

Review

Preclinical and Clinical Immunotherapeutic Strategies in Epithelial Ovarian Cancer

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Abstract: In the past 20 years, the immune system has increasingly been recognized as a major player in tumor cell control, leading to considerable advances in cancer treatment. While promising with regards to melanoma, renal cancer and non-small cell lung cancer, immunotherapy provides, for the time being, limited success in other cancers, including ovarian cancer, potentially due to insufficient immunogenicity or to a particularly immunosuppressive microenvironment. In this review, we provide a global description of the immune context of ovarian cancer, in particular epithelial ovarian cancer (EOC). We describe the adaptive and innate components involved in the EOC immune response, including infiltrating tumor-specific T lymphocytes, B lymphocytes, and natural killer and myeloid cells. In addition, we highlight the rationale behind the use of EOC preclinical mouse models to assess resistance to immunotherapy, and we summarize the main preclinical studies that yielded anti-EOC immunotherapeutic strategies. Finally, we focus on major published or ongoing immunotherapy clinical trials concerning EOC.

Keywords: epithelial ovarian cancer; immune contexture; tumor microenvironment; adaptive and innate immune responses; lymphocytes; immunogenicity; myeloid cells; immunotherapy; preclinical mouse models; clinical trials

1. Introduction

Ovarian cancer is the most lethal among gynecological malignancies, due to diagnosis at advanced stages of the disease and to intrinsic and acquired resistance to chemotherapy in a large proportion of patients. Although progress has been made in the treatment of ovarian cancer by more aggressive surgical approaches and the introduction of platinum-taxane regimens, the 5-year overall survival for the advanced disease is approximately 30% [1]. Small numbers of drug-resistant cells can persist and remain dormant in the peritoneal cavity, growing progressively and leading to death, despite aggressive treatment of the recurrent disease [2]. Ovarian cancer comprises remarkably heterogeneous diseases, with distinct clinico-pathological and molecular features and prognoses [3]. Despite the existence of a variety of ovarian cancer subtypes, these are treated as a single disease. The most frequent subtype, high-grade serous carcinoma (HGSC), accounts for approximately 80% of epithelial ovarian cancers (EOC). HGSC are characterized by poor prognosis and typical mutations in genes, such

as *TP53* and *BRCA1/BRCA2*, that are involved in at least 96% and 22% of HGSC cases, respectively [4]. The other subtypes of EOC are less frequent and may be distinguished by other genetic alterations, such as *KRAS* mutations, occurring in 75% of mucinous carcinomas (MC), or tumor suppressor *ARID1A*, which is found to be mutated in 50% of clear cell carcinomas (CCC) [4]. Even if maintenance therapy with inhibitors of poly ADP-ribose polymerase (PARP) drove a paradigm shift in the treatment of BRCA-mutated tumors, there is still the need for new therapeutic strategies to improve outcomes in the majority of patients.

Increasing evidence, from biological and clinical data, indicates that ovarian cancers are “immunogenic tumors” that can be recognized by the host immune system [5–8]. Indeed, EOC patients develop spontaneous antitumor immune responses, which can be detected in peripheral blood, tumors and ascites, and are likely associated with improved survival in some patients. In addition, evidence of tumor immune evasion mechanisms, associated with an immunosuppressive tumor microenvironment, and their association with shorter patient survival were also described [8]. Therapies that harness and enhance antitumor effector cells, such as immune checkpoint blockade (ICB), have led to clinical benefits for several malignancies, including melanoma, non-small cell lung cancer and renal cell carcinoma [9]. The tight relationship between preexisting antitumor immune responses and patient responses to ICB in many cancer types [10] suggests that EOC patients may benefit from immunotherapy approaches.

In this review, we will first describe the immune context of EOC, highlighting relevant major immune populations that infiltrate tumors, their related functions in immune rejection or tolerance, and their associations with clinical outcomes. We will then discuss the immunotherapeutic strategies that were investigated in EOC mouse models, for their potential to prevail over the highly immunosuppressive EOC tumor microenvironment, including ICB, adoptive T-cell therapy (ACT), immunosuppressive microenvironment targeting, cytokine-based therapy and cancer vaccines. Finally, we will present an overview of clinical trials designed to assess the potential benefit of immune intervention in the treatment of EOC patients.

