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Review

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Navigating immunotherapy for ovarian cancer: current landscape and future perspectives

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Abstract

Ovarian cancer (OC) is the leading cause of death related to gynecologic malignancies, with recurrence occurring frequently despite significant advances in surgical interventions and chemotherapy. Therefore, novel therapies are necessary to improve the long-term prognosis of the disease. Immunotherapy holds promise in OC treatment by harnessing the potential of the immune system to combat neoplastic cells. The effectiveness of immunotherapy has been demonstrated in numerous cancers and subsequently integrated into clinical practice. However, despite initial preclinical findings suggesting an immunogenic microenvironment in OC, immune checkpoint inhibitors have not shown significant outcomes in clinical studies thus far. Further investigation is needed to fully understand the role of immunity in OC and to develop more effective therapeutic strategies, including combinatorial approaches and the identification of predictive biomarkers for more accurate patient selection for immunotherapy.

Keywords: Ovarian cancer, immunotherapy, immune checkpoint inhibitors, PARP inhibitors, oncolytic viruses, adoptive cell therapy

INTRODUCTION

In the United States, approximately 22,000 patients receive an ovarian cancer (OC) diagnosis every year. This makes OC one of the most prevalent tumors among women and, specifically, the fifth most common cause of cancer-related fatalities among female individuals[1]. The focus of this manuscript is on epithelial OC, representing the most prevalent subtype, accounting for 90% of ovarian cancer cases. This decision is guided by the substantial clinical and pathological differences observed between epithelial and non-epithelial ovarian cancers[2]. The current protocol typically entails initial tumor reduction surgery succeeded by a regimen of platinum-based and taxane-based chemotherapy for ongoing management. After the initial treatment, cancer recurrence rates are high, affecting around 70% of patients with optimal debulking (< 1 cm of remaining malignancy) and around 85% of patients with non-ideal debulking (> 1 cm of remaining malignancy). As a result, the survival rate over a five-year period stands at approximately 45%. Efforts have been made to extend this interval via advancements in frontline maintenance therapy[3,4]. Maintenance therapies that have received approval, such as bevacizumab or Poly(ADP-ribose) polymerase (PARP) inhibitors, have shown effectiveness in extending the period of progression-free survival (PFS). However, they have not shown a similar impact on overall survival (OS). This underscores the necessity for maintenance therapies that are more potent and efficacious[5-7]. Currently, ongoing clinical studies primarily concentrate on targeted methodologies, including recent efforts to integrate immune-based therapeutics into ovarian cancer treatment strategies. Immunotherapy aims to enhance the anticancer immune response using various methods, including tumor antigen vaccines, immunostimulatory cytokines, and monoclonal antibodies focusing on inhibiting immune-suppressing signals produced by cancer cells. In this manuscript, we examine the clinical progress of immunotherapy in OC and emphasize the promising treatment avenues for future advancement.

Immune checkpoint inhibitors

One innovative approach to treating ovarian cancer (OC) is immune checkpoint inhibition, which targets molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) with its ligand CD80, and programmed death receptor-1 (PD-1) with its ligand PD-L1. These regulatory checkpoints play a crucial role in discerning between foreign pathogens and host cells. Upon interaction with a peripheral cell, a T-lymphocyte diligently scans for epitopes that align with its T cell receptor (TCR) affinity. Subsequently, it assesses whether the encountered entity is of pathogenic origin or a component of the host's own cells[8]. Immune checkpoints like PD-L1 indicate a self-cell to T cells. In their absence, the T cell recognizes the target as pathogenic, triggering a killing response. Tumor cells frequently increase the expression of immune checkpoints, thereby attenuating the nearby immune response and facilitating evasion of the immune system[9]. Immune checkpoint inhibitors (ICIs), such as those binding PD-1, PD-L1, or CTLA-4, disrupt the engagement among cancer and T cell checkpoints, thus re-establishing T cell cytotoxic activity[10,11]. ICIs represent innovative agents that elicit immunostimulatory effects by blocking CTLA-4, PD-1, or PD-L1. ICIs have emerged as a standard treatment option for various malignancies, such as advanced lung cancer and malignant melanoma[11]. However, specific immunotherapeutic agents approved for OC are currently lacking. Nevertheless, immune checkpoints hold promise as possible objectives for stimulating the body's immune response against OC. Several studies have documented a noteworthy occurrence of elevated PD-L1 expression in OC, with one study reporting approximately 70% of tissue samples from some OC patients showing such expression. Another investigation found that monocytes extracted from peripheral blood and ascites of OC patients displayed markedly higher levels of PD-L1 expression in comparison to benign ovarian tumors[12,13]. It is also interesting to note that OC is identified as a potentially immunoreactive tumor due to the correlation between the occurrence of tumor-infiltrating lymphocytes (TILs) and enhanced clinical results[14]. A molecular subtype characterized by heightened immune activity, featuring genes and signaling pathways associated with immune cells, has been identified, exhibiting a connection with prolonged OS[15]. T cells found within ovarian tumors exhibit compromised

