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Nanotechnology for boosting ovarian cancer immunotherapy

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Abstract

Ovarian cancer, often referred to as the "silent killer," is notoriously difficult to detect in its early stages, leading to a poor prognosis for many patients. Diagnosis is often delayed until the cancer has advanced, primarily due to its ambiguous and frequently occurring clinical symptoms. Ovarian cancer leads to more deaths than any other cancer of the female reproductive system. The main reasons for the high mortality rates include delayed diagnosis and resistance to treatment. As a result, there is an urgent need for improved diagnostic and treatment options for ovarian cancer. The standard treatments typically involve debulking surgery along with platinum-based chemotherapies. Among patients with advanced-stage cancer who initially respond to current therapies, 50-75% experience a recurrence. Recently, immunotherapy-based approaches to enhance the body's immune response to combat tumor growth have shown promise. Immune checkpoint inhibitors have shown promising results in treating other types of tumors. However, in ovarian cancer, only a few of these inhibitors have been effective because the tumor's environment suppresses the immune system and creates barriers for treatment. This hampers the effectiveness of existing immunotherapies. Nonetheless, advanced immunotherapy techniques and delivery systems based on nanotechnology hold promise for overcoming these challenges.

Keywords Adoptive cell therapy, Immune checkpoint blockade, Chimeric antigen receptor T-cell therapy, Clinical trials, Ovarian cancer, Photodynamic therapy, Photothermal therapy, Myeloid-derived suppressor cells, Tumor-associated macrophages, Regulatory T cells

Introduction

Ovarian cancer (OC) is a significant health concern, particularly in developed countries, where it is the leading cause of death among gynecological malignancies. It is estimated that around 19, 710 new cases of OC were diagnosed in the United States in 2023 [1]. The primary treatment approaches involve surgery and chemotherapy. Unfortunately, many patients experience a recurrence of the cancer, often developing resistance to chemotherapy within a few years of their initial treatment. While there have been recent advancements in understanding the underlying biology and molecular characteristics of OC, the prognosis for women with this disease remains poor due to the high incidence of recurrence and treatment resistance. The development of chemoresistant disease leads to recurrence within 16–22 months and a low 5-year survival rate of approximately 27%. More than one-third of OC patients present with malignant ascites at diagnosis, and the development of ascites is a crucial aspect of chemoresistant and recurrent disease. The asymptomatic nature of early-stage OC often leads

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to late diagnosis, typically at a metastatic stage, significantly reducing the chances of successful treatment outcomes [2]. Despite improvements in screening methods, high mortality rates associated with OC persist due to the lack of routine early detection approaches. Based on its histological features, ovarian cancer is classified into high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometroid carcinoma (EC), clear cell carcinoma (CCC), and mucinous carcinoma (MC). HGSC, which accounts for approximately 70% of ovarian cancer cases, is the most aggressive type of ovarian cancer [3].

In recent years, there have been incredible strides in the field of immunotherapy, completely transforming how we approach and treat different types of cancer. The effectiveness of immunotherapy hinges on specific physiological and physical processes known as transport barriers. These processes include activating T cells by antigen-presenting cells, migrating T cells into the tumor microenvironment, and moving nutrients and immune cells within the tumor. Immunotherapy has revolutionized cancer treatment, significantly improving survival rates for individuals with melanoma and lung cancer. However, its effectiveness in treating ovarian cancer has been limited due to the cold tumor immune microenvironment (TIME) [4]. Immune therapy, especially immune checkpoint inhibitors (ICIs), has radically changed cancer treatment and is now integrated into the management of many solid tumors, such as endometrial, cervical, melanoma, lung, head and neck, kidney, and urothelial cancers, triple-negative breast cancer, and microsatellite unstable tumors. Nevertheless, its use as a single agent or in combination with ovarian cancer has been quite disappointing, and there is currently no approved immune therapy strategy for the treatment of this malignancy.

In recent years, there have been significant advancements in OC treatment, especially in developing innovative drug delivery techniques. These methods aim to enhance the effectiveness of cancer treatments while minimizing adverse side effects. Nanotechnology plays a vital role in targeted therapy, allowing for direct interaction with cancer cells by binding to specific cell surface receptors, especially angiogenic endothelial cell surface receptors. This innovative approach aims to increase the concentration of drugs within cancer cells, thereby enhancing drug solubility, stability, and duration in the body [5].The term "nano vehicles for drug delivery" pertains to the use of tiny particles, typically ranging from 1 to 100 nanometers in size, to transport therapeutic agents such as drugs to specific locations in the body. As part of a targeted approach, these nano vehicles can be tailored to target specific cells or tissues. This improves drug effectiveness and reduces toxicity and adverse effects. An intriguing medical trend involves advancing targeted drug delivery systems, including nanoparticles (NPs) and liposomes (Fig. 1). These systems are designed to deliver drugs directly to cancer cells while minimizing damage to healthy tissue. Liposomes are small spherical vesicles with a unique structure, comprising a double layer of phospholipids enclosing a central aqueous compartment.

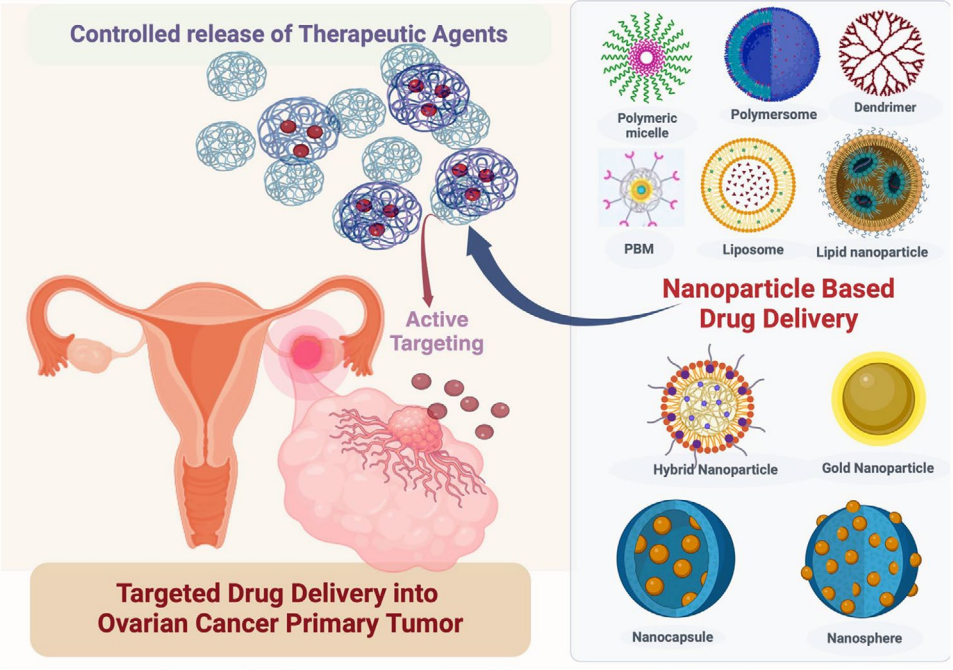

Fig. 1 Nanomedicine in cancer therapy: Various drug delivery systems for targeted drug delivery are employed in ovarian cancer

This structure makes them well-suited for encapsulating drugs that do not dissolve easily in water, making liposomes excellent for delivering such medications [6]. Dendrimers form a distinct class of polymers with a branched three-dimensional structure, providing high adaptability. They are NPs with an unimolecular micellar structure featuring a hydrophobic core and a hydrophilic outer layer. Similarly, polymeric micelles are characterized by their amphiphilic properties and can encapsulate hydrophobic drugs, making them suitable for drug delivery [7]. Furthermore, planetary ball milling nanoparticles (PBM-NPs) with folic acid attached to the surface can encapsulate drugs and effectively target cancer cells, addressing chemoresistance in ovarian cancer [8, 9]. This review will provide an in-depth analysis of various approaches to ovarian cancer immunotherapy, including the research and clinical evidence supporting immune checkpoint inhibitors and genetically modified T-cell therapies, either monotherapy or combined with chemotherapy and other targeted treatments. Furthermore, the review will explore the potential of nanotechnologies in improving the effectiveness of ovarian cancer immunotherapy.

Strategies for ovarian cancer immunotherapy

Nanotechnology-based approaches show great potential in addressing these transport barriers and enhancing the effectiveness of various cancer immunotherapies. Recent interest in immunotherapy for ovarian cancer treatment has surged, especially after studies demonstrated the positive impact of intra-tumoral (IT) T cells, particularly CD8+T cells, on the clinical outcomes and survival of treatment-naïve OC patients. Recent studies found that patients with IT T cells had a 5-year survival rate of 38%, whereas patients without IT T cells had a significantly lower rate of 4.5%. These findings underscore the significant role of IT T cells in OC. However, despite their importance, the anti-tumor responses of IT T cells are often impeded by various obstacles, with immune checkpoints being a major hindrance [10].

DC vaccines

Dendritic cells (DCs) are widely recognized as essential components of the immune system, playing a key role in initiating immune responses against tumors [11]. Harnessing the potential of DCs as a cancer vaccine to stimulate T cells to target tumor-specific antigens (TSA) has been a long-standing concept. The first pilot study of DC vaccination took place in 1996, involving four follicular B cell lymphoma patients who received personalized DCs loaded with tumor antigens. All patients exhibited positive responses, with some showing complete or partial regression of their tumors. This success has led to extensive research into the use of DC vaccines in various types of cancer, with over 400 clinical trials registered as of August 15, 2022. Results from completed studies have demonstrated that DC vaccines are generally well-tolerated, leading to favorable outcomes in a subset of patients [12]. This section evaluates the promise of DC vaccines in the context of advanced ovarian cancer treatment, leveraging findings from nanotechnology research to enhance therapeutic approaches.

A new type of nano vaccine called “mini-DC” has been created using biomimetic nanotechnology, which involves coating the vaccine with cell membranes derived from DCs. This innovative nano vaccine inherits the antigen presentation and T-cell stimulation abilities of DCs. In laboratory and animal studies, mini-DC has significantly enhanced T-cell activation. When tested in a mouse model of ovarian cancer, mini DCs demonstrated remarkable effectiveness in both treating and preventing cancer. They were found to slow down tumor growth and reduce the spread of cancer cells, outperforming traditional DC vaccines [11]. These results indicate that mini DCs could be a simple yet powerful option for enhancing cancer immunotherapy.