2. Immune Responses in Ovarian Cancer

2.1. Importance of the Immune Contexture in Cancer

Tumors are complex networks, in which tumor cells are surrounded by an intricate cellular microenvironment that encompasses immune cells. A large numbers and types of immune cells have opposite effects, leading to either the hinderance or promotion of tumor development [11]. Thus the immune contexture, defined by density, composition and functional state of the immune tumor-infiltrate, is a determining factor of tumor progression, and predictive for a patient’s prognosis and response to treatment [10,12], as recently validated for EOC [13]. Immune contexture is variable among tumor histological types and across anatomical sites in which tumors grow, thus considerably contributing to the tumor type- and localization-dependent outcomes [14,15]. We and others have established that, in addition to tumor cell-intrinsic factors, tumor growth regulation depends on local cues driven by tissue environment-specific components [15–18]. In agreement with this concept, distinct immune microenvironments were found in multiple tumor sites from a single EOC patient [7], or within a single organ [19], possibly explaining the heterogeneous fates of metastatic lesions. In a case of HGSC, immunogenomic approaches demonstrated that regressing and stable metastatic lesions were infiltrated by tumor-specific T lymphocytes, while, concomitantly, progressing metastases were “immune excluded”, and characterized by poor immune cell infiltration [7]. Tumors are infiltrated by adaptive immune cells (naïve, memory, effector, regulatory CD4⁺ or CD8⁺ T lymphocytes, and B cells) and innate immune cells [natural killer (NK) cells, macrophages, myeloid derived suppressor cells (MDSC), dendritic cells (DC), neutrophils and mast cells] [20] (Figure 1). In cancer, including EOC, each of these cellular components can paradoxically constrain and promote tumor development through a three-phase process referred to as cancer immunoediting, occurring during tumor progression and also in patients receiving anticancer immunotherapies [21]. In the first phase, called “elimination”, immune

cells can recognize and kill recently transformed malignant cells. During the second “equilibrium” phase, the rare tumor variants that have survived elimination can enter a non-growing dormant state that can last for long periods of time, during which immunogenicity is edited. Finally, in the third “escape” phase, tumor cells exit dormancy and proliferate again with the help of the immunosuppressive microenvironment [21] (Figure 1). The cancer immunoediting process provides the fundamental basis for studying immunity to EOC, and for the rational design of immunotherapies against EOC.