effector activities and express various inhibitory receptors, including CTLA-4, PD-1, and lymphocyte activation gene-3[16,17]. The secretion of interferon-γ (IFN-γ) by CD8-positive T cells that infiltrate tumors prompts the expression of PD-L1 on OC cells or macrophages. This process leads to the suppression of the functional capabilities of PD-1-positive TILs, consequently fostering immunosuppression within the tumor microenvironment (TME)[18]. Given that the presence of TILs is crucial for response to immune checkpoint blockade (ICB), it is anticipated that immunoreactive ovarian tumors will respond to PD-1 blockade[19]. However, it is worth emphasizing, without presuming to be exhaustive, that, as in other types of cancer, interactions with the tumor microenvironment can be crucial in influencing the antitumor response. Numerous factors may impede an effective immune response against cancer cells. Among these factors, the presence of myeloid-derived suppressor cells (MDSCs), T regulatory (Treg) cells, and tumor-associated macrophages (TAMs) within the tumor microenvironment plays a pivotal role. These immunosuppressive cells release reactive oxygen species (ROS) and other factors that inhibit the response of natural killer (NK) cells, which are crucial for tumor surveillance and elimination. Additionally, heightened levels of fibroblasts contribute to increased secretion of metalloproteinases, leading to the shedding of ligands that could interact with NK cells. Moreover, fibroblasts directly hinder NK cell function by preventing the upregulation of activating receptors induced by cytokines. These interactions underscore the complex interplay between immune cells and the tumor microenvironment in shaping the immune response against ovarian cancer[20].

ICI: monotherapy

Numerous clinical investigations have been undertaken in this context. For example, in a phase II study assessing nivolumab (an anti-PD-1 agent), the approximate best overall response rate (ORR) was 15%, with a disease control rate (DCR) of about 45%. Significantly, a sustained complete response rate was observed in patients undergoing treatment (UMIN Clinical Trials Registry UMIN000005714)[21]. In a very interesting phase II trial (KEYNOTE-100-NCT02674061), 376 OC patients were treated with pembrolizumab in a monotherapy regimen, yielding an ORR of solely 8%. It was then observed that higher expression of PD-L1, measured by a combined positive score (CPS) of 10 or more, led to an increased ORR (17.1%) compared to a CPS between 1 and less than 10 (10.2%) or less than 1 (5%)[22]. Overall, these trials demonstrated limited effectiveness of PD-1 blockade as a monotherapy in OC patients.

ICI: combination therapies

An avenue to improve the potency of PD-1 blockade involves combining it with other ICIs, which theoretically synergize with the immune system, thereby augmenting the clinical response. Some studies in the literature have shown that the association of PD-1/PD-L1 blockade and CTLA-4 blockade[23,24] is more effective as compared to PD-1/PD-L1 blockade alone in murine experimental systems of melanoma and OC. Specifically, the combination therapy of ipilimumab and nivolumab has demonstrated efficacy in treating metastatic melanoma and lung cancer, albeit with increased toxicity compared to using PD-1 blockade alone[25]. Consequently, researchers are exploring the potential of combining ipilimumab with nivolumab for the treatment of ovarian cancer patients[26]. In a randomized phase II trial conducted by Zamarin *et al.*, which enrolled 100 OC patients, the combination of nivolumab and ipilimumab demonstrated a significantly higher response rate compared to the use of nivolumab alone[27]. One intriguing aspect is the rationale behind combining antiangiogenic agents with ICI, leveraging the capacity of antiangiogenics to improve T cell circulation into tumors[28]. Preclinical models have shown that inhibiting VEGF signaling can boost anti-neoplastic immunity and improve the capability of ICI[29], while combining anti-PD-L1 with anti-VEGF has demonstrated combined effects *in vivo*[30]. In a phase II clinical investigation involving 38 OC patients, the concurrent use of nivolumab (an anti-PD1) and bevacizumab (an anti-VEGF) was evaluated[31]. The combination achieved an overall response rate (ORR) of 28.9%, with differing rates between platinum-sensitive and platinum-resistant groups (40% *vs.* 16.7%). The median