Moreover, the Th17-DC vaccines increased the presence of Th17 T-cells in the tumor microenvironment and positively impacted the myeloid microenvironment. Compared to conventional dendritic cell (CDC) vaccines, the Th17-DC vaccines were associated with improved survival rates in mice. While immune checkpoint blockade (ICB) showed limited effectiveness in OC, the use of Th17-inducing DC vaccination made the cancer more responsive to anti-PD-1 ICB. This led to long-lasting progression-free survival (PFS) by overcoming resistance mediated by *IL-10*. The effectiveness of Th17-DC vaccines, whether used alone or in combination with ICB, was attributed to CD4 T cells rather than CD8 T cells [13].

Cutting-edge research is uncovering the potential of using nanotechnology to enhance immunotherapies. Biocompatible, degradable polymers such as poly(lactic-co-glycolic acid) (PLGA) can be utilized to create particulate delivery systems. These systems can potentially address various challenges encountered during the transfer of antigens to DC. In DC-based cancer vaccines, encapsulating tumor cell lysates in PLGA nanoparticles has been shown to induce a specific Th1/inflammatory cytokine response from autologous CD8+T cells, making them a promising candidate for delivering tumor-associated antigens (TAA) [14]. This method of antigen loading has demonstrated the ability to stimulate in vitro anti-tumor CD8+responses by dendritic cells, which could be crucial in overcoming tumor tolerance associated with ovarian cancer recurrence and metastasis. These findings provide hope for potential clinical applications in OC treatment.

One study demonstrated the reprogramming of tumor-associated dendritic cells in vivo and the processing of NPs containing oligonucleotide duplexes that mimic the bulged structure of endogenous pre-miRNA. This manipulation significantly boosted the activity of miR-155, leading to widespread changes in gene expression and the suppression of multiple immune-inhibitory molecules [15]. The study highlighted how ovarian cancer-associated dendritic cells naturally exhibit increased endocytic activity, which can be leveraged to boost the immune-stimulating effects of miR-155.

Peptide/antigenic vaccines

Research on cancer immunotherapy has revealed promising new strategies for combating the disease. One particularly promising avenue involves the development of vaccines that can target localized and metastatic tumor cells. Unlike passive immunotherapy, which has shown limited long-term effectiveness using monoclonal antibodies, active cancer immunotherapy focuses on stimulating or enhancing the body's natural immune responses against tumor-associated antigens or tumor-specific antigens. These vaccines, which are based on primary proteins expressed in cancerous cells, have the potential to trigger robust and enduring immune memory responses. Peptide-based vaccines have emerged as a powerful form of neoadjuvant immunotherapy capable of directly targeting proteins expressed in tumor cells while being safe to produce and administer. Peptide cancer vaccines may be most effective in patients with a lower disease burden when the body's tolerance to cancer is minimized. Peptide vaccines offer a compelling alternative to whole protein vaccines by leveraging short peptides to trigger specific immune responses. They contain only the crucial immunogenic region, minimizing the risk of cross-reactions and associated adverse effects. Additionally, peptide vaccines show immense potential as cancer treatments, given their stability and non-toxic nature.

In a phase 1 clinical trial, patients with specific human leukocyte antigen (HLA) types and epithelial ovarian, fallopian tube, or primary peritoneal carcinoma were given a combination of synthetic peptides derived from ovarian cancer-associated proteins. The vaccine-related side effects were generally mild, the most common being injection site reactions, fatigue, and headache. T-cell responses to the peptides were evaluated, and CD8 T-cell responses were observed in many participants. Notably, all four *HLA-A2* and *HLA-A3*-restricted peptides were found to be immunogenic, including two peptides that were being evaluated in human vaccines for the first time: folate binding protein (FBP191-199) and *Her-2/neu*754-762 [16]. Furthermore, the E39 and granulocyte macrophage-colony stimulating factor (GM-CSF) combination therapy is currently being tested in a phase I/IIa trial for preventing recurrence in OC patients at high risk of relapse following standard care therapy. Based on the final 24-month landmark analysis results, the treatment has demonstrated both safety and effectiveness when administered at an optimal dose of 1000 μg to patients with low folate-binding protein (FBP) levels. E39, a peptide derived from FBP, is specific to *HLA-A2*, making it immunogenic. FBP is known to be widely expressed in various cancers and is considered an ideal target for this vaccine due to its high expression in malignant cells and rarity in normal tissues. The immune system can easily recognize FBP, and when presented by dendritic cells, FBP triggers the release of tumor-specific cytokines and cytolysis [17]. Another study evaluated the safety and immune response generated by a multi-epitope folate receptor alpha (FRα) peptide vaccine. The vaccine, which contained FR30, FR56, FR76, and two other components, along with GM-CSF, was administered to patients with stage II-IV ovarian, primary peritoneal, or fallopian tube cancer. These participants had completed systemic therapy at least 90 days prior and showed no evidence of disease. The study findings suggest the vaccine can boost immunity against the folate receptor (FR) tumor antigen. Furthermore, the results indicate that the vaccine could benefit most patients with FR-expressing tumors, regardless of their HLA genotype. This study reported that the vaccination was well-tolerated, with no significant adverse effects of grade≥3 observed. Additionally, over 90% of the patients exhibited enhanced or induced immunity following the vaccination [18].

Moreover, CT (cancer-testis) antigens are a promising target for immunotherapy due to their high expression in adult male germ cells, low expression in normal tissues, and variable expression in cancer cells [19]. A study identified NY-ESO-1 as a potential target for immunotherapy in epithelial ovarian cancer (EOC), and its expression was found in 40.7% of tumors in a group of 1002 patients. It was most commonly found in older and higher-stage patients (85% stage III/IV). The study concluded that the high expression of NY-ESO-1 is associated with poor clinical outcomes, highlighting the need for targeted therapy against this antigen [20]. In the phase I clinical trial, 18 OC patients with minimal disease burden were immunized with ESO(157–170) mixed with incomplete Freund's adjuvant. This resulted in specific immune responses in a high proportion of patients, without causing serious vaccine-related adverse events. The vaccine-induced T cells were able to recognize tumor targets expressing NY-ESO-1 [21].

The advancements in nanotechnology have led to the formation of various NPs with unique characteristics [22]. These NPs have been tailored to tackle the obstacles related to cancer immunotherapy. Cancer vaccines targeted at neoantigens hold the potential to stimulate and

diversify the T-cell response against tumors. Nevertheless, these vaccines have shown limited success due to the weak immune response to peptide antigens. To address this challenge, scientists have devised a technique to bolster the innate immune response by combining cGAMP and monophosphoryl lipid A (MPLA) within a specialized nanocarrier [23]. This formulation has been shown to boost the expression of *CD86* and the secretion of key pro-inflammatory cytokines such as *IFN-β* and *IL-6*. Studies have demonstrated that delivering synergistic adjuvants, along with peptide neoantigens, using a pH-responsive nanoparticle platform can lead to increased activation of dendritic cells and improved presentation of peptide antigens on MHC-I, potentially enhancing the body's CD8+T cell responses.

Adoptive cell therapy (ACT)

Adoptive cell therapy (ACT) stands at the forefront of cancer treatment, representing a groundbreaking approach that leverages the body's immune system. This innovative method involves extracting specific immune cells, like T-cells, from either the patient's own body or a donor's through leukapheresis, and then culturing and activating ex vivo to bolster their ability to identify and combat cancer cells (Fig. 2). Subsequently, these modified cells are reintroduced into the patient's body with recombinant interleukin-2 (rIL-2) after lymphodepleting chemotherapy. Recent studies by the National Cancer Institute (NCI) showcased the promising potential of T-cell immunotherapy in eliminating solid tumors. These studies involved the adoptive transfer of in vitro selected tumor-infiltrating lymphocytes (TILs) (Fig. 2). However, isolating and manufacturing TILs is quite complex and has only proven successful in certain patients. The use of TILs in adoptive cell therapy has not been extensively studied. In a recent preclinical study, scientists examined the effectiveness of ACT using expanded TILs from ovarian cancer tumors. The study successfully established minimally expanded TILs (Young TILs) from ovarian cancer patients that showed a high frequency of CD3+cells with varying CD4/CD8 ratios [24]. These findings suggest ovarian cancer patients may benefit from ACT in future clinical trials.

In a preliminary study, researchers found that combining TIL therapy with a decrescendo *IL-2* regimen in patients with advanced ovarian cancer was possible with manageable side effects. They observed clinical signs of treatment benefits and suggested combining therapies to target immune checkpoint inhibition could enhance clinical effectiveness [25]. Recently, the investigators completed a clinical trial (NCT03287674) of T-cell therapy combined with checkpoint inhibitors for patients with metastatic ovarian cancer. The treatment regimen included Ipilimumab, Cyclophosphamide, Fludarabine, Nivolumab, TILs, and *IL-2*. TILs were extracted from the patient's tumor tissue, expanded, and activated in vitro for 4–6 weeks before being infused back into the patients. Prior to TIL infusion, patients underwent a week of

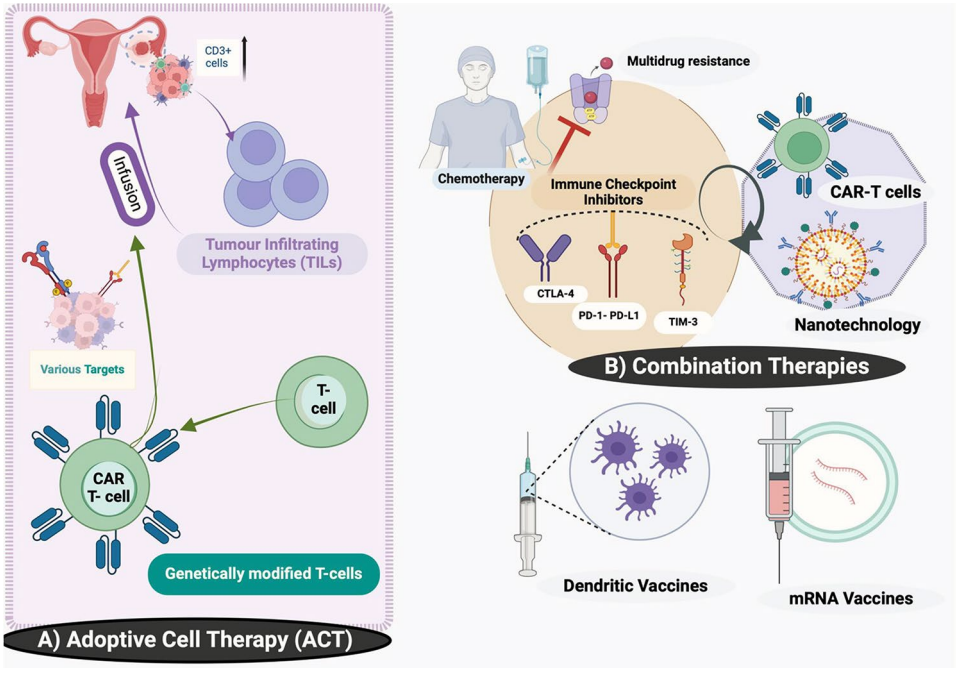

Fig. 2 (**A**) Adoptive immunotherapy using autologous young TILs and T-cells for ovarian cancer; (**B**) Combination of immunotherapy strategies (immune checkpoint blockade inhibitors and immunotherapeutic vaccines) with innovative targeted therapies (CAR-T cells, nanotechnology) to evade multidrug resistance in ovarian cancer

preconditioning chemotherapy with cyclophosphamide and fludarabine. Following TIL infusion, Interleukin-2 was administered to aid T cell activation and proliferation in vivo. Unlike other forms of immunotherapy, such as vaccines, ACT allows for the precise selection and expansion of immune cells, leading to a more robust and targeted immune response against the tumor. However, acquiring sufficient tumor-specific immune cells is a key obstacle in implementing ACT. To tackle this challenge, researchers are delving into genetic modifications, such as T-cell receptors (TCRs) and chimeric antigen receptors (CARs), to augment the therapy's efficacy.