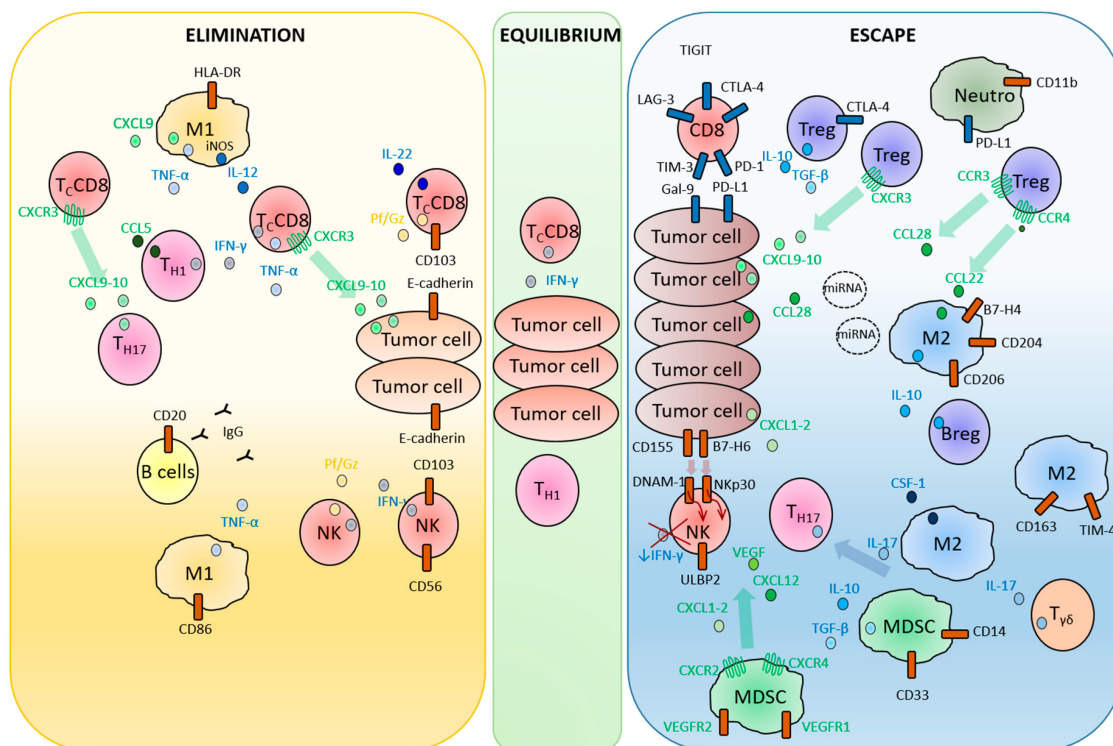


Figure 1. The immune landscape of epithelial ovarian cancer (EOC): cells, mechanisms and factors involved in tumor elimination or escape. EOC tumor elimination implicates cytotoxic cells, such as cytotoxic CD8⁺ T-cells (T_CCD8) or natural killer (NK) cells, that produce cytolytic perforin/granzymes (Pf/Gz), and various effector cytokines and CD20⁺ B cells, as well as IgG-producing plasmocytes. T_CCD8 are recruited to the tumor site via chemokine receptor expression and chemokines released in the microenvironment by other cells, including T_H17. Both T_CCD8 and CD56⁺ NK cells are retained at the tumor site through CD103–E-cadherin interactions. Finally, myeloid cells such as CD86⁺HLA-DR⁺ type-1 polarized macrophages (M1) perform antitumor roles through iNOS enzyme expression, secretion of TNF- α and T_H1–T_CCD8-stimulating cytokine IL-12. The intermediate equilibrium phase involves adaptive immunity components, in particular INF- γ ⁺ T_CCD8 and Th1 cells. In contrast, cells such as regulatory CD4⁺ T-cells (Treg), type-2 macrophages (M2), B regulatory cells (Breg), myeloid-derived suppressor cells (MDSC), suppressive neutrophils (Neutro), IL-17-producing $\gamma\delta$ T-cells (T $\gamma\delta$) and T_H17 generate an immunosuppressed microenvironment, favoring tumor escape. Treg are recruited to tumors via CXCL9, CXCL10, CCL28 or M2-secreted CCL22, and prevent antitumor response through IL-10, TGF- β and cell–cell contact-dependent mechanisms. In addition, M2 produce miRNA-containing exosome, IL-10 and CSF-1, all of which promote tumor progression. MDSC are recruited to tumors through vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, CXCR2 and CXCR4 expression, and VEGF, CXCL1, CXCL2 (CXCL1-2) and CXCL12 in the microenvironment. Breg and MDSC also secrete immunosuppressive IL-10 and TGF- β . Their recruitment, together with M2, is increased through T_H17-secreted IL-17. Finally, T_CCD8 and NK cells’ antitumor functions are inhibited via checkpoint expression, and via downregulation of DNAM-1 and Nkp30, following binding with tumor cells-expressed CD155 and B7-H6, thus triggering downregulation of IFN- γ production.

2.2. Adaptive Immune Responses in EOC

T lymphocytes: These represent central components of antitumor immunity. In EOC, CD8 and CD4 T-cells infiltrate tumor tissues and ascites, and exert antitumor functions through specific recognition of tumor antigens (TA) [22]. Following seminal studies on the key role of tumor-infiltrating lymphocytes (TIL) in predicting patient outcome [5,12,23], an important body of data corroborates the correlation between TIL and favorable prognosis in multiple solid cancers, including EOC. The survival benefit of TIL in EOC was actually studied as early as 1991 [24]. Coukos and colleagues, in particular, observed that 55% of advanced-stage EOC patients, with detectable intraepithelial CD3⁺ TIL, had a 5-year survival of 38%, in contrast to 4.5% in patients whose tumors contained no TIL [5].