progression-free survival (PFS) was 9.4 months, with variations observed between sensitive and resistant patients (12.1 *vs.* 7.7 months). Notably, approximately 90% of participants experienced grade 3 or higher adverse events associated with the treatment. In a placebo-controlled randomized phase III trial conducted by Pignata *et al.*, involving 1,300 individuals diagnosed with stage III-IV OC, the efficacy of atezolizumab in combination with standard carboplatin-paclitaxel-bevacizumab (experimental arm) was compared to placebo and standard treatment (control arm)[32]. The results indicated that the experimental arm did not demonstrate any prognostic advantage over the control arm in terms of PFS. However, another study highlighted a favorable trend toward atezolizumab in a subset of patients with higher PD-L1 expression. Furthermore, it has been shown that the combination of ICIs with PARP inhibitors could represent a promising strategy, as tumors with anomalies in DNA repair mechanisms (specifically, homologous recombination deficiency - HRD) may evade immune control[33] [Table 1]. PARP inhibitors can induce DNA damage that may stimulate an effective immune response and restore the TME[34]. Indeed, various experiments conducted in animal models have already suggested that the combination of PARP inhibitors and ICIs can be particularly effective and ensure a more favorable prognosis for OC patients[35-37]. In Table 2, we have listed all the ongoing phase III clinical trials investigating the efficacy of ICIs in combination with PARP inhibitors and/or antiangiogenic agents in OC patients, either when combined with chemotherapy or used as maintenance therapy.

Vaccines

Numerous tumor-related antigens have been recognized in OC, including sialyl-Tn, NY-ESO-1 (also called Cancer testis antigen 1, or CTAG1B), mucin antigen 1, EGFR2/neu, amino enhancer of split protein, mesothelin, p53, mucin antigen 16/cancer antigen, folate-binding protein, human telomerase reverse transcriptase, and surviving[38-43]. These antigens could be valuable focal points for tumor vaccine development, but the molecular heterogeneity of the tumor has complicated the selection of an appropriate compound capable of eliciting a robust immunological response against tumors[44]. For instance, NY-ESO-1 emerges as one of the most intriguing targets due to its absence in healthy tissues beyond the gonad and its presence being detected in approximately 40% of tumors in a sample of 1,000 OC patients[45]. Several clinical studies have been carried out to examine the efficacy of NY-ESO-1-based vaccines, demonstrating their ability to extend patients' overall survival no later than 2 years[46,47]. Nonetheless, doubts arise regarding the enduring effectiveness of these vaccines, which aim at a self-antigen that is wrongly expressed by cancerous cells. This skepticism arises from tumors' inclination to develop escape strategies, such as losing antigens through immunoediting, thus avoiding detection by the immune system[48]. Consequently, further vaccine developments are necessary to overcome these evasion mechanisms. In particular, neoantigens emerge from DNA mutations in tumor cells and serve as a promising target for cancer vaccines because they are recognized as foreign by the immune system. Somatic mutations, which may be truncal or clonal, generate neoantigens expressed only by tumors. These antigens can trigger a robust and specific immune response against the tumor, contrasting with the weak immune response against normal body antigens[49]. Tumors with a high mutation load appear to respond better to immunotherapies, suggesting that a greater quantity of neoantigens may boost the immune system's response against the tumor[50]. However, the private nature of neoantigens complicates the development of universal vaccines[51]. Furthermore, while it was previously believed that ovarian tumors lacked a sufficient mutation load for neoantigen-based therapy, a study revealed the presence of numerous neoantigens and specific T cells in OC patients[52]. Autologous vaccines might have a pivotal role in the advancement of cancer immunotherapy[53]. An exemplification of this strategy is autologous vaccines, engineered to enhance the immune response against tumor cells while concurrently counteracting their immune evasion mechanisms. A preliminary study assessed the efficacy of this association in six patients with advanced metastatic OC resistant to chemotherapy. The combined therapy included Ipilimumab, followed by surgical intervention and the infusion of TILs that have been multiplied outside the body before, along with IL-2 and Nivolumab. The outcomes were encouraging, as

