52.27%)	Olaparib: 46/178 (25.84%), Chemotherapy: 14/76 (18.42%)	2015–2022	[17]
III	NCT02855944/ARIEL4	Rucaparib	Studying the patients with ovarian, fallopian tube, and primary peritoneal cancer will best respond to treatment with Rucaparib versus chemotherapy	mPFS: Chemotherapy: 7.4 m, Rucaparib: 5.7 m; ORR: Chemotherapy: 40.3%, rucaparib:32.3%	Chemotherapy: 4/113 (3.54%), Rucaparib: 16/232 (6.90%)	Chemotherapy: 14/113 (12.39%), Rucaparib: 66/232 (28.45%)	2017–2022	[59]

mPFS: Median Progression Free Survival; mOS: Median Overall Survival; ORR: Objective Response Rate; HGSOC: High-grade serous ovarian cancer

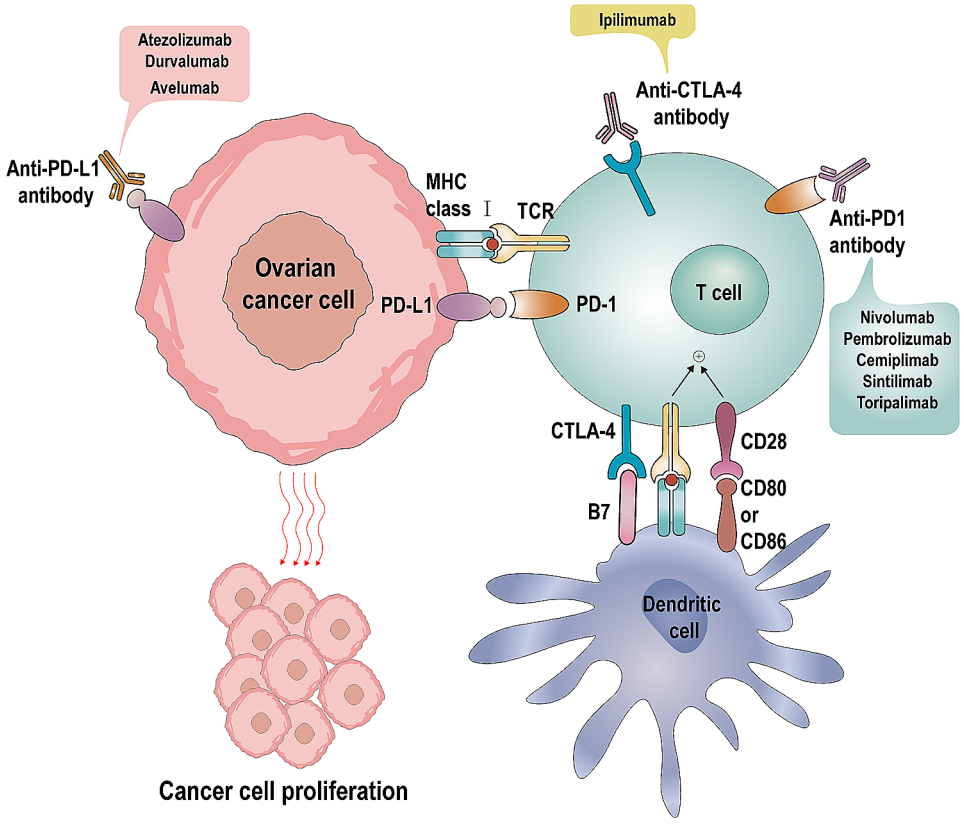

Fig. 2 Mechanism of immune checkpoint inhibitors. PD-1/PD-L1 Pathway: Ovarian cancer cells express PD-L1 on their surface, which binds to PD-1 receptors on T cells, thereby inhibiting T cell activity. Anti-PD-1 and anti-PD-L1 antibodies can block this interaction, restoring the cytotoxic activity of T cells. CTLA-4/B7 Pathway: Dendritic cells express B7 molecules on their surface, which bind to CTLA-4 on T cells, inhibiting T cell activity. Anti-CTLA-4 antibodies can block this interaction, enhancing T cell activity. MHC/TCR Pathway: Dendritic cells present antigens via MHC class I molecules, which activate T cell receptors (TCR), further activating T cells

resulting in co-stimulation, or with CTLA-4, triggering co-inhibition reactions [68].