Immune checkpoint blockade

Over the past two decades, immunotherapy advances have transformed how we approach the treatment of various cancers. In ovarian cancer, successful immunotherapy hinges on stimulating antigen-presenting cells, reducing the immunosuppressive environment, and enhancing the activity of effector T cells. Inhibitory and stimulatory signals regulate the immune response mediated by T cells. Immune checkpoint receptors play a crucial role in regulating T cell activation. However, the expression of immune checkpoints in various tumors can lead to immune evasion. Therefore, immune checkpoint blockade inhibitors are a pivotal aspect of immunotherapy, with the potential to significantly enhance antitumoral immunity in patients with ovarian cancer [26].

However, in the tumor microenvironment, they substantially suppress the magnitude, quality, and duration of immune responses. Several molecules, such as PD-1, *CTLA-4*, *LAG-3*, and *TIM-3*, are involved in immune checkpoints. The latest focus of cancer research lies in immune checkpoint inhibitors, particularly *CTLA-4* and PD-1/PD-L1 inhibitors, which have shown promise in reversing signals from the immunosuppressive tumor microenvironment [27]. In ovarian cancer, the PD-1/PD-L1 pathway is the most extensively studied immune checkpoint target. PD-1, also expressed in T cells, regulates the activation of effector T cells, primarily in the peripheral tissue and the tumor microenvironment. By binding with its ligands, PD-L1 or PD-L2, PD-1 is phosphorylated, recruiting an inhibitory phosphatase that can rapidly dephosphorylate *CD28* and inhibit the co-stimulatory signaling pathway. An antibody targeting PD-1 can counteract its inhibitory effects.

The use of immune checkpoint inhibitors, such as nivolumab, a type of human programmed death receptor 1 (PD-1)–blocking monoclonal antibody, has shown significant improvements in the treatment outcomes for several types of solid tumors, including non–small cell lung cancer and melanoma. However, combining immunotherapy with traditional chemotherapy for newly diagnosed ovarian cancer has not shown significant benefits thus far. A phase III clinical trial did not support the use of ICIs in newly diagnosed OC, highlighting biological and molecular differences between different tumor types. In the IMagyn050 randomized phase III clinical trial, combining atezolizumab with bevacizumab and chemotherapy did not show improvement in OC efficacy. The median PFS was 20.2 months with a placebo, but it was not reached in atezolizumab-treated patients; the IMagyn050 randomized phase III clinical trial demonstrated that the addition of atezolizumab to bevacizumab and chemotherapy did not lead to improved efficacy in treating ovarian cancer. Although the median PFS was not reached in atezolizumab-treated patients, the placebo group had a PFS of 20.2 months, showcasing an early and sustained separation [28]. Another clinical trial, ATALANTE/ENGOT-ov29, enrolled patients with recurrent EOC, including those with 38% PD-L1-positive tumors. The study involved providing atezolizumab or a placebo for up to 24 months in combination with bevacizumab. After a median follow-up of 3 years, there was no significant difference in PFS between the atezolizumab and placebo groups for the overall study population and the PD-L1-positive subgroup. Furthermore, the preliminary overall survival (OS) analysis showed a hazard ratio of 0.81. It's worth noting that a high percentage of patients in both groups experienced grade ≥ 3 adverse events (AEs), with 88% of atezolizumab-treated patients and 87% of placebo-treated patients being affected [29].

A recent international, randomized, double-blind, phase III clinical trial named ATHENA demonstrated that immune checkpoint inhibitors used as monotherapy are highly effective in treating ovarian cancer. The trial consisted of two independent comparisons: the assessment of rucaparib as monotherapy (ATHENA–MONO) and the evaluation of rucaparib combined with nivolumab (ATHENA–COMBO). Both treatment regimens were investigated as maintenance therapies following a positive response to frontline treatment (comprised of surgery and platinum-based chemotherapy) in newly diagnosed OC patients [30]. Additionally, a recent study indicated that rucaparib monotherapy is particularly effective as a first-line maintenance treatment, showing significant benefits compared to a placebo for patients with advanced ovarian cancer, regardless of their homologous recombination deficiency (HRD) status. The results of this phase III clinical trial demonstrated that rucaparib led to a median PFS of 28.7 months compared to 11.3 months with a placebo in the HRD population [31]. Understanding the tumor microenvironment and the impact of immune cells infiltrating the tumor on patient prognosis has driven significant progress in cancer immunotherapy. However, effectively applying this knowledge to treat ovarian cancer has been challenging.

Research has demonstrated that the dual inhibition of PD-L1 and PD-L2 is more effective in cancers expressing both PD-L2 and PD-L1, including ovarian cancer, than anti–PD–1 or PD-L1 monotherapy [2]. A relatively low incidence (~8%) of PD-L1 expression has been reported for ovarian cancer patients. However, the correlation between PD-L1 expression and response to ICIs in patients with ovarian cancer is still uncertain, as clinical trials have shown conflicting data. Exosomes expressing PD-L1 have been identified as suppressing anti-tumor immune responses. Understanding the role of exosomal PD-L1 in immune-oncology is crucial, as inhibiting exosome production may be an exploitable strategy for potential new therapies. Additionally, the receptor ligands CD80/86 expressed on the surface of antigen-presenting cells act as ligands for the co-stimulatory receptor *CD28* and the inhibitory receptor *CTLA-4*, both of which are expressed on CD4+and CD8+T-cells, mediating opposing immunoregulatory functions. While CD80/86 interaction with *CD28* induces T-cell stimulation, it inhibits T-cell responses in the presence of *CTLA-4*. Although the mechanisms involved are not fully understood, it is believed that *CTLA-4* competes with *CD28* for ligand binding [32]. Dual checkpoint inhibition targeting PD-1 (nivolumab) and *CTLA-4* (ipilimumab) has shown enhanced antitumor activity compared to PD-1 inhibition monotherapy. In a randomized phase II clinical trial, the addition of ipilimumab to nivolumab in treating epithelial ovarian cancer led to a higher response rate and improved PFS compared to using nivolumab alone while still managing toxicities effectively [33]. Nemvaleukin alfa, also known as ALKS 4230, is a promising cytokine designed to maximize the therapeutic benefits of *IL-2* while minimizing its associated toxicity. By selectively activating the intermediate-affinity *IL-2* receptor, this treatment aims to boost the expansion of memory CD8+T cells and natural killer cells while minimizing the impact on CD4+regulatory T cells. The ongoing global phase III open-label and randomized clinical trial, known as the ARTISTRY-7 trial, seeks to evaluate a new combination of nemvaleukin and pembrolizumab compared to chemotherapy in patients with platinum-resistant ovarian cancer [34].

Additionally, the intricate interplay between miRNAs and immune checkpoints, specifically PD-1/PD-L1 and *CTLA-4* pathways, is significantly involved in shaping the strategies for cancer immunotherapy. Recent research has identified the up-regulation of *FGD5-AS1* in ovarian cancer, which is associated with positive local lymph node metastasis and higher T stage in patients. Furthermore, it has been observed that *FGD5-AS1* negatively regulates miR-142-5p, which in turn positively regulates the expression of PD-L1 [35]. This study suggests that the *FGD5-AS1*/miR-142-5p/PD-L1 axis plays a critical role in regulating ovarian cancer progression. Moreover, studies have highlighted the involvement of PD-L1 in the chemoresistance of ovarian cancer. In vivo studies have reported that the miR-34a-5p/PD-L1 axis regulates chemoresistance in ovarian cancer cells, providing valuable insights for treating this cancer type [36].

Over the past two decades, research on immune checkpoint inhibitors has raised numerous questions about their application in cancer treatment. One major challenge is achieving long-lasting responses in advanced cancer cases while reducing the adverse effects of these inhibitors. Recent studies propose that incorporating nanoparticle delivery systems into immunotherapy may increase the targeted delivery and persistence of antibodies in specific cells. Encapsulating immune checkpoint inhibitors in NPs may improve immunotherapy's effectiveness and mitigate off-target effects [37]. Moreover, using nanotechnology to precisely deliver immune-boosting chemokines and immune checkpoint inhibitors to tumor sites can potentially transform the immune-suppressive tumor microenvironment for cancer treatment [38]. This approach holds great promise as a form of immunogene therapy in clinical settings.

Further, researchers utilized Folic acid (FA)-functionalized polyethyleneimine (PEI) polymers to inhibit PD-1/PD-L1 interactions. This was achieved by delivering PD-L1 siRNA to epithelial ovarian cancer cells [39]. The authors targeted PD-L1, prevalent in healthy organs like the placenta and eyes, to deliver siRNA to epithelial cancer tissues. Using polymer/siRNA nanocomplexes, researchers observed improved T-cell immunotherapy for EOC-inhibiting PD-L1 on SKOV-3 cells. The alteration with FA or PEG-FA reduced PD-L1 expression by 40-50% and boosted tumor cell uptake. This investigation suggests that nanoplatforms can serve as an effective method for drug delivery, thereby enhancing the immune response against cancer and impacting ovarian cells directly or indirectly [2].

As immune checkpoint inhibitors have shown limited success, researchers are now exploring novel approaches for treating ovarian cancer (Fig. 2), monotherapy or combined with chemotherapy. One particularly promising approach is the combination of these inhibitors with targeted therapies and innovative immunotherapy strategies (Table 1).