Table 1. Efficacy and toxicity of ICIs in both monotherapy and combination therapies

First author, year	Drugs	Study phase	No. of patients	Efficacy	Response rate	Toxicity*
Hamanishi *et al.*, 2015[21]	Nivolumab	II	20	Median PFS: 3.5 months (95%CI: 1.7 to 3.9 months); median OS: 20.0 months (95%CI: 7.0 months to not reached)	Two patients with durable complete responses (in the 3 mg/kg cohort) Best ORR 15.0% DCR: 45.0%	Grade 3/4 TRAEs: 40% (lymphocytopenia, anemia, albumin decreased, maculopapular rash, thyroiditis-induced fever and tachycardia)
Nishio *et al.*, 2020[22]	Pembrolizumab	II	376	NR	ORR: 8.0% (95%CI: 5.4-11.2)	All grades TRAEs: 61.9% (hyperthyroidism, hypothyroidism) Grade > 3: 23.8% (severe skin toxicity, nephritis)
Zamarin *et al.*, 2020[27]	Nivolumab *vs.* Nivolumab and Ipilimumab	II	100	Median PFS nivolumab group: 2 months, nivolumab plus ipilimumab group 3.9 months; HR for PFS (nivolumab plus ipilimumab *vs.* nivolumab alone): 0.53 (95%CI: 0.34- 0.82)	ORR within 6 months: nivolumab group: 12.2% nivolumab plus ipilimumab group: 31.4%	Grade ≥ 3 TRAEs: nivolumab group: 33% (pancreatic enzyme elevation) nivolumab plus ipilimumab group: 49% (pancreatitis, anemia, thrombocytopenia, acute kidney injury) No treatment-related deaths were reported
Liu *et al.*, 2019[31]	Nivolumab and Bevacizumab	II	38	Median PFS: 8.1 months (95%CI: 6.3-14.7 months)	ORR: 28.9% (95% exact binomial CI: 15.4%-45.9%) in platinum-sensitive participants: 40.0% (95%CI: 19.1%-64.0%) in platinum-resistant participants: 16.7% (95%CI: 3.6%-41.4%)	All grades TRAEs: 89.5% Grade > 3: 23.7% (serum lipase level increases)
Pignata *et al.*, 2023[32]	Atezolizumab *vs.* Placebo Both with Paclitaxel, Carboplatin, Bevacizumab	III	1,301	HR for OS in PD-L1-positive population: 0.83 (95%CI: 0.66-1.06; $P = 0.13$); median OS: atezolizumab not estimable; placebo 49.2 months HR for OS in ITT population: 0.92 (95%CI: 0.78-1.09), median OS: atezolizumab 50.5 months; placebo 46.6 months	Not indicated	Not indicated
Kurtz *et al.*, 2023[33]	Atezolizumab *vs.* Placebo Both with Platinum-based chemotherapy	III	614	HR for investigator-assessed PFS in the ITT population: 0.83 (95%CI: 0.69-0.99); median PFS: atezolizumab 13.5 months, placebo 11.3 months	Not indicated	Grade ≥ 3 TRAEs: atezolizumab-treated patients 13% (hypothyroidism, hyperthyroidism, hepatitis or transaminitis, colitis or severe diarrhea) placebo-treated patients 8% (hematologic)

CI: Confidence interval; DCR: disease control rate; HR: hazard ratio; ITT: intent-to-treat; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TRAE: treatment-related adverse events. *Most frequent events reported in the study.

evidenced by one patient achieving a partial response and five patients achieving disease stabilization at the 12-month mark. These outcomes were compared to those obtained without Ipilimumab, demonstrating an increase in the efficacy of *ex vivo* expanded TILs, particularly an enhancement in CD8+ T cell activity[54]. This study underscores the potential benefits of combining personalized vaccines with ICI therapies. A different individualized immunogen, Vigil,