PD-L1 is present in approximately one-third of advanced ovarian cancer tumors, while the majority of tumor-infiltrating lymphocytes exhibit PD-1 expression [69]. Early studies have shown that PD-L1 expression in tumors is positively correlated with ovarian cancer survival [70]. This may also indicate that PD-1/PD-L1 plays a key role in the tumor immune response to ovarian cancer. Due to the lack of cytotoxic T lymphocytes and the immunosuppressive tumor microenvironment, ovarian cancer is included in the cold tumor range [71]. Cold tumors are tumors that have low activity to suppress immune cells and respond to treatment with tumors that are lower than those in the heat-immune category. Other names with the same category include invasive exclusion, non-inflammatory, or non-immunoreactive tumors [72].

The clinical use of ICIs in ovarian cancer has demonstrated limited efficacy, with clinical trial objective response rates typically ranging from approximately 6% to 15%. This outcome falls short of the substantial impact that immunotherapy has achieved in the treatment of metastatic and recurrent cervical cancer [73]. This may be related to low expression levels of PD-L1, low mutation load, and weak immunogenicity in ovarian cancer [71, 74, 75]. In September 2021, the National Comprehensive Cancer Network (NCCN) in the United States endorsed the utilization of Pembrolizumab for recurrent ovarian cancer patients who exhibit high microsatellite instability (MSI-H) or have deficient DNA mismatch repair (dMMR) and are either platinum-sensitive or platinum-resistant [76–78]. Currently, immunotherapy is often considered as a post-treatment option for ovarian cancer. This means that ICIs have emerged as a potential treatment choice for ovarian cancer. However, the outcomes have not been entirely satisfactory [79–82]. Finding new combinations to improve the efficacy of immunotherapy for ovarian cancer is a feasible approach.

Effects of PARPi on Immune Regulation

The effectiveness of ICIs relies on several factors, such as the level of PD-L1 expression, the quantity of tumor-infiltrating lymphocytes, the neoantigen load, and the tumor mutation burden [83, 84]. In terms of their mechanism of action, PARPi work by impeding DNA repair processes, amplifying DNA damage, generating new antigens and

cytoplasmic DNA, activating the interferon pathway and initiating anti-tumor immune responses. Next, let's outline the rationale behind combining PARPi with ICIs.

PARPi upregulates PD-L1

Research has revealed that Niraparib has the capacity to increase the expression of PD-L1 on the outer surface of ovarian cancer cells. This leads to an augmentation in the quantity and effectiveness of CD8+T cells while simultaneously exerting immunosuppressive effects within the tumor microenvironment [85]. Several studies have demonstrated that PARPi can elevate the expression of PD-L1 in breast cancer cell lines and animal models. PARPi weakens the anti-cancer immune response by upregulating PD-L1, while concurrently blocking PD-L1 to enhance the sensitivity of cancer cells treated with PARPi to T cell-mediated killing. When compared to each drug administered individually, the combined treatment of PARPi and anti-PD-L1 significantly enhances the therapeutic efficacy in vivo [86]. Furthermore, research has identified that in an advanced serous ovarian cancer mouse model, the administration of Olaparib leads to an increase in PD-L1 expression. The combination of Olaparib and PD-L1 exhibits a notable effect, whereas the efficacy of anti-PD-L1 treatment alone is minimal or unresponsive [87]. Shen et al. conducted a study using a different model than the previous one, which involved combining talazoparib with anti-PD-L1 under normal homologous recombination (HR) conditions. In this study, they once again observed an upregulation of PD-L1 expression and a significant tumor response to the combined treatment of PARPi and ICIs [25]. In a recent study conducted by Jiao et al., it was suggested that PARPi can induce the expression of PD-L1. Their research involved treating MDA-MB-231 and BT549 breast cancer cells with olaparib or talazoparib, and the results demonstrated an increase in PD-L1 expression both in vitro and in vivo [86].

Research on the mechanism behind the upregulation of PD-L1 can generally be categorized into three main aspects. Firstly, studies have revealed that Niraparib triggers the activation of the cyclic GMP-AMP synthase (cGAS) –stimulator of interferon genes (STING) pathway, consequently leading to the upregulation of IFN-β. This represents a direct mechanism responsible for the increased expression of PD-L1 [85]. Secondly, in a separate study, it was demonstrated that PARPi primarily upregulates PD-L1 expression by deactivating glycogen synthase kinase-3 (GSK3β) [86, 88]. At last, Another study suggests that an alternative pathway through which PARPi upregulates PD-L1 involves the ATM-ATR-Checkpoint Kinase 1 (CHEK1) pathway, which functions as a kinase sensor for DSB. Upon activation of ATM, the signal kinase transitions from ATM to ATR. This switch from ATM to ATR activation subsequently triggers CHEK1 activation, further initiating the activation of the Janus kinase/signal transducer and transcriptional protein activator (JAK/STAT) signaling pathway, ultimately resulting in the upregulation of PD-L1 expression [89, 90].