Chimeric antigen receptor T-cell (CAR-T) therapies

CAR-T therapy, known as chimeric antigen receptor T cell therapy, is gaining significant attention as a type of adoptive cellular immunotherapy designed to target tumors specifically. These therapies involve using synthetic receptors known as chimeric antigen receptors to target T cells with specific antigens on the surface of cancer cells. By genetically modifying a patient's T cells to

Table 1 Active/ recruiting clinical trials in ovarian cancer patients with different types of therapies

Clinical trial registration number	Study design	Intervention/ Treatment	Type of therapy	Type of ovarian cancer/ Patients
NCT03602586 (Phase II)	Single group assignment and open label	Combination of epacadostat and pembrolizumab	Monoclonal antibody and IDO1 inhibitor	Clear cell carcinoma
NCT03249142; GINECO-OV127b (Phase I - II)	Randomized, open label, comparative, multi-center	Combination of durvalumab, tremelimumab with standard carboplatin-paclitaxel chemotherapy	*CTLA-4* / PDL-1 Immunotherapy	Fallopian tube or primary peritoneal adenocarcinoma
NCT02571725; INST 1419 (Phase I – II)	-	Combination of olaparib and tremelimumab	PARP-inhibition and *CTLA-4* Blockade	Patients with BRCA mutation-associated OC
NCT02785250; (Phase Ib/II)	-	DPX-Survivac and cyclophosphamide with or without epacadostat	Immunotherapeutic Vaccine (T cell activating therapy and IDO1 inhibitor)	Patients with recurrent OC
NCT02650986 (Phase I/IIa)	Non-randomized and open label	Cyclophosphamide and TGFbdnRII	TGFβ Blockade in TCR-Engineered T-cell cancer Immunotherapy	Patients with malignancies expressing NY-ESO-1
NCT04034927 (Phase II)	Randomized and open label	Olaparib with or without tremelimumab	PARP-inhibition and *CTLA-4* Blockade	Patients with ovarian, fallopian tube, or peritoneal cancer
NCT05397093 (Phase Ia/Ib)	Multicenter	ITIL-306-201	TIL cell therapy targeting folate receptor α	Epithelial ovarian cancer
NCT03836352 (Phase II)	Open label and multicenter	Combination therapy of DPX-Survivac, cyclophosphamide, and pembrolizumab	Immunotherapeutic Vaccine	Patients with Recurrent Ovarian Cancer
NCT03761914 (Phase I/II)	Open label, non-comparative, and multicenter	Combination of galinpepimut-S and pembrolizumab	Peptide immunotherapeutic vaccine and PD1 inhibitor	Patients with advanced ovarian cancer
NCT00799110 (Phase II)	-	GM-CSF and Imiquimod	Dendritic Cell/Tumor Fusion Vaccine	Patients with ovarian, fallopian tube, or primary peritoneal cancer
NCT05963100 (Phase I/II)	-	TCR-like CAR-T Cells	Modified Immune cells (chimeric antigen receptor T cells)	MSLN-positive OC patients
NCT03907527 (Phase I/Ib)	-	PRGN-3005 UltraCAR-T cells	Autologous chimeric antigen receptor T cells	Patients with advanced-stage platinum-resistant OC
NCT05211557 (Phase I)	Open-label, Non-randomized, and Single center	fhB7H3.CAR-T cells	Fully human scFv-armed B7H3 targeting chimeric antigen receptor T cells	Patients with recurrent advanced OC
NCT05225363 (Phase I)	-	TAG72- CAR T cells	Modified Immune cells (chimeric antigen receptor T cells)	Platinum-resistant patients with epithelial OC
NCT03522246 (Phase III)	Randomized, double-blind, and multicenter	Rucaparib and Nivolumab	Immune checkpoint inhibitors	Front-line treatment in newly diagnosed OC patients
NCT05116189 (Phase III)	Randomized, and double-blind study	Pembrolizumab plus paclitaxel with or without bevacizumab and placebo plus paclitaxel with or without bevacizumab	Immune checkpoint inhibitors	Platinum-resistant recurrent OC patients
NCT02346747 (Phase IIb)	Randomized, multi-center, double-blind, and placebo-controlled study	Vigil (Gemogenovatucel-T)	Autologous tumour cell vaccine	Maintenance in frontline stage with III/IV high-grade serous, endometrioid, or clear cell OC patients

express these synthetic receptors, the therapy enhances the T cells' ability to precisely target and attack cancerous cells, leading to improved treatment precision and effectiveness. Ovarian tumors often lack TSA, so immunotherapy typically targets one or more tumor-associated antigens. However, tumor cells may evade this therapy by losing or downregulating antigen expression, a phenomenon known as antigen escape. Therefore, careful consideration is needed to minimize potential toxicity to non-cancerous cells due to target antigen expression.

For ovarian cancer, CAR-T therapy targets a range of antigens including erb-b2 receptor tyrosine kinase 2 (*ERBB2*), programmed cell death-ligand 1 (PD-L1), programmed cell death 1 (PD-1), epithelial cell adhesion molecule (Ep-CAM), anti-Müllerian hormone receptor type 2 (*AMHR2*), annexin A2 (*ANXA2*), trophoblast glycoprotein (*TPBG*), mesothelin (*MSLN*), mucin

16 (*MUC16*), and *CD24*. Folate receptor alpha (FRα) is another important target, as it is highly expressed in EOC [40].

ERBB2 amplification is frequently found in gynecologic malignancies, particularly in high-risk endometrial histologic subtypes such as serous carcinoma, carcinosarcoma, and mucinous ovarian carcinoma. The prevalence of *ERBB2/HER2* amplifications and overexpression in ovarian cancer can vary, and patients have shown poor responses to *ERBB2/HER2* inhibitors. Therefore, there is a need to develop treatments that target recurrent disease and enhance sensitivity to *ERBB2/HER2*-targeted therapy. Among 6961 patients, the highest incidence of *ERBB2* amplification (14.4%) was observed in mucinous ovarian carcinoma. In contrast, lower incidences were noted in patients with ovarian clear cell, endometrioid, low-grade, and high-grade serous ovarian carcinoma [41]. Approximately 75% of ovarian cancer patients experience relapse and/or develop chemo-resistant disease after initially responding to platinum-based therapies. In a patient-derived xenograft OC study, *HER2*-targeted therapy, when combined with chemotherapy, led to significant regression of tumor growth after 6 weeks of treatment compared to monotherapy [42].

Mesothelin, a cell surface glycoprotein, is known for its ability to bind to CA-125 and is prominently present in OC, particularly in serous subtypes. It is a compelling target for immunotherapies due to its high expression in about 30% of OC [43]. While mesothelin is also found in normal human tissues, its lower nonspecific toxicity has led researchers to develop various therapeutic approaches to target it. These approaches include antitoxins, antibody-based therapy, cancer vaccines, and adoptive T-cell therapy. However, *MSLN* CAR T cells face challenges in the solid-tumor microenvironment that may limit their antitumor effectiveness. To address this, numerous strategies are being evaluated to optimize the efficiency of CAR T cells, such as taming the host tumor microenvironment or creating "armored" CAR T cells capable of overcoming immune barriers. Both preclinical and clinical studies have shown promising antitumor effects, positioning mesothelin as a potential therapeutic target. Furthermore, the presence of mesothelin can aid in distinguishing between primary and metastatic ovarian carcinomas in diagnostic pathology. Recent research has highlighted that non-mucinous ovarian carcinomas, especially clear-cell carcinomas, endodermal sinus tumors, and clear-cell and transitional-cell carcinomas, often exhibit strong reactivity to mesothelin. Additionally, *MSLN*-specific antibody immune responses were observed in ovarian and pancreatic cancer patients, confirming the immunogenicity of *MSLN* and supporting the safety of its immunotherapeutic targeting. In another preliminary research phase preceding clinical trials, researchers developed a novel form of anti-*MSLN* CAR and pinpointed an exceptionally potent anti-*MSLN* single-chain Fv antibody with comparable binding capabilities and minimal off-target effects using a human phage display library. The utilization of these anti-*MSLN* CAR-T cells in the treatment of OC has displayed encouraging outcomes in both in-vitro and in-vivo experiments, with patients experiencing PFS times of 5.8 and 4.6 months [44]. In a study, fully human anti-mesothelin chimeric antigen receptors have been developed and tested. These CARs comprise a specific type of antibody called P4 scFv and T cell signaling components. They have shown promise in killing mesothelin-expressing tumors in human OC, both in vitro and in vivo. This study is significant as it addresses concerns about immune system reactions to the treatment, potentially making CAR T cell therapy safer and more productive [45]. Moreover, a phase I clinical trial investigated the use of lentiviral-transduced CART-meso in patients with chemotherapy-resistant malignant pleural mesothelioma, ovarian carcinoma, and pancreatic ductal adenocarcinoma. Results showed that the treatment was generally well tolerated with limited side effects, but its clinical impact was somewhat limited [46]. Likewise, in a murine ovarian cancer model, injecting a specific type of CAR-modified T cells known as CARMA-hMeso directly into the abdominal cavity inhibited tumor growth and improved survival in a dose-dependent manner. Repeat administrations of CARMA-hMeso further prolonged disease control and survival without causing significant unintended toxic effects. These findings suggest that CARMA-hMeso has the potential to be a valuable treatment for ovarian cancer and other cancers that express mesothelin [47].

Folate, a vital vitamin that the body cannot produce independently, must be obtained from the diet. Folate is transported into cells by three types of folate transporters: reduced folate carrier (RFC), proton-coupled folate transporter (PCFT), and folate receptors (FRs). RFC serves as the primary transporter in the body. At the same time, PCFT absorbs dietary folate in the small intestine, and FRs uptake folate in specific tissues through a process known as endocytosis. RFC and PCFT are classified as low-affinity, high-throughput transporters, while FRs are considered high-affinity, low-throughput transporters [48]. Among four members of the FRs family, FRα, encoded by the *FOLR1* gene, is an appealing therapeutic target due to its prevalent and high expression in EOC cells. Following an initial positive response to platinum-based chemotherapy in the majority of patients with OC, unfortunately, recurrence occurs in up to 80% of cases. Furthermore, a significant proportion of these patients will go on to develop platinum-resistant ovarian cancer (PROC), signifying disease progression within 6

months of their last platinum treatment. In the realm of non-platinum chemotherapies for PROC, there is considerable interest in the potential of mirvetuximab soravtansine (MIRV). This antibody-drug conjugate targets FRα in platinum-resistant epithelial ovarian cancer (PROC) patients. In November 2022, mirvetuximab soravtansine was granted approval in the United States for treating adult patients diagnosed with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have undergone 1–3 previous systemic treatment regimens [49]. In a SORAYA clinical trial, researchers conducted a single-arm, phase II study to assess the effectiveness and safety of MIRV. The trial included one hundred six patients with FRα-high PROC who had received one to three prior therapies, including prior bevacizumab. The trial's primary endpoint was successfully met, with an investigator-assessed confirmed overall response rate (ORR) of 32.4% and a median duration of response of 6.9 months [50].