Table 2. Ongoing phase III clinical trials of immunotherapy combined with other drugs in OC

Study, NCT	No. of patients	Treatment	Primary outcome
AGO DUO NCT03737643	1,407	Platinum-based chemotherapy plus bevacizumab ± durvalumab followed by maintenance bevacizumab ± durvalumab ± olaparib	PFS
ATHENA NCT03522246	1,000	Platinum-based chemotherapy followed by maintenance ± rucaparib in combination with ± nivolumab	PFS
FIRST NCT03602859	1,402	Carboplatin+paclitaxel plus bevacizumab in combination with ± dostarlimab followed by ± niraparib ± dostarlimab maintenance therapy	PFS
ENGOT OV 43 NCT03740165	1,367	Paclitaxel/carboplatin in combination with ± bevacizumab (investigator choice) ± pembrolizumab followed by maintenance ± bevacizumab ± pembrolizumab ± olaparib	PFS OS
NRG-GY009 NCT02839707	443	Pegylated liposomal doxorubicin hydrochlorid ± bevacizumab ± atezolizumab	DLT PFS OS
ANITA NCT03598270	414	Platinum-based chemotherapy ± atezolizumab followed by maintenance niraparib ± atezolizumab	PFS
AGO-OVAR 2.29 NCT03353831	550	Platinum-based chemotherapy plus bevacizumab in combination	OS PFS
ATALANTE NCT02891824	614	Platinum-based chemotherapy plus bevacizumab in combination with ± atezolizumab followed by maintenance bevacizumab ± atezolizumab	PFS
KEYNOTE-B96/ENGOT-ov65 NCT05116189	616	Pembrolizumab + paclitaxel ± bevacizumab and placebo comparator: placebo + paclitaxel ± bevacizumab	PFS
NCT03914612	759	Active comparator: arm I placebo, paclitaxel, carboplatin - Experimental: Arm II pembrolizumab, paclitaxel, carboplatin	PFS

www.clinicaltrials.gov. PFS: Progression-free survival; OS: overall survival; DLT: dose-limiting toxicities.

aims to instruct T cells in identifying tumor-specific clonal neoantigens, representing a logical advancement. A phase I clinical trial assessed the association of Atezolizumab and Vigil in patients with recurrent OC. The optimal timing of administration emerged as crucial, as the findings not only demonstrate promising efficacy but also underscore the treatment's safety profile. In particular, Vigil was administered first, followed by Atezolizumab. This sequence of administration was correlated with increased efficacy while also resulting in the advantage of causing fewer side effects. Median progression-free survival remained indeterminate in the Vigil-treated cohort and reached 10.8 months in the Atezolizumab-treated group (hazard ratio 0.33). These outcomes parallel prior research on Vigil, indicating potential enhanced clinical utility, particularly among BRCA wild-type patients[55]. The observed safety profile and clinical efficacy in this limited patient population underscore the necessity for additional investigation.

Oncolytic viruses

The approach with oncolytic viruses (OVs) represents an innovative perspective in the field of cancer therapy. These viruses are designed to specifically target tumor cells, sparing healthy ones, and can be genetically modified to enhance their efficacy in combating cancer[56]. Furthermore, the use of oncolytic viruses offers potential advantages over conventional therapies such as chemotherapy and radiotherapy, which can cause damage to surrounding healthy tissues and significant side effects[57]. On the other hand, OVs can be engineered to be highly selective in destroying tumor cells, while minimizing damage to healthy tissues. The combination of OVs with immunotherapy, such as ICIs, represents a promising area of research[58]. The synergistic effect of these two approaches can improve the immune response against cancer, thereby enhancing treatment efficacy. Additionally, ongoing preclinical and clinical studies are exploring further administration methods of OVs and new viral engineering strategies to optimize their antitumor activity and reduce the likelihood of developing resistance. In addition to OVs, other experimental treatments for OC include various viruses such as the reovirus, adenovirus, and others[59]. Some of these have shown antitumor activity in phase I and II studies. For example, it has been demonstrated that a herpes

simplex virus engineered to express interleukin-12 (IL-12) effectively eradicates both murine and human ovarian cancer cell lines. This treatment also regulates ovarian cancer metastases and enhances survival rates in murine models when administered directly into the omentum and peritoneal cavity[60]. The concurrent application of intratumoral Newcastle disease virus (NDV) therapy alongside anti-CTLA-4 blockade has demonstrated therapeutic efficacy in preclinical animal models. This is substantiated by observable tumor regression and enhanced survival rates[61]. Nevertheless, notwithstanding these encouraging advancements, additional clinical investigations are imperative to elucidate the precise role of OVs in OC treatment and to warrant their regulatory approval.