CD8⁺ T lymphocytes: Although the overall CD3⁺ TIL population was shown to provide survival benefits for EOC patients [5], among CD3⁺ cells, intraepithelial CD8⁺ TIL appear to be central players in tumor immune control [25–27]. A meta-analysis, comprising 1815 ovarian cancer patients, encompassing all tumor grades, stages and histologic subtypes, validated CD8⁺ TIL as a robust outcome predictor [6]. In HGSC, CD8⁺ T-cells' migratory abilities, through the CXCL9/CXCL10-CXCR3 axis [28], as well as their tissue residency phenotype, characterized by α_E integrin CD103 expression [29,30], were associated with increased survival. St Paul et al. demonstrated that IL-22, produced by highly cytotoxic CD8⁺ TIL, was correlated with improved recurrence-free survival in EOC patients [31]. Following tumor infiltration, CD8⁺ TIL performs antitumor effector functions, through the exocytosis of perforin and cytotoxic granzymes, or through the release of interferon (IFN)- γ and tumor necrosis factor (TNF)- α [32]. In their seminal study, Coukos and colleagues highlighted that intratumoral TIL were associated with increased intratumor expression of IFN- γ and IL-2 [5]. As tumors progress, TIL become gradually exhausted, with increased expression of inhibitory receptors and reduced effector functions [33]. In EOC, CD8⁺ TIL express immune checkpoints (IC), including programmed cell death 1 (PD-1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), T-cell immunoglobulin and mucin domain-containing (TIM)-3 [34], the lymphocyte-activation gene (LAG)-3 [35] and CD112R (PVRIG) [36]. We and others have demonstrated in EOC that, despite their exhausted status, CD8⁺ TIL exhibit a sustained potential for cytokine production and proliferation [34,37].

CD4⁺ T helper lymphocytes: CD4⁺ T helper (T_H) cells provide support for CD8⁺ T-cell proliferation and expansion, via activation of antigen-presenting cells and the secretion of cytokines such as IFN- γ [38]. Similar to CD8⁺ TIL, a high frequency of CD4⁺ TIL correlates with improved EOC patient survival [39–42]. We previously demonstrated that the circulating NY-ESO-1-specific CD4⁺ T-cells in EOC patients are most commonly IFN- γ -secreting T_H1, and not immunosuppressive FOXP3⁺ T regulatory cells (Treg) [43]. In addition, we developed MHC Class II/NY-ESO-1 tetramers [44], allowing direct ex vivo quantification of NY-ESO-1-specific CD4⁺ T-cells in EOC ascites and solid tumor masses [45]. We showed that T_H1 cells accumulating in ovarian tumors are able to maintain an antitumor effector phenotype, despite a concomitant high infiltration by FOXP3⁺ Treg [45]. In an EOC preclinical model, T_H1 cells produced high levels of CCL5, enabling the recruitment and activation of DC in the tumor microenvironment, which eventually induces tumor-specific CD8⁺ T-cell activation [46]. In addition, T_H17 cells, accumulating in EOC tumor ascites, are able to recruit CD8⁺ effector T-cells through the production of CXCL9 and CXCL10, thus contributing to antitumor immunity [47]. Accordingly, T_H17 are associated with improved patient survival [47]. In contrast, another study demonstrated that, in mice and patients, chronic production of TNF- α in ovarian tumors promotes IL-17 production by T_H17, leading to myeloid cell recruitment, which in turn participate in tumor progression [48]. Since then, other studies have confirmed the accumulation of T_H17 in EOC, although their correlation with patient survival remains debatable [49,50].

CD4⁺ T regulatory lymphocytes (Treg): CD4⁺FOXP3⁺CD25⁺ Treg are strong suppressors of antitumor immunity through mechanisms including cell–cell interactions, via, for instance, CTLA-4 expression, and transforming-growth factor (TGF)- β and IL-10 cytokine secretion [51]. In EOC tumors, Treg preferentially accumulate in tumors and ascites [52,53]. Treg infiltration in ovarian tumors and

ascites often correlates with poor patient outcome [54,55], as they specifically suppress antitumor T-cells *in vivo*, and contribute to tumor growth [56]. Treg infiltration in ovarian tumors increases throughout EOC progression. Fiavola et al. characterized a strong T_H17 response in the early-stage disease, while stage II tumors are infiltrated by high numbers of Treg, as well as macrophages and DC, which produced CCL22, enabling the further recruitment of Treg [57]. Other chemokines induce Treg recruitment in ovarian tumors, such as CCL28, the overexpression of which was associated with the poor outcome in EOC patients [58]. In addition, we previously demonstrated that a major subset of $CXCR3^+T\text{-bet}^+Helios^+FOXP3^+$ Treg selectively accumulated in ovarian tumors, and suppressed the proliferation of $IFN-\gamma$ production by effector T-cells [59]. In contrast, Treg frequencies may also represent significant predictors of favorable prognosis in patients with familial ovarian cancer [60], or in optimally debulked HGSC patients. Nonetheless, the improved survival was also positively associated with other TIL markers, such as CD8 and CD3 [61].