Furthermore, in experiments utilizing a BRCA1 deficient ovarian cancer mouse model, it has been demonstrated that PARPi enhances the therapeutic effectiveness of CTLA-4 blockade [91]. The above findings illustrate PARPi's capability to augment the therapeutic impact of ICIs.

PARPi activate the cGAS-STING signaling pathway

The immune pathway primarily comprises several signaling pathways, including the Toll-like receptors (TLRs) signaling pathway, C-type lectin receptors (CLR) signaling pathway, RIG-I-like receptor signaling pathway, and the cyclic cGAS-STING signaling pathway [92–95]. PARPi has the capability to activate the cGAS-STING innate immune pathway, which ultimately results in the production of type I interferons (IFN). This activation leads to a range of immunogenic effects and associated immune responses [96–98]. As a crucial innate immune sensor, the cGAS-STING pathway plays a pivotal role in regulating tumor growth and progression by facilitating the recruitment, initiation, and activation of anti-tumor immune cells [99, 100]. As mentioned previously, Niraparib triggers the activation of the cGAS-STING pathway, resulting in the upregulation of IFN-β and the elevation of PD-L1 expression. Conversely, when DNA binds to cGAS, it initiates the recruitment and activation of STING, which in turn facilitates the significant expression of CCL5 and CXCL10 via the involvement of TRAF family member-associated NF-kappa-B activator (TANK) binding kinase 1 and interferon regulatory factor 3. This process results in the recruitment of T cells and enhances the function of lymphocytes within ovarian cancer [85, 101, 102]. Olaparib's inhibition of PARP elicits robust local and systemic anti-tumor immunity, encompassing both adaptive and innate immune responses, primarily via STING-dependent mechanisms in mice with BRCA1-deficient ovarian cancer. Furthermore, when combined with a PD-1 inhibitor, this effect is further intensified [87]. Additionally, certain studies have discovered that the treatment of ovarian cancer cells with talazoparib leads to a notable increase in the phosphorylation of two pivotal components within the STING pathway, namely IRF3 and TBK1 [25]. The sustained release of IFN-I from PARPi within the tumor microenvironment (TME) plays a vital role in promoting various immune functions. This includes the activation of dendritic cells, the preservation of cross-presentation of tumor-derived antigens to T cells, the support of NK cell-mediated anti-tumor

immunity, and synergistic activation with Toll-like receptor 4 (TLR4) ligands like HMGB1 to stimulate M1 anti-tumor macrophages [103, 104].

PARPi increases genomic instability

Because of HRD and BRCA mutations, cancer cells exhibit heightened genomic instability, rendering them more immunogenic. Following PARPi administration, the induction of severe DNA damage leads to the accumulation of DNA fragments within the cytoplasm. As a consequence, this process generates a greater number of novel antigens and exposes them on the cell surface, resulting in heightened activation of the immune response. This, in turn, leads to an increase in tumor mutational burden (TMB) and elevated immunogenicity [105, 106]. Especially in cells with HRD, it becomes feasible to reestablish a productive Th1 immune response and reset the tumor microenvironment. Moreover, PARPi induces sustained DNA damage, resulting in epigenetic alterations within tumor cells. These changes render tumor cells more receptive to the influence of T cells and NK cells, ultimately culminating in an enhanced intrinsic immunogenicity of the tumor cells [107]. Conversely, ICIs can rescue the tumor microenvironment from the consequences of inadequate immune cell infiltration and facilitate the recognition of newly formed antigens resulting from chronic DNA damage induced by PARPi [27].

In summary, PARPi exert their effects through several key mechanisms. Firstly, they can activate the cGAS-STING pathway, leading to the activation of GSK3β. Concurrently, through the ATM-ATR-CHEK1 pathway, they upregulate PD-L1 expression. Secondly, PARPi activate the immune pathway, resulting in the release of IFN-I and the promotion of the expression of chemokines CCL5 and CXCL10. Finally, PARPi can increase genetic instability, resulting in a higher TMB and heightened immune responsiveness (Fig. 3).