Adoptive T cell therapy

An alternative cellular-based strategy involves the application of Adoptive Cell Therapy (ACT) employing TILs, known as TIL-ACT[62]. This individualized immunotherapeutic approach entails harvesting autologous TILs, expanding them *ex vivo*, and subsequently reintroducing them into the patient alongside IL-2 in high dosage to augment the *in vivo* T cell-mediated antitumor response. Prior to TIL-ACT administration, a nonmyeloablative lymphodepleting chemotherapy regimen is administered, inducing transient lymphopenia and leukopenia, crucial for ensuring successful engraftment of the transferred T cells[63]. Despite extensive investigation primarily in metastatic melanoma, yielding consistent clinical responses, averaging approximately 50% overall response rates and complete responses that endure over time, seen in up to a quarter of patients, TIL-ACT application remains limited in other malignancies[64]. In the case of OC, the efficacy of TIL-ACT remains undetermined. Challenges hindering its effectiveness in this context include inefficient *ex vivo* amplification of TILs, less than ideal lymphodepletion regimen or IL-2 support, and disease-specific properties. Advances in *ex vivo* TIL expansion methods have sparked optimism, prompting ongoing clinical investigations. In an initial investigation comprising six patients who had undergone extensive prior treatments for advanced recurrent OC, infusion of 18 to 91 × 10^{-9} TILs along with IL-2 resulted in disease stabilization as the optimal response in four patients at 3 to 5 months[65]. However, disease progression mainly stemmed from the emergence of new lesions, underscoring the hurdles associated with TIL-ACT in OC patients, including intralesional heterogeneity, TIL exhaustion, or low tumor-reactive TIL frequency in the infusion[66].

CAR-T cell therapies

CAR-T cell therapies utilizing genetically engineered T cells expressing redirected TCRs or chimeric antigen receptors (CARs) have garnered significant attention. Specifically, CAR-T cells are patient-derived leukocytes genetically engineered to recognize surface antigens on tumor cells and initiate a targeted immune response[67]. Although CAR-T cell therapy has advanced in recent years and shown effectiveness in hematologic malignancies, comparable results have not been observed in solid tumors. The primary challenge lies in identifying tumor-specific antigens that are overexpressed while avoiding damage to healthy tissues[68]. In the realm of CAR-T therapy for OC, prevalent targets include mucin-16 (MUC16), folate receptor-α (FRα), and human epidermal growth factor receptor 2 (HER2)[69,70]. Noteworthy findings from Chekmasova *et al.* affirm the capacity of MUC16 CAR-T cells to significantly impede tumor progression in murine models, offering promising insights into potential therapeutic avenues[71]. FRα protein exhibits minimal expression in normal cells, particularly in OC[72]. Utilizing CAR technology to target folate receptor 1 (FOLR1, also known as FRα) has been explored as a potential strategy for OC therapy. Folate receptor 1 (FOLR1, also known as FRα) is identified as a promising target for cancer therapies due to its abnormal expression in various epithelial tumors, including OC, and its minimal expression in healthy tissues. FRα is inaccessible in normal tissues and remains unaffected by chemotherapy. In a preclinical study, high FRα expression was confirmed in primary OC samples, and CAR-T cells were engineered using plasmids encoding humanized single-chain variable fragments from clinical antibodies MORAb-003 and M9436A specific to FRα. These CAR-T cells demonstrated significant efficacy both

in vitro and *in vivo*, even under immune-suppressive conditions[73]. In both breast cancer and OC, there is notable overexpression of HER-2[74]. A study highlighted the utility of imaging of HER2 using radiolabeled pertuzumab, enabling swift and precise identification of OCs with HER2 overexpression[75]. Combining shHER2-RNA therapy and cisplatin resulted in augmented anticancer efficacy against OC by suppressing HER2[76]. Investigations into synthetic Notch CAR cells interacting with HER2 have been conducted in murine models, suggesting the potential development of clinical therapeutics involving HER2-CAR-T cells in the foreseeable future. Despite the significant prospective of CAR-T cell therapy and its achievement in blood cancers, satisfactory outcomes have not been observed in solid tumors and OC. The investigation of combining CAR-T cell therapy with other treatments is encouraged to enhance efficacy, provided it is based on sound rationale, particularly by facilitating the infiltration and persistence of immune cells within tumor.