Antigen-specific T-cell responses in EOC: Tumor antigens (Ag), recognized by $\alpha\beta$ T lymphocytes, can be classified into multiple categories, including neoantigens that are derived, specifically in tumors, from genetic alterations, cancer-testis Ag (CTA), tissue differentiation Ag, overexpressed Ag, and other factors [62]. Importantly, the good prognostic value of tumor Ag is related to the appropriate expression of Ag-processing machinery, as well as to a strong T-cell infiltration of ovarian tumors [63]. The neoantigen load in EOC is rather low, as comprehensive genomic profiling revealed a low overall tumor mutational burden among subtypes (e.g., 3.6 mutations/megabase in HGSC) [64]. In addition, like in other tumor types, few mutations (only 1.3%) are recognized by autologous tumor-associated T-cells in HGSC patients [65]. Nonetheless, comprehensive analyses of advanced EOC-associated T-cells revealed that, despite a relatively low number of somatic mutations, the identification of neoepitope-specific $CD8^+$ T-cells is achievable in EOC [66]. The presence of neoantigen-reactive T-cells in EOC patients was associated with improved survival [31]. CTA have been extensively studied in EOC, in particular the frequently expressed and highly immunogenic Ag NY-ESO-1. We previously delineated the phenotypes of NY-ESO-1-reactive $CD4^+ T_H1$ cells [43,45] and $CD8^+$ cytotoxic T-cells [34] accumulating in ovarian tumors. In particular, we showed that NY-ESO-1-specific $CD8^+$ EOC TIL are characterized by high IC expression, as well as by the expression of CD39 and tissue-resident memory T-cell markers [34]. Evidence of spontaneous humoral and cellular immune responses to NY-ESO-1 was reported in EOC patients [67,68], supporting the strategy of targeting it with vaccination [69]. In addition, recent mass spectrometry analyses in EOC tumors confirmed the presentation of peptides derived from other CTA, such as CAGE, which could be recognized by antigen-specific TIL [70], and MUC16, which are presented by MHC-I molecules and are highly immunogenic *in vitro* [71].

B lymphocytes: A body of data supports the role of B cells and plasma cells in shaping cancer immune responses [72]. In EOC, stromal or intraepithelial B lymphocytes are detected in tumors, but their role in tumor progression is debated [61]. Indeed, several B-cell subtypes, including naïve and memory B cells and regulatory B cells (Breg), accumulate in EOC and exhibit both pro- and antitumor functions [73]. Combined $CD20^+$ B and $CD8^+$ T HGSC TIL shows a higher prognostic value than $CD8^+$ TIL alone [26,74]. In addition, Balkwill's group demonstrated that HGSC omental metastases are infiltrated by memory B cells, directed at a restricted repertoire of Ag and producing tumor-specific IgG, thus supporting the development of an antitumor response [75]. Conversely, studies demonstrated that B cells infiltrating epithelial tumor tissues and omental metastases negatively correlate with patient survival [76–78]. Indeed, Breg subtypes, able to produce IL-10 and suppress the antitumor immune response, have been described in many cancer types, including EOC [79]. In particular, IL-21 was shown to induce granzyme B (GrB)-expressing Breg, which may reside within the EOC microenvironment and contribute to the suppression of adaptive immune responses by Treg-like mechanism [80].