In recent years, there has been significant progress in evaluating the safety and potential of CAR-T therapy in targeting various antigens associated with OC, including clinical trials (Table 1). In combination with studies of CAR-T cell therapy, a Phase I study (NCT05057715) is being conducted to assess the safety and feasibility of lentiviral transduced huCART-meso cells in combination with VCN-01 (oncovirus) for patients with serous epithelial ovarian cancer. There is also an early phase clinical trial registered (NCT04503980) to study the use of αPD1-MSLN-CAR T Cells secreting PD-1 nanobodies for treating MSLN-positive advanced solid tumors with an unknown status.

Despite these advancements, CAR-T-cell therapy for ovarian cancer still faces challenges such as off-target effects, tumor antigen escape, heterogeneity of ovarian tumors, immunosuppressive tumor microenvironment, toxicity like cytokine release syndrome (CRS), and neurotoxicity [43]. CRS, in particular, is a major concern as it can lead to severe symptoms ranging from fever and fatigue to shock, multi-organ failure, and even death. Additionally, CAR-T cells face obstacles in effectively targeting and infiltrating tumor cells, including challenges posed by the extracellular matrix and the immunosuppressive microenvironment. By improving the homing capability of CAR-T cells and exploring combination therapies, there is potential to enhance their efficacy in eradicating tumor cells. Our previous study delved into the potential of using CAR-T-modified T cells to treat OC. Still, it was observed that their effectiveness is hindered by side effects and toxicity [9]. Therefore, we proposed utilizing liposomal, mRNA, and transposase system-mediated gene transfer as a safer and more straightforward alternative to viral or non-viral transduction methods. However, the complexity of targeting T-cell trafficking, tumor site infiltration, histology, and vascular leakage in solid tumor heterogeneity poses significant challenges. Recent studies have explored CAR-T therapy in combination with nanoparticulate RNA vaccination to regulate cell proliferation in solid tumors [51]. This research has focused on factors such as RNA-lipoplexes (RNA-LPX) dose [52] and the tight junction protein claudin 6 (*CLDN6*) [53] in solid tumors. Additionally, the research employed a customized nanoemulsion (Clec9A-TNE) vaccine to enhance antigen presentation, CAR-T cell proliferation in vivo, and the treatment of solid tumors [51, 54]. Based on these findings, we believe that RNA nano vaccines have the potential to infiltrate tumor cells, including those found in solid tumors and OC, given the aberrant vasculature, enhanced permeability and retention (EPR), and hypoxia within tumor microenvironments.

Nanotechnologies to enhance ovarian cancer immunotherapy

Immunotherapy has greatly improved survival rates for melanoma [55] and lung cancer patients [56], but its effectiveness in ovarian cancer is limited due to the cold tumor immune microenvironment. Various immunosuppressive factors contribute to tumor progression and poor prognosis, such as *VEGF*, interleukin 6 (*IL-6*), *IL-10*, prostaglandin E2 (*PGE2*), and overexpression of indoleamine 2,3-dioxygenase. *VEGF* also inhibits the maturation and function of dendritic cells and increases PD-L1 expression on myeloid DCs. Additionally, increased regulatory T cells, immature myeloid cells, and myeloid-derived suppressor cells play a part in immunosuppression within the ovarian tumor microenvironment.

The effectiveness of chemotherapy in treating metastatic disease is often reduced due to various biological barriers that prevent drugs from accumulating in tumors. These barriers include limitations in drug distribution to non-tumor tissues, challenges in drug delivery across tumor cell membranes, and resistance to multiple drugs. Researchers have been investigating nanoscale delivery systems like liposomes, nanoparticles, and polymeric micelles to deliver anticancer drugs simultaneously. A cutting-edge nanoscale drug delivery system using a custom-modified polypropylene imine (PPI) dendrimer as a carrier has been synthesized to minimize the adverse effects of chemotherapy. This innovative system incorporates the potent anticancer drug paclitaxel, a synthetic analog of luteinizing hormone-releasing hormone (LHRH) peptide to target tumor cells specifically, and siRNA directed against *CD44* mRNA. The aim is to enhance the effectiveness of chemotherapy while reducing its side effects [57]. This inventive system was meticulously synthesized and rigorously tested both in laboratory settings in vitro and in vivo, using metastatic

OC cells obtained from patients suffering from malignant ascites. The research focuses on the importance of *CD44*, an integral cell surface glycoprotein recognized as a significant marker for metastasis and progression of certain types of cancer, including ovarian carcinoma. Additionally, the study explores luteinizing hormone-releasing hormone analogs (LHRHa) as a targeting agent for ovarian tumor cells. These analogs can bind specifically to LHRH receptors, which are highly expressed on the extracellular membrane of ovarian tumor cells. Another research aspect involves using negatively charged cholesterol succinimide (CHS) to create negatively charged docetaxel-loaded liposomes [58]. Additionally, folic acid (FA) has become an increasingly important targeting component in targeted drug delivery due to its ability to interact specifically with cells expressing the folate receptor (FR). By utilizing high-capacity carriers, it is possible to improve the site-specific delivery of drugs to tumors using FR [59]. These carriers can effectively incorporate multiple drug molecules into a single particle and target them to the disease sites, enhancing the overall effectiveness of drug delivery to the targeted areas. Moreover, micellar NPs composed of linear polyethylene glycol (PEG)-block-dendritic cholic acids (CA) copolymers, also known as telodendrimers, have been developed for the precise delivery of chemotherapeutic drugs in cancer treatment [60]. A study found that PTX-loaded OA02-NPs demonstrated significantly better anti-tumor effects and lower systemic toxicity in nude mice compared to equivalent doses of non-targeted PTX-NPs.

However, multifunctional NPs have been designed to address the biological barriers by actively targeting tumors and enabling controlled release of drugs, but their success in clinical applications has been limited. Recently, NPs have shown the potential to enhance the effectiveness of OC immunotherapy by influencing the tumor immune microenvironment. Nanotechnology-mediated photothermal and photodynamic therapy have been found to induce immunogenic cell death of tumor cells, promote antigen presentation, and enhance the infiltration of T cells into tumors. Additionally, NPs can serve as effective carriers for immunomodulators such as adjuvants, cytokines, and siRNA, which can help regulate immunosuppressive cells and inhibit immune checkpoints within the tumor microenvironment. Overall, nanoparticle-mediated immunotherapy shows promise in modulating the TIME of ovarian cancer and enhancing treatment outcomes. In recent decades, various NPs have been used in treating ovarian cancer and in combination with immunotherapy.

This section focuses on understanding how the immune system is suppressed within the tumor microenvironment. This includes looking at how inhibitory molecules are increased and how suppressive cell populations (Fig. 3), such as myeloid-derived suppressor cells

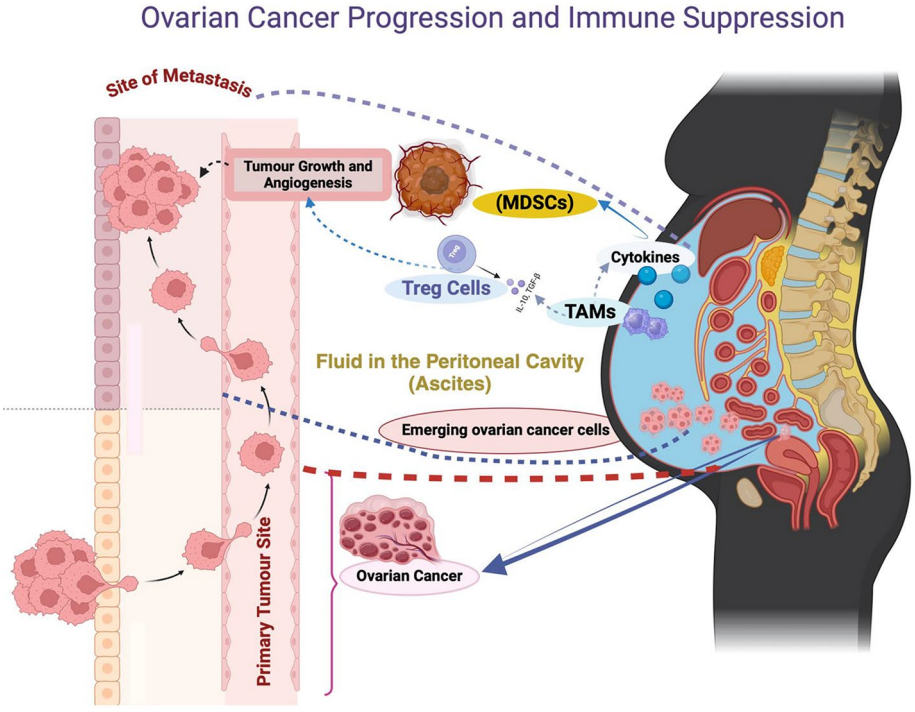

Fig. 3 Immunosuppressive environment in the tumor: suppressive cell populations **(**MDSC, TAMs, and Treg cells) inside the peritoneal cavity fostering tumor growth and metastasis in ovarian cancer

(MDSC), tumor-associated macrophages (TAM), and regulatory T (Treg) cells, are recruited.

Tumour-associated macrophages (TAMs)

TAMs play a crucial role in ovarian cancer progression and immune suppression. These macrophages are found abundantly in the tumor tissues and ascites of ovarian cancer patients, where they actively promote tumor growth, metastasis, and immunosuppression. Researchers have been exploring TAMs as potential targets for therapy to reverse the immunosuppressive environment in the tumor and enhance the effectiveness of immunotherapy. TAMs hinder the body's immune response against the tumor through various mechanisms, such as the production of cytokines and chemokines that inhibit the activity of immune cells that could potentially combat the tumor (Fig. 3).

For example, TAMs produce *CCL22*, which facilitates the migration of Tregs and other suppressive immune cells to the tumor microenvironment [61]. In addition, TAMs can release *IL-10*, which suppresses the function of antigen-presenting cells, further dampening the immune response. Furthermore, a specific subtype of TAMs, known as M2-like TAMs, has been identified in ovarian cancer and other solid tumors. These M2-like TAMs actively suppress the function of cytotoxic T cells by releasing factors such as *TGF-β* and depleting essential amino acids required for T cell activation [62].

Additionally, TAM-derived exosomes containing *ARG1* have been found to inhibit the proliferation of specific T cells, contributing to immune suppression in ovarian cancer patients. It is important to note that macrophages, including TAMs, demonstrate significant functional adaptability, with distinct subtypes such as the proinflammatory M1 and immunosuppressive M2 types. TAMs are generally associated with the M2 subtype and are implicated in tumor progression, metastasis, and poor patient prognosis. However, there is hope for targeting TAMs as a therapeutic strategy. Activating macrophages and redirecting them towards the proinflammatory M1 phenotype could potentially enhance antigen presentation and facilitate the recruitment of tumor-targeting T cells. Such a strategy could complement ICB antibodies, which rely on T cells within the tumor environment for efficacy.