Clinical study of PARPi combined with ICIs in ovarian cancer

In recent years, ICIs including anti-PD-1 antibodies and anti-PD-L1 antibodies, have demonstrated notable efficacy in various types of tumors [108]. The combination of ICIs with PARPi appears to be a viable approach. Preclinical data suggests that this combination therapy of ICIs and PARPi may yield synergistic effects, particularly benefiting ovarian cancer patients who may not be suitable candidates for platinum-based retreatment [25, 50].

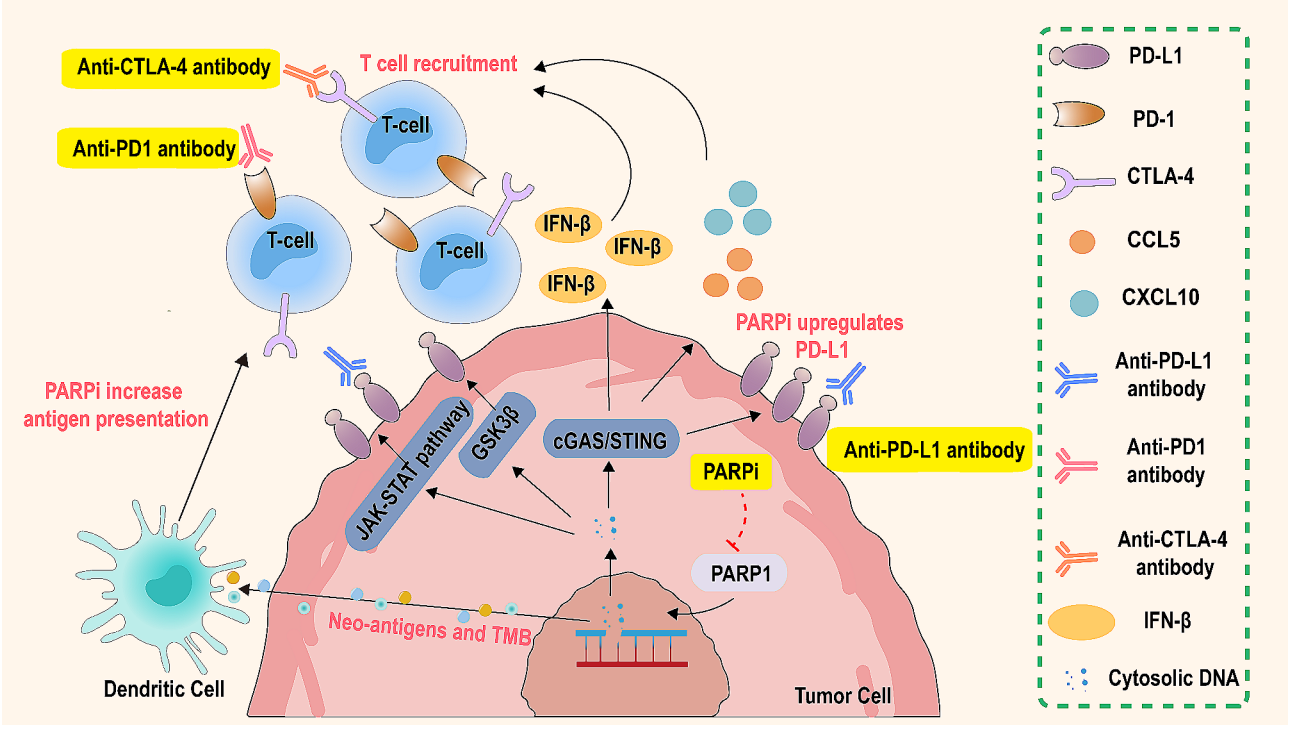

Fig. 3 The interaction between PARP inhibitors and immune checkpoint inhibitors. PARP inhibitors enhance tumor immunogenicity and the presentation of neoantigens in the tumor microenvironment (TME) by increasing antigen presentation and upregulating PD-L1 expression. Dendritic cells, through the cGAS/STING pathway, activate and present these neoantigens, promoting the recruitment and activation of T cells. Immune checkpoint inhibitors restore the cytotoxic activity of T cells by blocking the PD-1/PD-L1 and CTLA-4/B7 pathways, further enhancing the anti-tumor immune response. The combined use of PARP inhibitors and immune checkpoint inhibitors not only increases antigen presentation and T cell activity but also upregulates PD-L1 expression. Additionally, this combination promotes the secretion of IFN-β through the JAK-STAT and GSK3β pathways, further enhancing the immune system's attack on tumor cells

This could potentially offer novel treatment alternatives for a subset of advanced ovarian cancer patients who currently lack effective therapeutic options. In summary, it is a feasible approach to improve the efficacy of ICIs by using PARPi to influence the immune system and tumor microenvironment. And this combination has been carried out in many clinical trials.