FUTURE PERSPECTIVES

The array of immunotherapeutic options presents intriguing prospects for managing advanced recurrent OC. Specifically, Figure 1 illustrates the latest approaches to immunotherapy in treating OC, as previously discussed.

With the ongoing expansion in drug choices and combinations, there is a growing need for conceptual frameworks and rational study designs to hasten clinical progress[77]. While much headway has been made in extending survival for recurrent OC, recent successes in immunotherapy foster optimism for discovering curative treatments. Priority in clinical development should be given to frontline scenarios, where the greatest benefits are anticipated.

The emergence of PARP inhibitors, coupled with promising evidence of their synergy with ICIs in tumors with homologous recombination deficiency (HRD), underscores the potential for personalized therapy and a significant impact in frontline care. In HRD cells, PARP inhibitors block the repair of single-strand DNA breaks, leading to the accumulation of double-strand breaks that cannot be efficiently repaired. This results in synthetic lethality due to the dual impairment of DNA repair pathways. Furthermore, this genomic instability increases the load of tumor neoantigens, enhancing the potential efficacy of ICI. Investigating the combination of PARP inhibitors with PD-1/PD-L1 blockade as a frontline strategy for these patients represents a paradigm shift that could yield profound and enduring responses, potentially replacing current chemotherapy regimens. Moreover, evidence indicating that hypoxia downregulates BRCA1 and RAD51 expression, consequently affecting the HR pathway and sensitizing hypoxic cancer cells to PARP inhibitors, suggests that antiangiogenic drugs could augment the efficacy of PARP inhibitors via contextual synthetic lethality[78-81]. This may enhance the response of tumors lacking BRCA mutations to PARP inhibitors, thereby providing a rationale for combining antiangiogenic drugs, PARP inhibitors, and ICIs in this clinical setting[82,83]. Considering the synergistic potential of both antiangiogenic agents and PARP inhibitors with ICB, exploring such combinations could yield significant advances in OC cases with proficient homologous recombination, warranting investigation in frontline settings if confirmed. Consolidation strategies have long been explored in OC due to the high rate of disease recurrence following initial treatments. Immunotherapy holds promise in augmenting both the rate of curative response and the survival duration for patients who retain residual disease following initial treatment. Combining vaccines, particularly those directed against neoepitopes, with immunomodulatory agents like low-dose cyclophosphamide or ICB may offer low-toxicity treatment options. Additionally, for individuals enduring persistent disease subsequent to initial treatment, the application of ACT involving TILs or targeted T cells might emerge as a promising alternative, considering its distinctive method of administration. Beyond the aforementioned strategies, there exists a compelling rationale for investigating pharmaceutical agents directed against prevalent immunosuppressive factors in OC, whether employed singly or in combination. Immunomodulatory