Research has shown that NPs can serve as effective carriers for delivering therapeutic and imaging substances to TAMs. An emerging strategy involves using a toll-like receptor (TLR) agonist called Resiquimod (RSQ) to improve the effectiveness of ICB treatment for ovarian cancer. This approach would require delivering RSQ specifically to tumor-associated macrophages in the ovaries while minimizing its impact on the rest of the body. A recent study found that large, anionic liposomes administered into the peritoneal cavity efficiently target TAMs and can effectively deliver RSQ. When delivered in this targeted manner, Resiquimod activated M1 macrophages, increased T-cell infiltration, and reduced the proportion of Tregs in the tumor microenvironment [63]. Ultimately, using liposome-encapsulated RSQ significantly improved the effectiveness of PD1 blockade in combating ovarian tumors in preclinical models.

The precise delivery of NPs with specific size and charge into ovarian tumor-associated macrophages represents a promising avenue for advancing future immunotherapy. This finding paves the way for investigating diverse NP compositions with the assurance of effectively targeting ovarian TAMs. A recent study elucidated that the route of administration and the size and charge of the NPs played pivotal roles in selectively labeling tumors. By methodically altering the properties of silicon NPs (SiNPs), researchers discovered that selective tumor labeling occurred over several days and was contingent on the particles being relatively large (>200 nm), anionic, and administered intraperitoneally. This behavior was also observed with large anionic NPs composed of poly (lactic-co-glycolic acid) (PLGA) or polystyrene. The accumulation of SiNPs in ovarian TAMs resulted in an augmentation of TAMs at metastatic tumor sites, potentially influencing these TAMs to display the M1 phenotype. Particles smaller than 100 nm or cationic, as well as those administered intravenously (i.v.), showed no targeting of TAMs. Furthermore, this study demonstrated that the selective tumor labeling with NPs extended beyond mouse models to encompass human tumor surfaces in freshly excised surgical samples, with minimal labeling of normal tissues [64].

Regulatory T cells (Treg cells)

Treg cells are critical for regulating immune responses to self-antigens, allergens, and various microorganisms and reactions to infections and tumors. The transcription factor *FOXP3* is central to Treg cell function, and its absence can lead to severe autoimmune disease in both mice and humans [65]. The protein *FOXP3* plays a direct role in suppressing the transcription of the *IL-2* gene while also increasing the transcription of *CTLA-4* and *CD25*. One of the main ways Treg cells exert their suppressive activity is through various mechanisms, including inhibiting the maturation of antigen-presenting cells (APCs) via the *CTLA-4* pathway. Treg cells also consume *IL-2* by expressing high-affinity *IL-2* receptors, specifically the *CD25* subunit, and secrete inhibitory cytokines such as *IL-10*, *TGF-β*, and *IL-35*. Additionally, they degrade ATP, an important energy source for cells, and express granzyme and perforin, which can eliminate effector T cells and APCs. *CTLA-4* interacts with B7 molecules on APCs, inhibiting co-stimulatory signaling through *B7* and *CD28* on effector cells, ultimately preventing APC maturation

[66]. Studies have indicated that Treg cells may hinder immune surveillance against cancer in healthy individuals, impede the development of effective anti-tumor immunity in patients with tumors, and even support tumor progression. Naturally occurring $CD25^{+}CD4^{+}$ Treg cells, which consistently express the transcription factor *FOXP3*, are vital for maintaining immune tolerance and balance by suppressing abnormal or excessive immune responses that could harm the host. In various cancers, such as ovarian cancer, a high presence of Treg cells among tumor-infiltrating lymphocytes is associated with unfavorable outcomes, particularly when combined with insufficient infiltration by $CD8^{+}$ cytotoxic T cells. Targeting terminally differentiated effector Treg cells instead of all $FOXP3^{+}$ T cells could promote effective tumor immunity without triggering autoimmunity. Cell surface molecules expressed explicitly by effector Treg cells, such as the chemokine receptor CCR4, could be potential targets for depleting these cells using specific cell-depleting monoclonal antibodies [67]. Targeting specific Treg cells and combining them with cancer vaccines or immune checkpoint blockade can improve cancer immunotherapy. Understanding the characteristics and roles of Treg cells in cancer settings could potentially enhance disease-specific therapies targeting Treg cells and reduce the occurrence of immune-related adverse effects resulting from Treg cell inhibition.

In an ovarian cancer xenograft humanized mouse model, scientists investigated the behavior of two types of monoclonal antibodies (mAb2-3), IgG1 and IgG4. Their findings revealed that both IgG1 and IgG4 isotypes had similar abilities to hinder the movement of $CCR4^{+}$ Treg cells in in vitro experiments. However, in vivo studies disclosed different mechanisms of action of these two isotypes. Specifically, the mAb2-3 IgG1 isotype notably reduced Treg cell levels, limited the infiltration of tumor cells, and effectively suppressed tumor growth, whereas the IgG4 isotype did not produce the same results. These results suggest that mAb2-3 functions as an agonist antibody, enhancing anti-ovarian cancer immunity by modulating Treg activity [68].

Recently, it has been discovered that nanostructure scaffolds hold great promise in addressing the challenges associated with T-cell immunotherapies, particularly in the context of cancer treatment. These scaffolds offer a new perspective on the intersection of cancer immunotherapy and nanotechnology. Within solid tumors, the bulky environments often impede the immune system and obstruct the activation of ACT therapy, enabling cancer cells to evade. Compared to systemic or topical T-cell therapy, employing biodegradable polymeric scaffolds to transfer lymphocytes can potentially augment the proliferation and release of tumor-degrading T-cells while minimizing the risk of cancer progression [69]. Furthermore, research by Sacchetti et al. delved into the internalization of PEG-modified single-walled carbon nanotubes (PEG-SWCNTs) within the tumor microenvironment [70]. The focus was on ligands that target Treg-specific receptors, particularly the glucocorticoid-induced TNFR-related receptor (GITR), which is overexpressed in intratumor Treg cells compared to peripheral Treg cells. The study showed that PEG-SWCNTs loaded with GITR ligands effectively internalized Treg cells via receptor-mediated endocytosis in ex vivo and in vivo models. Additionally, Ou et al. explored the targeting of TME Treg cells with tLyp1 peptide-conjugated hybrid nanoparticles. When combined with checkpoint-blockade using anti-*CTLA-4*, this approach resulted in an increase in CD8+T cells within the tumor [71]. Using nanoparticles, specifically Lipid-PLGA/tLyp1, enhanced tumor inhibition, reduced intratumoral Treg cells, and improved overall survival. While the primary focus of this study was on melanoma cancer, the implications of the findings may extend to researchers studying ovarian cancer. The prognosis of ovarian cancer patients is negatively affected by the ratio of tumor Treg to CD8+T cells. Strategies to block Treg differentiation, migration, or immunosuppressive functions may bolster ovarian patients' antitumor immune responses [72].

Myeloid-derived suppressor cells (MDSCs)

MDSCs form a diverse group of immature myeloid cells with distinct morphology and functions compared to fully developed myeloid cells like macrophages, dendritic cells, and neutrophils. These MDSCs exhibit immunosuppressive properties and promote tumor growth, spread, and the development of new blood vessels (angiogenesis). In ovarian cancer, higher levels of circulating or tumor-infiltrating MDSCs are associated with a more advanced disease stage and a poorer prognosis. MDSCs can be categorized into two main subsets: monocytic MDSCs (M-MDSCs) with similarities to monocytes, and polymorphonuclear (PMN) MDSCs, also known as granulocytic MDSCs, which resemble neutrophils. In cancerous conditions, tumor-derived cytokines and growth factors play a role in stimulating the generation of MDSCs from myeloid precursors [73]. Chemokines play a crucial role in guiding the movement of MDSCs during their migration. In the ascites of ovarian cancer patients, high levels of specific cytokines such as *IL-6*, *IL-10*, *IL-1β*, VEGF, *PGE2*, and TNF-α trigger the accumulation of MDSCs. It's worth noting that MDSCs could enhance the stem cell-like characteristics of ovarian cancer cells [74]. MDSCs act as key players in cancer immune evasion, and understanding these cells can be valuable for predicting cancer progression and may serve as promising targets for new cancer treatments.

Recent research has shown that granulocyte colony-stimulating factor (G-CSF)-induced myeloid-derived suppressor cells are crucial in advancing TRL-positive ovarian cancer. These MDSCs have been found to hinder the activity of CD8+T cells and enhance the stemness of ovarian cancer cells. Furthermore, they contribute to increased expression of PD-L1 in tumors by producing prostaglandin E2 (PGE2) through the *PI3K-AKT-mTOR* pathway. A study investigated how MDSCs impact the development of cancer stem-like cells (CSCs) and the expression of PD-L1 in ovarian cancer. The findings indicate that MDSCs may impede anti-tumor immunity by fostering the production of CSCs [75]. However, further research is required to fully comprehend the interactions among CSCs, MDSCs, and immune checkpoint molecules in the tumor microenvironment.

In addition, research suggests that vascular endothelial growth factor A (*VEGF-A*) is pro-angiogenic and possesses immunosuppressive properties. *VEGF-A* has been found to induce the accumulation of immature dendritic cells, MDSCs, and Treg cells while also impeding the migration of T lymphocytes to the tumor site. To investigate the relationship between *VEGF-A* and MDSCs and to elucidate the roles of MDSCs in tumor immunity, a study was conducted using mouse models of ovarian cancer and clinical samples. The results unveiled that MDSCs within the tumor express both *VEGFR1* and *VEGFR2*, and their migration and differentiation are enhanced by VEGF signaling. The study concluded that within peritoneal dissemination, VEGF and MDSCs play a critical role in the progression of ovarian cancer. Furthermore, silencing *VEGF-A* in tumor cells reduced MDSC infiltration and increased CD8+T-cell infiltration [76]. Consequently, addressing MDSCs induced by VEGF signaling could potentially enhance the outlook for ovarian cancer patients. Another study in mouse ovarian cancer models found that hypoxia in tumors induced by anti-VEGF antibody treatment led to an increase in the expression of GM-CSF. This, in turn, resulted in the recruitment of MDSCs to the tumor sites, suppressing the immune response and progression of the tumor. Therefore, this led to resistance to anti-VEGF therapy [77].