2.3. Innate Immunity in the Context of EOC

Natural killer (NK) cells: Through an equilibrium between signals transduced by inhibitory and activating receptors, these innate lymphoid cells are able to exert immediate cytolytic activity through lytic granule release [81]. Increased numbers of CD56⁺ NK cells were reported in HGSC and endometrioid carcinoma (EC) subtypes, compared to MC and CCC [40], in particular in ascites. However, they seem to be functionally impaired [82,83]. Cells in the EOC microenvironment can express B7-H6 and CD155 that, respectively, trigger the downregulation of the NK cell-activating receptors Nkp30 and DNAM-1, hence impairing their IFN- γ production and cytolytic functions [84,85]. In addition, the MUC16 Ag, expressed by EOC cells, may protect them from recognition by NK cells, by inhibiting synapse formation, leading to the increased ability of EOC cells to metastasize [86]. Thus, the prognostic value of EOC-infiltrating NK cells is still under debate. Expression of NK cell receptor ligand ULBP2 by EOC tumors was correlated with less infiltration of T-cells, and poor prognosis [87]. In contrast, NK cell co-infiltration with cytotoxic T-cells into tumors has been associated with better EOC patient survival [29,78]. CD103-expressing NK cell infiltration, along with T-cell infiltration, correlates with increased 5-year survival rates in EOC patients [88]. The presence of CD56⁺ NK cells in EOC ascites was also associated with better patient outcome, and their antitumor functions could be boosted by IL-15-receptor stimulation [89]. Increased NK cell activity was also detected in the peripheral blood of EOC patients, and was correlated with significantly increased progression-free survival [90]. The ability of NK cells to mediate the killing of EOC tumors has been extensively described [91]. For instance, NK cells efficiently eliminate EOC tumor cells in 3D tumor spheroids, and reduce tumor progression in EOC tumor-bearing mice [92].

Macrophages: These myeloid cells can typically exert dual roles in cancer, by enhancing antitumor immune responses, or supporting progression through the establishment of an immunosuppressive microenvironment [93]. In EOC, long-lived resident macrophages and short-lived infiltrating macrophages are the two main sources of macrophages, both acquiring specific phenotypes through signals from the surrounding microenvironment [94]. In EOC, both resident and infiltrating macrophages differentiate into a mixed population of pro-tumorigenic type 2-like macrophages (M2) and antitumor type 1-like macrophages (M1), and constitute, in ascites in particular, a large fraction of immune cells [95]. Reinartz et al. analyzed the transcriptome of human ovarian tumor-associated macrophages (TAM), and revealed mixed populations, expressing either CD163 and IL-10 M2 markers or CD86 and TNF- α M1 markers. In this study, CD163 surface expression was correlated with ascites IL-6 and IL-10 concentrations, and was inversely correlated with patient relapse-free survival [96]. In EOC tumors and ascites, TAM are characterized by the expression of M2-related markers, such as CD163, CD204, CD206 and IL-10 [97], and their presence correlates with tumor progression [60,98] and poor patient survival [99]. Functionally, EOC TAM suppress antitumor responses by producing Treg-attracting chemokines, such as CCL22 [56] or CCL18 [100], and by expressing co-inhibitory molecules, such as B7-H4, which inhibits T-cell cytotoxicity [101]. Zhou et al. demonstrated the ability of EOC TAM to release miRNAs-enriched exosomes, which suppress the STAT3 transcription factor and induce a Treg/T_H17 imbalance, thus facilitating EOC progression and metastasis [102]. In addition, TAM secrete the colony-stimulating factor 1 (CSF-1) that contributes to tumor growth, invasion and metastasis in serous and mucinous EOC [98]. EOC TAM, such as B7-H4⁺ TAM, are also able to interact with other immunoregulatory cells such as Treg, which in turn stimulate IL-10 and IL-6 production by TAM, further enhancing the immunosuppressive tumor microenvironment and contributing to poor patient outcome [54]. Protumorigenic TAM polarization and its functions in EOC are regulated by transcription factors such as proliferator-activated receptor (PPAR) β/δ , targeting multiple genes, such as *LRP5* or *CD300A*, associated with tumor progression [103], or *GATA3*, the expression of which was associated with poor prognosis in HGSC [104]. While TAM are key suppressors of antitumor immune responses, they also increasingly appear to be crucial in promoting the development of the premetastatic niche and metastatic spreading during EOC [105–107], in particular a unique subset of CD163⁺Tim4⁺ resident omental macrophages [108].

In contrast, some studies highlighted that intratumor, but not stromal, M1-polarization, characterized by HLA-DR and inducible nitric oxide synthase (iNOS) expression, may also be associated with the extended overall survival of EOC patients [109,110]. In EOC ascites, M1 are able to produce IL-12 and TNF- α , which will prompt a cytotoxic T-cell response against tumor cells [111,112]. Recently, Coukos and colleagues demonstrated that IFN- γ induces CXCL9-expression by macrophages and DC, thus orchestrating T-cell infiltration in EOC tumors in patients responsive to immunotherapy [113].