The MEDIOLA trial is a multicenter, open-label, phase 1/2 clinical trial conducted to assess the treatment of solid tumors using Duvalizumab and Olaparib. In this trial, the objective response rate (ORR) for the combination of Duvalizumab and Olaparib reached an impressive 71.9% in patients with platinum-sensitive recurrent ovarian cancer who had gBRCA mutations [109]. The early results of the Phase II study of MEDIOLA (NCT02734004) showed good efficacy and safety in the combination of olapanib and Duvalizumab in platinum sensitive recurrent ovarian cancer with germline BRCA1 and/or BRCA2 mutations (gBRCAm). In gBRCAm patients, the ORR of Olapanib combined with Duvalizumab was 92.2%, and over 40% of patients had CR [110]. The findings from this study suggest that the combination of Olaparib and Duvalizumab demonstrates encouraging anti-tumor activity and safety in the context of recurrent ovarian cancer.

Based on the preliminary research results of the MEDIOLA trial, a Phase III DUO-O trial was conducted, The DUO-O study is a randomized, double-blind, placebo-controlled multicenter phase III study aimed at exploring the efficacy of Bevacizumab + Olaparib + Duvalizumab in first-line maintenance therapy for BRCA wild-type newly diagnosed ovarian cancer. The results showed that patients receiving triple maintenance therapy had significantly higher PFS than those receiving bevacizumab monotherapy, at 24.2 months and 19.3 months, respectively [111]. TOPACIO/KEYNOTE-162 is a Single-Arm, Phases 1/2 trial. The study is designed to evaluate the efficacy of Niraparib in combination with pembrolizumab in patients with relapsing platinum resistance. In the population with ovarian cancer, the ORR was 18% and the disease control rate was 65%. Among them, 3 (5%) confirmed complete remission, 8 (13%) confirmed partial remission, 28 (47%) were stable, and 20 (33%) were progressing [112]. This study demonstrates that the combination of Niraparib and Pembrolizumab therapy exhibits promising anti-tumor activity in ovarian cancer patients and is worthy of further research.

The MOONSTONE study is an open-label, single-arm Phase 2 trial. It aims to assess the effectiveness and safety of combining Niraparib and Dostarlimab. This study includes participants with advanced, relapsed high-grade ovarian, fallopian tube, endometrioid, clear cell ovarian, or primary peritoneal cancer. These participants do not possess a known breast cancer susceptibility gene (BRCA) mutation. They also have platinum-resistant disease and have previously undergone treatment with Bevacizumab. However, the results of this study did not meet the desired level of satisfaction [113] (Table 2).

Both preclinical and clinical data suggest that monotherapy with PARPi and ICIs have limitations in the management of ovarian cancer [114]. The clinical studies mentioned above have been completed, but it's worth noting that there are numerous ongoing or actively recruiting clinical trials that are exploring the combination of PARPi and ICIs. These trials hold significant promise and merit our attention.

Discussion

Recent clinical studies have demonstrated that the treatment combination of PARPi and ICIs holds practical clinical significance, particularly for advanced ovarian cancer patients with limited treatment options. Notably, both the MEDIOLA study and the TOPACIO study have highlighted that the synergy between PARPi and ICIs can be harnessed effectively in the context of ovarian cancer treatment.

Immunotherapy has transformed cancer treatment, but it's important to note that the effectiveness of ICIs, whether used as standalone treatments or in combination with chemotherapy is not yet satisfactory. Hence, there is a need to investigate alternative combination approaches and novel immunotherapy techniques for targeted medications. The triple combination of ICIs, PARPi, and anti-angiogenic drugs appears to yield promising outcomes in the treatment of recurrent ovarian cancer. The results from the MEDIOLA trial demonstrate that the response rate to the triple therapy is significantly higher compared to the dual therapy of PARPi and ICIs. This presents a novel clinical treatment approach for consideration. Furthermore, the quest for novel biomarkers can aid in the identification of patients with a higher likelihood of responding favorably to combination therapy protocols. Moreover, it is imperative to uncover distinct resistance mechanisms to PARPi and ICIs, thereby establishing a fresh theoretical framework for the integration of these strategies. There is an urgent need to explore novel biomarkers for the precise screening of individuals suitable for this combination approach. The toxic attributes of PARPi, primarily associated with bone marrow suppression, result in adverse events for some patients undergoing monotherapy. These toxicities also impose limitations on the application of PARPi within certain otherwise viable combination strategies, such as in conjunction with chemotherapy [115]. However, it's worth noting that immunosuppressants typically do not exhibit a significant bone marrow suppression effect. Consequently, the combination regimen can mitigate the overlap of drug side effects, thereby enhancing the safety profile of this