Additionally, there are increased levels of serum CXCL1/2 in patients with ovarian cancer. These elevated levels are associated with the expression of Snail, infiltration of MDSCs, and shorter overall survival. Snail is a key regulator of gene expression that suppresses E-cadherin, leading to a process called epithelial-mesenchymal transition (EMT). This process promotes cancer progression by increasing the production of CXCR2 ligands and recruiting MDSCs. A study was carried out to investigate the relationship between Snail and MDSCs in ovarian cancer patients. The findings suggest that blocking CXCR2 could be a potential immunological strategy to inhibit the progression of tumors with high levels of Snail and undergoing EMT [78]. The high expression of Snail in ovarian cancer has also been linked to the development of resistance to apoptosis, including resistance to anoikis, as well as resistance to various chemotherapeutic agents [79].

Recent studies have focused on developing therapeutic strategies to counteract the immunosuppressive effects of MDSCs in cancer patients. Despite ongoing clinical developments, the specific molecular mechanisms governing the behavior of MDSCs in the context of cancer immunopathogenesis remain poorly understood [80]. A study has provided new insights into the mechanisms behind the anti-tumor effects of metformin, a widely used medication. The study reveals that metformin also targets MDSCs and is a powerful immunomodulatory agent. Both in vitro and in vivo experiments show that metformin enhances the functionality of anti-tumor CD8+T cells, leading to increased survival rates in patients with ovarian cancer. Significantly, metformin treatment is found to counteract MDSC-mediated immune suppression by reducing the expression of *CD73* and *CD39* on MDSCs. This mechanism is achieved through activating AMP-activated protein kinase (AMPKα) and suppressing the HIF-1α pathway [81]. Additionally, another research also investigated how combining dabigatran etexilate, a direct thrombin inhibitor, with a low dose of cisplatin affected the murine ID8 ovarian cancer model. They found that this combination strategy significantly reduced the levels of specific immune cells, namely Gr1+/CD11b+MDSCs and CD11b+/CD11c+dendritic cells in the ascites of *ID8* tumor-bearing mice [82].

Numerous studies have delved into the exploration of nanomedicines as a means to target MDSCs within the tumor immune microenvironment [2]. These investigations have unveiled promising findings, indicating that nanomedicines can potentially disrupt early recruitment and reduce the presence of MDSCs across various cancer types. In ovarian cancer, researchers investigated how tumor-associated DCs that expressed *CD11c* and PD-L1 interacted with linear polyethylenimine-based (PEI-based) nanoparticles encapsulating siRNA. It was observed that the uptake of these NPs resulted in T-cell-mediated tumor regression and extended survival. Importantly, this effect was found to be dependent on the myeloid differentiation primary response gene 88 *(MyD88)* [83]. Further advancements in harnessing the transport oncophysics of the peritoneal cavity are expected to enhance delivery strategies for treating OC [84].

Cancer immunotherapy with nanoparticles

Ovarian cancer presents a significant challenge in terms of treatment, with a 5-year survival rate of less than 40%.

The cancer can spread through various routes, posing a major obstacle to successful treatment [85]. Multidrug resistance, caused by a range of factors, including cellular and physiological changes, further complicates chemotherapy. Despite these challenges, a promising non-invasive photodynamic therapy (PDT) treatment has been gaining attention. PDT utilizes a photosensitizer at a specific wavelength along with oxygen to achieve its therapeutic effects. When the photosensitizer is exposed to light, it produces reactive oxygen species (ROS) that can specifically target cancer cells, leading to cell death, damage to tumor blood vessels, and a local inflammatory response [86]. This selective approach holds the potential for effectively targeting malignant cells. PDT can be administered right after surgery for ovarian cancer, and it can also be used during surgery to target any remaining tumors in high-risk areas around the time of the operation. In addition, PDT can potentially address spreading tumor nodules and slow down the advancement of peritoneal cancer.

However, PDT has faced challenges due to the lack of tumor specificity of the photosensitizers used, leading to reduced effectiveness and increased side effects. The biological environment drug solubility and systemic toxicity challenges highlight the need for optimized drug delivery systems such as nano preparations. Nanotechnology offers the potential to enhance the physical and chemical properties of therapeutic agents, and in the context of cancer management, it has significant implications for the field of medicine. One key application is using nanomaterials to integrate multiple functions into a single entity, offering immense potential for advancing biological research (Table 2). Nanoparticles, serving as excellent carriers, facilitate the accumulation of drugs in tumor tissues through the enhanced permeability and retention effect (EPR). They can leverage the EPR to promote the accumulation of drugs in these tissues. The field of nanotechnology has emerged as a powerful tool, drawing attention from clinicians, researchers, and pharmaceutical companies due to its ability to transform the way we approach cancer treatment fundamentally. In the context of PDT, NPs play a crucial role in protecting photosensitizers (PSs) from the surrounding environment while ensuring the production of reactive oxygen species (ROS) is not compromised. Additionally, using NPs opens up the possibility of multiple irradiations, reducing the need for repeated administration of treatments. Since many photosensitizers are hydrophobic, various nanoplatforms have been developed to facilitate their delivery. One notable approach is the covalent combination of photosensitizers and nanoparticles, which minimizes unnecessary bleaching of the photosensitizers while maintaining their photodynamic activity [93]. The first-generation photosensitizers faced various challenges, including limited selectivity, large drug doses required to achieve optimal efficiency, heightened skin sensitivity, and restricted clinical applications. As a result, researchers developed second and third-generation photosensitizers to address these issues in OC [88].

A new drug delivery system, called immunoliposomes, has shown promise in improving cancer treatment both in vitro and in vivo. Recently, nanomedicine-based photodynamic therapy has also gained attention as a way to enhance targeted PDT (TPDT) by specifically targeting

Table 2 Nanoparticle-mediated therapies in the treatment of ovarian cancer

Nanoparticle	Functional moieties	Type of therapy	Preclinical studies	References
TPD@TB/KBU2046	KBU2046 (small molecule inhibitor), TB (photodynamic-AIEgens) and TPD- TMTP1 (a targeting peptide	Photodynamic therapy	in vitro and in vivo (ovarian tumor models) studies	[85]
PPI dendrimer-based nanoplatforms	Phthalocyanine (Pc) as the near-infrared (NIR) photosensitizer (functionalized with PEG and LHRH peptide) and siRNA as a *DJ-1* gene suppressor	Photodynamic therapy	in vitro and in vivo (subcutaneous xenografts of A2780/AD cancer cells) studies	[87]
Hy-loaded PLA Nanoparticles	Hypericin (Hy), a natural photosensitizer (PS), and polylactic acid (PLA)	Photodynamic therapy	in vitro phototoxicity assay	[88]
NLC- verteporfin	Verteporfin, a photosensitizer and nanostructured lipid carriers	Photodynamic therapy	in vitro cytotoxicity assay and in vivo (ovarian tumor models) studies	[89]
Photo-immuno-conjugate-associating-liposome (PICAL)	Benzoporphyrin derivative monoacid A (BPD), the Cetuximab antibody, and Preformed Plain Liposome (PPL)	Photodynamic therapy	in vitro phototoxicity assay	[90]
FBPD Nanoparticles	NIR laser responsive nanoparticles (PLGA-PEG-FA encapsulating Bi_2S_3, PFP, and Dox	Photothermal therapy	in vitro and in vivo studies	[91]
Biodegradable photoresponsive Nanoparticles	Poly(lactic-*co*-glycolic nanoparticles, carboplatin drug (CP), and the near-infrared (NIR) photosensitizer indocyanine green (ICG)	Chemo phototherapy (Combination of phototherapies and chemotherapy)	in vitro studies	[92]

epithelial and vascular growth factors. Over-expression of EGFR in ovarian cancer has been linked to poor prognosis and has been shown to correlate with worse survival outcomes in women with advanced ovarian cancer who have undergone surgery and combination chemoimmunotherapy. The precision of nanomedicine's ability to target specific areas and controlled light exposure could significantly reduce the overall toxicity associated with traditional PDT in ovarian cancer [90].

PDT is a treatment method that harnesses the unique ability to target specific areas by utilizing photosensitizer accumulation and light targeting. Unlike traditional treatments, PDT is nonthermal, which allows it to preserve surrounding collagen structures and nerves. It has proven effective for targeting infiltrative and nonresectable tumor components due to the short distance that ROS can travel. However, it's important to note that in some cases, the accumulation of photosensitizers in the skin can lead to photosensitivity, which poses safety risks and can complicate treatment [94].

On the other hand, photothermal therapy (PTT) is an emerging cancer treatment that employs light, usually in the near-infrared (NIR) region, to raise tissue temperature and achieve local photocoagulation. The heat generated from the assimilation of optical energy via light-assimilating agents accumulated in the tumor area post-NIR irradiation is used to kill tumor cells and tissues. Compared to visible light and ultraviolet, NIR laser is considered safe because it causes minimal harm to healthy tissue and allows for deep penetration [91]. A novel combination therapy for ovarian cancer was developed using a hybrid biomimetic coating (IRM) by fusing a murine-derived ID8 ovarian cancer cell membrane with a red blood cell (RBC) membrane. This coating camouflaged indocyanine green (ICG)-loaded magnetic nanoparticles (Fe3O4-ICG@IRM), exhibiting specific self-recognition of ID8 cells in vitro and in vivo. The therapy showed promising results, with the NPs inducing photothermal therapy, leading to tumor necrosis and the release of tumor antigens. This, in turn, enhanced antitumor immunotherapy by activating CD8+cytotoxic T cells and reducing regulatory Foxp3+T cells, thus targeting both primary and metastatic tumors [95]. PTT can effectively target hypoxic tumor regions that are resistant to traditional oxygen-dependent PDT. Furthermore, it may induce additional cell death in areas where local oxygen levels have been depleted after PDT, and its cytotoxicity can be further enhanced due to tumor acidification in poorly oxygenated tumor regions resulting from the Warburg effect.

Treatment of ovarian cancer: challenges and future perspectives

Ovarian carcinoma, a deadly disease with a low cure rate, presents unique challenges in terms of its biology and treatment. Unlike hematogenous metastasizing tumors, ovarian cancer cells primarily spread within the peritoneal cavity, making early detection and treatment difficult. The rapidly increasing tumors compress visceral organs and are only temporarily sensitive to chemotherapy. Despite the initial sensitivity to intraperitoneal chemotherapy, most patients experience relapse and face death. Furthermore, the administration route, resistance to therapy with recurrence, and the need for precise cancer targeting further compound the treatment difficulties. Ovarian carcinoma also presents other challenges, such as multidrug resistance, genetic and epigenetic changes, and the impact of ascites on prognosis. Ascites, the accumulation of fluid in the peritoneal cavity, is indicative of poor prognosis in OC patients and is postulated to play a dominant role in cancer metastasis and chemoresistance. Therefore, gaining a comprehensive understanding of the biology of the ascites microenvironment is imperative for the development of effective therapeutic interventions for metastatic ovarian cancer. Moreover, resident cells in ascites or primary tumors exhibit characteristics of cancer stem cells (CSCs), including self-renewal, multilineage differentiation, and tumor initiation capabilities in vivo. CSCs possess the capacity to colonize distant sites and withstand the effects of chemotherapy. In addition, ovarian carcinoma may originate from the surfaces of the ovary, the fallopian tube, or the mesothelium-lined peritoneal cavity. The development of ovarian carcinoma can occur in one of two ways: through a stepwise mutation process from a slow-growing borderline tumor to a well-differentiated carcinoma (referred to as type I), or as a genetically unstable high-grade serous carcinoma that spreads rapidly (referred to as type II). As the disease progresses, it becomes increasingly challenging to treat and manage. Only 20% of cases are detected in the early stages, and healthcare professionals often misdiagnose OC because its symptoms can be similar to those of other urologic, abdominal, and gynecologic conditions, resulting in delayed diagnoses.