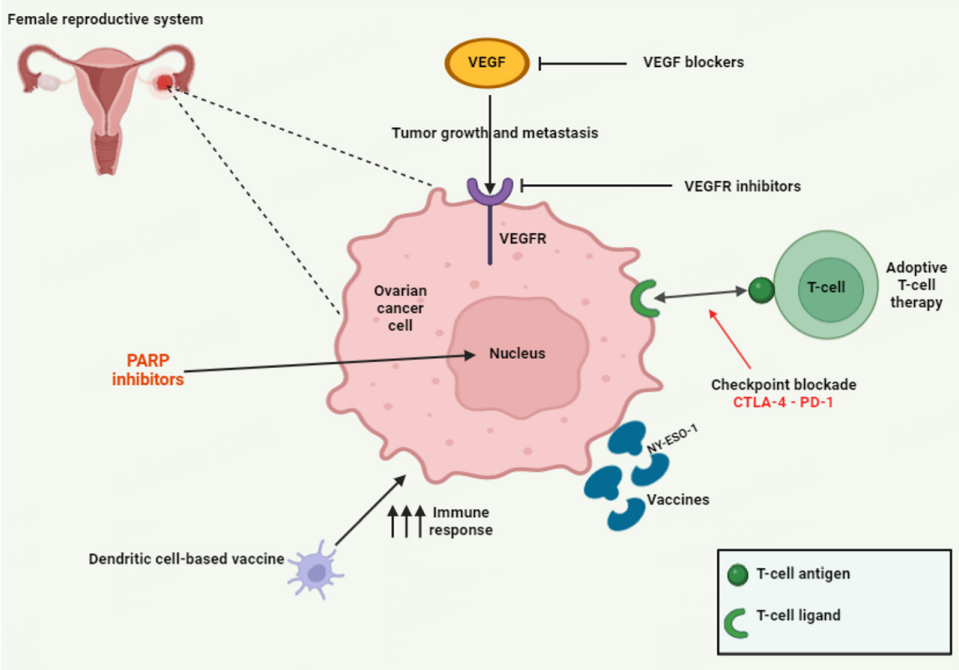

Figure 1. Mapping current immunotherapy strategies for ovarian cancer. A visual representation.

substances such as transforming growth factor-beta (TGF-β), IL-10, the adenosine pathway, indoleamine 2,3-dioxygenase-1 (IDO-1), and proinflammatory mediators like TNF-α, IL-6, M2 macrophages, myeloid-derived suppressor cells (MDSCs), and others represent promising targets for therapeutic innovation and development[84-86].

Finally, in this context, it is essential to emphasize the PI3K pathway as a novel frontier for innovative treatments in epithelial OC. This pathway is often upregulated in OC and plays a crucial role in chemoresistance and the maintenance of genomic stability, as it is implicated in various processes related to DNA replication and cell cycle regulation. Inhibiting the PI3K pathway could potentially induce genomic instability and mitotic catastrophe by reducing the activity of the spindle assembly checkpoint protein Aurora kinase B, thus promoting the occurrence of lagging chromosomes during prometaphase and enhancing the efficacy of ICI[87].

Clinical advancement should involve validating early-phase adaptive study methodologies, enabling the efficient evaluation and selection of drug candidates for combination therapies, alongside the integration of biomarkers. The latter requirement entails acquiring tumor biopsy samples, a procedure that might be partially substituted by employing molecular imaging methods and liquid biopsies. Additionally, concurrent clinical trials that assess the identical drug association in various therapeutic, neoadjuvant, and surrogate tumor environments should promptly provide essential insights to accelerate clinical advancement.

CONCLUSION

While the immune system's role in OC pathogenesis is crucial, the translation of immunotherapy into clinical practice for this cancer type has predominantly remained confined to preliminary investigations. These investigations have highlighted OC's immunogenicity and the potential of antitumor immunity activation as a viable therapeutic approach for a disease prone to recurrence. Initial endeavors explored

cytokine treatment in OC, yet failed to provide compelling data from phase III trials. Conversely, ICI has emerged as a significant immunostimulant increasingly utilized in oncology, leveraging OC's immunological attributes for therapeutic intervention. Nevertheless, ICI monotherapy has demonstrated modest efficacy in pre-treated ovarian cancer patients, prompting the exploration of combination therapies to improve outcomes. Consequently, various strategies have been developed to sensitize OC to immunotherapy through combination with chemotherapy, antiangiogenics, PARP inhibitors, radiotherapy, and dual ICI. A primary concern remains the identification of optimal prognostic markers to enhance candidate selection for ICI regimen.

A deeper understanding of underlying biological mechanisms, alongside ongoing technological advancements, is imperative to expand the scope of immune therapies and achieve meaningful advancements in clinical outcomes for OC patients.

DECLARATIONS

Authors' contributions

Conceptualization, writing - original draft, methodology, supervision, validation: Capuozzo M
Conceptualization, writing - original draft: Ferrara F
Writing - original draft: Cinque C
Writing - review & editing: Farace S
Supervision, validation: Lauritano D
Conceptualization, writing - original draft: Ottaiano A

Availability of data and materials

Full availability of data and materials. All stated data can be provided to the reader upon request.

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Consent for publication

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