Table 2 Clinical trials combining PARP inhibitors and immune checkpoint inhibitors in ovarian cancer

Phase	NCT number/name	Drug	Aim	Study Design	Outcome	Start and end dates	Reference
PD-1 inhibitor + PARPi							
I/II	NCT02657889/TOPACIO/KEYNOTE-162	Pembrolizumab + Niraparib	Studying the safety and efficacy of combination treatment with Niraparib and Pembrolizumab in recurrent ovarian cancer	Arm: Pembrolizumab + Niraparib; 62 recurrent platinum-resistant-ovarian cancer patients	ORR: 18%	2016–2021	[115]
III	NCT03740165	Pembrolizumab + Olaparib	Studying the efficacy and safety of treatment with Pembrolizumab and Olaparib in epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	Arm 1: Pembrolizumab + Olaparib, Arm 2: Pembrolizumab, Arm 3: placebo; 1367 BRCA non-mutated advanced epithelial ovarian cancer patients	Active, not recruiting	2018-	-
II	NCT03955471/MOONSTONE	Dostarlimab + Niraparib	Studying the safety and efficacy of combination treatment with Niraparib and Dostarlimab in platinum-resistant ovarian cancer	Arm: Dostarlimab + Niraparib; 41 platinum-resistant ovarian cancer patients	ORR: 7.3%, mPFS: 2.1months, mOS: 10.61months	2019–2022	[110]
II	NCT04417192	Pembrolizumab + Olaparib	Studying the efficacy and safety of Olaparib monotherapy and Olaparib plus Pembrolizumab combination therapy in patients with untreated stage III, IV high-grade serous or Grade 3 endometrioid ovarian cancer with HRD positivity	Arm 1: Olaparib, Arm 2: Pembrolizumab + Olaparib; 30 untreated stage III, IV high-grade serous or grade 3 endometrioid ovarian cancer with HRD positivity patients	Active, not recruiting	2020–2023	-
II/III	NCT03651206	Dostarlimab + Niraparib	Studying the efficacy of Olaparib with or without Dostarlimab in metastatic or recurrent endometrial or ovarian carcinosarcoma	Arm 1: Niraparib, Arm 2: Dostarlimab + Niraparib, Arm 3: chemotherapies; 18 metastatic or recurrent endometrial or ovarian carcinosarcoma patients	Recruiting	2020-	-
Ib	NCT04673448	Dostarlima + Niraparib	Studying the efficacy of combination treatment with Dostarlimab and Niraparib in BRCA-mutated breast, pancreas, ovary, fallopian tube, or primary peritoneal cancer	Arm 1: Dostarlimab + Niraparib; 18 BRCA-mutated breast, pancreas, ovary, fallopian tube, or primary peritoneal cancer patients	Recruiting	2021-	-
PD-L1 inhibitor + PARPi							
II	NCT02484404	Durvalumab + Olaparib	Studying tolerability and efficacy the combination of these drugs in treating advanced solid tumor	Arm 1: Durvalumab + Cediranib, Arm 2: Durvalumab + Olaparib, Arm 3: Durvalumab + Olaparib + Cediranib; 35 recurrent ovarian cancer patients	PR:15%	2015-	[116]

Table 2 (continued)