Furthermore, exosomes, small extracellular vesicles released by the primary ovarian tumor, play a crucial role in preconditioning the distant tumor microenvironment for accelerated metastatic invasion. They have been found to modulate chemoresistance in ovarian cancer cells through various mechanisms, including the transfer of miRNAs and proteins. These exosome-mediated processes can promote resistance by inhibiting either apoptosis or enhancing drug efflux. The significance of exosomes in fostering tumor growth and metastasis has been the subject of extensive research. However, there is

a scarcity of studies exploring the impact of exosomes on the immune response in OC. Exosomes play a key role in the communication between tumor cells, normal stroma, cancer-associated fibroblasts, and local immune cells within the tumor microenvironment. However, the specific impact of exosomes on modulating the immune system in OC is not well understood. Further investigation is needed to determine whether exosomes act as stimulators and/or suppressors of the immune system. Although immunotherapy shows promise as a treatment for OC, its effectiveness is limited by the complex immunosuppressive network created by tumor cells. This leaves tumor-infiltrating lymphocytes with insufficient support, causing them to ultimately succumb to the tumor cells. Understanding the immune microenvironment in OC is crucial for identifying effective breakthrough points to extend the clinical success of cancer immunotherapy. One key factor in poor treatment outcomes for OC is the upregulation of tyrosine-protein kinase Met (*c-Met*), which impacts cell proliferation, infiltration, angiogenesis, and endurance while also being linked to chemoresistance. For patients with poor responses to chemotherapy, dose-dense chemotherapy is a promising option, and PARP inhibitors are an emerging class of drugs that, when used in combination therapy with traditional chemotherapy drugs, show promise. Additionally, Bevacizumab has been recently approved for the treatment of epithelial ovarian cancer. Folate receptor targeting requires further research to be considered as a treatment option. Furthermore, regular screening for the Breast cancer susceptibility gene (*BRCA*) in all ovarian cancer patients is essential for better selection of targeted therapy. Another emerging treatment option is CAR-T therapy, which involves genetically engineered T-cells to fight against certain types of blood cancers that do not respond to traditional treatments. However, the most common targeting domain of CAR-T cells, known as scFvs, has limitations that can affect the safety and effectiveness of CAR-T therapy. Further research is needed to target cancer cells and address these challenges effectively.

There is an urgent need for a personalized model system to improve translational research and clinical application. The patient-derived organoid (PDO) model has demonstrated significant potential in advancing OC research and translating laboratory discoveries into real-world clinical outcomes. Nevertheless, the protocols for creating OC organoids still require refinement. Organoids precisely mimic the original patient's tumor and can be utilized for drug testing and analyzing tumor diversity. Gaining insights into the key elements of the tumor microenvironment, including immune cells, stromal cells, and endothelial cells, within PDO models could play a vital role in devising effective therapeutic interventions. Also, research exploring the utilization of artificial ovaries or scaffolds in ovarian transplantation is on the rise. Therefore, developing methods to enhance follicular recovery rate, refine scaffold design, improve transplantation techniques to prevent postoperative ischemia, and address genetic safety concerns is crucial. These advancements are necessary to ensure safer and more reliable human clinical applications. Moreover, scientists have recently developed a machine learning system that delivers accurate predictions of how different types of cancer will respond to immune checkpoint inhibitors. This system relies on network-based biomarkers to make highly precise prognoses about the effectiveness of ICI-based treatments. Because the current treatment options for ovarian cancer patients have limited effectiveness, there is an urgent need to apply machine learning models and statistical analyses in this area.

Ovarian cancer is a severe condition that poses unique challenges in diagnosis and treatment. The ovaries' lack of a peritoneal covering allows the cancer to spread locally to the peritoneal cavity, leading to specific symptoms. However, the absence of effective testing tools and equipment further delays the detection process for OC. Understanding the intricate biology of diseases is crucial for early diagnosis and predicting patient response to treatment. In the case of ovarian cancer, studies have explored the use of interferon-activating medications to potentially boost anti-tumor immunity. Additionally, chemical and biological nano-sensors have been developed to detect various cancers, including OC. Nanotechnology aims to improve therapeutic and diagnostic approaches, focusing on combining the two (theranostics) for diseases like ovarian cancer. By integrating nanotechnology with physiological biomarkers and therapeutic agents, novel nano-theranostic systems have been created. Superior detection technologies such as optical biosensors, microfluidic chips, and electrochemical biosensors, in conjunction with nanomaterials like carbon nanomaterials, quantum dots, polymer materials, and metal nanoparticles, enhance the performance of detecting ovarian cancer-related biomarkers and enable real-time monitoring and diagnosis, as well as simultaneous delivery of therapeutic agents for treatment.

Conclusions

Persistent research is delving into diverse approaches to enhance ovarian cancer treatment, such as the potential utilization of nanomedicine, targeted therapy, immunotherapy, and their combination. Nanotechnology-based drug delivery methods offer significant advantages compared to traditional treatments. Although still in its early stages, nano-based cancer immunotherapy has successfully enhanced the safety and effectiveness of cancer vaccines. These nanotechnology-based products show great

promise for personalized medical planning. Highly effective nanoparticle therapeutic outcomes in cancer immunotherapy could accelerate the translation of engineered nano-immunotherapeutics into cancer management clinics. However, a definitive cure for ovarian cancer remains elusive, and the potential of nanomedicines for managing OC has not been fully harnessed. None of the proposed nano-enabled approaches have displayed significant clinical benefits yet, and there is a lack of comprehensive discussion on the in vivo biodistribution of the proposed nanoplatforms. This emphasizes the challenge of effectively reaching tumor masses due to the complex changes within the peritoneal cavity. Continuous research and exploration of nanotechnology can potentially revolutionize future ovarian cancer therapy and diagnosis. Recent advancements in nanotechnology hold promise for substantially enhancing recovery and survival outcomes in OC patients. Nonetheless, there is an urgent need to develop improved methods for the early diagnosis of OC and treatment options that minimize drug toxicity and address drug resistance. Our review aims to raise ovarian cancer awareness by discussing potential pre-clinical and clinical therapeutic applications of nanotechnology to augment immunotherapy, which holds promising implications for improving treatment outcomes in ovarian cancer patients. Our review identified a number of ongoing clinical trials involving both randomized and non-randomized studies exploring different treatment combinations in platinum-resistant recurrent OC patients. These trials are looking into the effects of various therapies, such as CTLA-4 / PDL-1 immunotherapy, the combination of PARP-inhibition and CTLA-4 blockade, different immunotherapeutic vaccines, TIL cell therapy targeting folate receptor α, the combination of peptide immunotherapeutic vaccine and PD1 inhibitors, modified immune cells (CAR-T cells), and various immune checkpoint inhibitors within a variety of clinical scenarios. Over the past forty years, progress has been made in systemic treatments for ovarian cancer based on evidence from clinical trials. Current studies focus on addressing resistance to immunotherapy by implementing dual or triple immune checkpoint blockades, aiming to benefit patients with OC potentially. These advancements may have contributed to reduced mortality, as patients have seen improved survival rates after introducing new and effective treatments.

Abbreviations

HGSC	High-Grade Serous Carcinoma
LGSC	Low-Grade Serous Carcinoma
EC	Endometroid Carcinoma
CCC	Clear Cell Carcinoma
MC	Mucinous Carcinoma
ICIs	Immune Checkpoint Inhibitors
PBM-NPs	Planetary Ball Milling Nanoparticles
IT	Intra Tumoral
DCs	Dendritic Cells
CDC	Conventional Dendritic Cell
ICB	Immune Checkpoint Blockade
PLGA	Poly(lactic-co-glycolic acid)
TAA	Tumor-Associated Antigens
TSA	Tumor Specific Antigens
HLA	Human Leukocyte Antigen
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
FBP	Folate Binding Protein
ACT	Adoptive Cell Therapy
TILs	Tumor Infiltrating Lymphocytes
TCRs	T-cell Receptors
CARs	Chimeric Antigen Receptors
PFS	Progression-Free Survival
HRD	Homologous Recombination Deficiency
EOC	Epithelial Ovarian Cancer
CAR-T	Chimeric Antigen Receptor T Cells
PD -1	Programmed Cell Death 1
CTLA-4	Cytotoxic T-lymphocyte Associated Protein 4
LAG-3	Lymphocyte Activation gene 3
TIM-3	T cell Immunoglobulin- and Mucin-domain-containing 3
TGF-β	Transforming Growth Factor-β
ERBB2	Erb-b2 receptor tyrosine kinase 2
Ep-CAM	Epithelial Cell Adhesion Molecule
AMHR2	Anti-Müllerian Hormone Receptor Type 2
ANXA2	Annexin A2
TPBG	Trophoblast Glycoprotein
MSLN	Mesothelin
MUC16	Mucin 16
FRs	Folate Receptors
RFC	Reduced Folate Carrier
PCFT	Proton Coupled Folate Transporter
PROC	Platinum-Resistant Ovarian Cancer
MIRV	Mirvetuximab Soravtansine
CRS	Cytokine Release Syndrome
IL-6	Interleukin 6
PGE2	Prostaglandin E2
Tregs	Regulatory T cells
LHRH	Luteinizing-hormone Releasing Hormone
PEG	Polyethylene Glycol
NPs	Nanoparticles
TIME	Tumor Immune Microenvironment
MDSC	Myeloid-Derived Suppressor Cells
TAM	Tumor-Associated Macrophages
TLR	Toll-Like Receptor
SiNPs	Silicon NPs
APCs	Antigen Presenting Cells
GITR	Glucocorticoid-Induced TNFR-related Receptor
CSCs	Cancer Stem-like Cells
VEGF-A	Vascular Endothelial Growth Factor A
EMT	Epithelial-Mesenchymal Transition
PDT	Photodynamic Therapy
ROS	Reactive Oxygen Species
PTT	Photothermal Therapy

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Data availability
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Declarations

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