Phase	NCT number/name	Drug	Aim	Study Design	Outcome	Start and end dates	Reference
I/II	MEDIOLA	Durvalumab + Olaparib	Studying the effectiveness, safety, and antitumor activity of study drugs Durvalumab in combination with Olaparib and Durvalumab in combination with Olaparib and Bevacizumab in advanced solid tumors	Arm 1: Durvalumab + Olaparib, Arm 2: Durvalumab + Olaparib, Arm 3: Durvalumab + Olaparib + Bevacizumab; 32 non-germline BRCA-mutated platinum-sensitive relapsed ovarian cancer patients	DCR:9.4% mOS:23.2months	2018–2022	[109]
III	NCT03598270	Atezolizumab + Niraparib	Studying the efficacy of Niraparib maintenance with or without Atezolizumab in recurrent ovarian, tubal or peritoneal cancer and platinum treatment-free interval > 6 months	Arm 1: Niraparib, Arm 2: Atezolizumab + Niraparib; 414 recurrent ovarian, tubal or peritoneal cancer and platinum treatment-free interval > 6 months patients	Active, not recruiting	2018-	[117]
II	NCT04015739	Bevacizumab + Olaparib + Durvalumab	Studying the safety and efficacy of the bevacizumab, Olaparib and Durvalumab combination in patient with high grade serous or high grade endometrioid or other high grade epithelial non mucinous ovarian tumor	Arm: Bevacizumab + Olaparib + Durvalumab; 74 advanced epithelial ovarian patients	Active, not recruiting	2019-	[18]
II	NCT04742075	Durvalumab + Olaparib + UV1	Studying the efficacy of UV1-Olaparib-Durvalumab combination as maintenance therapy after platinum combination therapy for BRCAwt patients with relapsed ovarian cancer	Arm 1: Olaparib, Arm 2: Durvalumab + Olaparib, Arm 3: Durvalumab + Olaparib + UV1; 184 recurrent BRCAwt ovarian cancer patients	Recruiting	2021-	-
CTLA-4 inhibitor + PARPi							
I/II	NCT02571725	Tremelimumab + Olaparib	Studying the efficacy and safety of combination treatment with Tremelimumab and Olaparib in recurrent BRCA mutation-associated ovarian cancer	Arm 1: Tremelimumab + Olaparib; 50 recurrent BRCA mutation-associated ovarian cancer patients	Active, not recruiting	2016-	-
II	NCT04034927	Tremelimumab + Olaparib	Studying the efficacy of Olaparib with or without Tremelimumab works in treating patients with ovarian, fallopian tube, or peritoneal cancer that has come back	Arm 1: Olaparib, Arm 2: Tremelimumab + Olaparib; 58 platinum-sensitive recurrent ovarian cancer patients	Active, not recruiting	2019-	-

mPFS: Midian Progression Free Survival; mOS: Midian Overall Survival; ORR: Objective Response Rate; DCR: Disease Control Rate

combination approach. During the execution of clinical trials, it is imperative to take into account the potential adverse reactions associated with combination therapy. This entails a thorough investigation of the optimal dosage and timing of administration, with the ultimate goal of ensuring patient tolerance and safety. To steer clinical trials toward a sensible combination of treatments.

PARPi currently face several issues in clinical use, such as acquired resistance in a significant portion of patients after initial treatment [116]. The restoration of HRR is a primary cause of PARPi resistance. Other factors, including reversion mutations, replication fork protection, epigenetic modifications, restoration of ADP-ribosylation (PARylation), and pharmacological changes, also contribute to PARPi resistance [117, 118]. HRR restoration includes secondary mutations in BRCA1/2 genes and regulation of other proteins in the HRR pathway. Recent studies have revealed that PARPi can activate STING-dependent intrinsic immunity in tumor cells [97, 119]. This immune activation has inspired the combination of ICIs with PARPi, as suggested by clinical trial results, which seem to indicate that ICIs can reverse PARPi resistance. Additionally, PARPi primarily target BRCA1/2 gene mutations or HRD. However, in high-grade serous ovarian cancer, only 25% of patients with BRCA mutations are more sensitive to platinum-based chemotherapy and PARPi, while the remaining 75% are BRCAwt patients [120]. Clinical exploration for the benefits of PARPi in BRCAwt patients is ongoing. The NORA study showed that in the BRCAwt subgroup, the niraparib group had a significantly extended PFS compared to the placebo group (11.1 vs. 3.9 months) [53]. Results from the 2022 SGO Annual Meeting showed that niraparib monotherapy maintenance extended the median PFS for the "BRCA and HRD double-negative" population to 14 months, compared to 5.5 months for the placebo group. This demonstrates the efficacy of PARPi in BRCAwt populations, but more clinical trials are needed to verify this. Moreover, long-term use of PARPi can lead to severe bone marrow suppression and other adverse effects. To address these issues, combining PARPi with other drugs such as ICIs can overcome resistance. Additionally, developing PARPi with higher selectivity and potency but fewer side effects is essential.

It is noteworthy that in recent years, RAS has played a crucial role in the development and progression of ovarian cancer. RAS is an important signaling protein belonging to the small GTPase family, including three main proteins: KRAS, NRAS, and HRAS [121]. In ovarian cancer, the mutation status of RAS, especially KRAS at codons 12, 13, and 61, accounts for 6% to 65%. KRAS mutations are also considered biomarkers of poor outcomes and resistance to various drugs in ovarian cancer [122]. RAS is also a determinant for several small molecule therapies, such as MEK inhibitors [123]. Interestingly, studies have found that KRAS mutant tumor models exhibit resistance to PARPi, anti-PD-L1, and the combination of PARPi and PD-L1 inhibitors. MEK inhibitors can trigger and amplify PARPi-induced DNA damage, cytoplasmic dsDNA accumulation, STING pathway activation, and CD8+T cell recruitment. Additionally, MEKi reduces myeloid-derived suppressor cell (MDSC) infiltration, at least partially by decreasing IL-6 and GM-CSF. The results of this study demonstrated significant efficacy of the triple therapy of PARPi, MEKi, and anti-PD-L1 blockade in KRAS mutant tumor models [124]. This suggests that RAS and possibly other proteins play significant roles in resistance to ovarian cancer treatments. Utilizing drugs targeting these proteins in combination with PARPi and ICIs might yield better results. This area warrants further research and clinical trials, and we look forward to better therapeutic combinations in the future.

It is well-known that glutamine metabolism plays a central role in altered metabolism in cancer cells [125]. As mentioned earlier, KRas itself is considered undruggable. Some studies have utilized the late G1 glutamine (Gln)-dependent cell cycle checkpoint bypass in cancer cells with KRAS mutations [126]. Upon Gln deprivation, KRas-driven cancer cells enter the S phase and stall due to insufficient nucleotide biosynthesis [127]. Cells stalled in the S phase are more susceptible to cytotoxic drugs, resulting in better cancer cell killing effects. For example, in ovarian cancer, platinum-resistant tumor cells show increased glutamine metabolism, and glutaminase (GLS) inhibitors BPTES and 968 can sensitize chemotherapy-resistant ovarian cancer cells to platinum-based chemotherapeutic agents [128]. Recent studies have found that treatment with the GLS inhibitor CB-839 makes cells susceptible to Olaparib and extends survival in tumor-bearing mice, suggesting that combined treatment with GLS inhibitors and PARPi can effectively treat chemotherapy-resistant ovarian cancer [129]. Therefore, could the combination of GLS inhibitors, PARPi, and ICIs achieve better efficacy in ovarian cancer? This could be a future direction for exploration.

Conclusion

PARPi and ICIs are both effective treatments for ovarian cancer. PARPi have become a standard element in the treatment of ovarian cancer, while immunotherapy with ICIs is well-suited for addressing non-resectable or metastatic microsatellite instability or mismatch repair deficiency solid tumors. PARPi can regulate the immune microenvironment by upregulating PD-L1, activating immune pathways, increasing genomic instability, and promoting tumor response to ICIs. Current conversion and preclinical data provide strong evidence for

the synergistic potential of combining PARPi with ICIs. However, additional investigation is necessary to delve deeper into the clinical trial results. In summary, the synergistic combination of PARPi and ICIs holds promise for improving outcomes in patients with advanced ovarian cancer.

Abbreviations

PARPi	Polyadenosine diphosphate ribose polymerase inhibitors
ICIs	Immune checkpoint inhibitors
HRD	Homologous recombination deficiency
BER	Base excision repair
DSBs	DNA double-strand breaks
NHEJ	Non-homologous end joining
PFS	Progression-free survival
FDA	Food and Drug Administration
EMA	European Medicines Agency
OS	Overall survival
NHEJ	Non-homologous end joining
HRR	Homologous recombination repair
HRD	Recombination repair defect
HGSC	High-grade serous ovarian cancer
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
CTLA-4	Cytotoxic T lymphocyte-associated protein 4
Th2	T cell 2
CTL	Cytotoxic T lymphocyte
NCCN	Comprehensive Cancer Network
MSI-H	High microsatellite instability
dMMR	Deficient DNA mismatch repair
GSK3β	Glycogen synthase kinase-3
CHEK1	Checkpoint Kinase 1
TMB	Tumor mutational burden
ORR	Objective response rate
DDR	DNA damage response

Author contributions

Fen Xiao: Investigation, Visualization, Writing original draft. ZhiBin Wang: Writing & editing. Liu Qiao: Writing & editing. Xiu Zhang: Writing & editing. Nayiyuan Wu: Conceptualization, Writing & editing. Jing Wang: Supervision, Writing & editing. Xing Yu: Supervision, Writing & editing.

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Data availability

No data was used for the research described in the article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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