Myeloid Derived Suppressive Cells (MDSC): These are a heterogeneous population of immature myeloid cells, which contribute to tumor progression and potentially dampen antitumor immune responses, through mechanisms including the expression of immunosuppressive mediators (e.g., arginase, TGF- β , IL-10) [114]. Cui et al. established, for the first time, the clinical impact of CD33⁺ MDSC, which were significantly associated with shorter overall survival and a reduced disease-free interval in HGSC [115]. Recently, the same group determined that the monocytic-MDSC subset appears to be the best predictor of poor survival [116]. MDSC, in particular CD14⁺HLA-DR^{low} MDSC, are enriched in peripheral blood and ascites during EOC, and their suppressive activity is correlated with ascites-derived IL-6 and IL-10 [117]. The immune profiling of EOC patient blood demonstrated a major involvement of MDSC in innate immunosuppression [118]. MDSC recruitment induces EOC progression, and may involve chemokine receptors such as CXCR2, which ligands are upregulated in tumor cells via *Snai1* transcriptional factor action [119]. In addition, prostaglandin (PG) E2 appears to play a central role in CXCL12 production and CXCR4-mediated MDSC accumulation, as demonstrated by Obermajer et al., who correlated the PGE2 and CXCL12 levels in EOC ascites with the presence of CD11b⁺CD14⁺CD33⁺CXCR4⁺ MDSC [120]. Vascular endothelial growth factor receptor (VEGFR) expression in EOC tumors can induce MDSC recruitment and inhibit local immunity [121]. However, while targeting VEGF to inhibit MDSC recruitment seems an interesting therapeutic option, it may also trigger, in parallel, tumor hypoxia and GM-CSF expression, which will sustain MDSC recruitment in ovarian tumors [122].

Other cells: $\gamma\delta$ T-cells, in particular the V δ 1⁺ subtype, were significantly increased in EOC patient tumors compared to normal ovarian tissue [123]. Rei et al. demonstrated, using a syngeneic EOC mouse model, that V γ 6⁺ $\gamma\delta$ T-cells were able to promote tumor growth through secretion of IL-17, allowing the recruitment of suppressive peritoneal macrophages [124]. Abundant IL-17-producing $\gamma\delta$ T-cells are positively correlated with larger tumor sizes and lymph node metastases in advanced EOC patients [125]. In addition, neutrophils are contributors to innate immunity, representing new biomarkers of EOC outcome and new therapeutic targets [126]. Indeed, a high neutrophil-to-lymphocyte ratio is predictive of poor overall survival in advanced stage EOC [127]. Neutrophil influx into the omentum was identified, in orthotopic mouse EOC models, as a prerequisite premetastatic step through the formation of neutrophil extracellular traps [128]. Neutrophils, exhibiting a suppressor phenotype, can also suppress T-cell antitumor activity in the EOC microenvironment [129], for instance through upregulation of PD-L1 [130].

3. Preclinical Investigations for the Development of Effective Immunotherapies in Ovarian Cancer

3.1. Use of Mouse Models for the Design of Immunotherapies

Mouse models have permitted considerable advances in the understanding of EOC biology and the development of therapeutic strategies, including immunotherapy. They have been shown to recapitulate the anatomical features of various human EOC subtypes, mimicking tumor growth, metastatic spread and the tumor immune microenvironment, and recapitulating patient responses to therapies [131]. Important characteristics, relevant to most human EOC subtypes, have been taken into account in the design of EOC mouse models. Genetic modifications, for instance, are well recapitulated in genetically engineered mouse models (GEMM), including genetic alterations in *Tp53* and *Brca* genes [132]. GEMM are relevant models for assessing immunotherapy efficacy, as

genetic alterations, such as those occurring in the *Tp53* gene, may be involved in modulating the tumor immune microenvironment, such as in the increased expression of PD-L1 [133] or the production of pro-inflammatory cytokines [134]. Recently, Balkwill and colleagues used GEMM, a knockout for *Tp53*, *Brca2* and *Pten* genes, to establish new syngeneic EOC mouse cell lines [135]. Once implanted orthotopically, the tumors develop microenvironments relevant to human primary EOC tumors and metastases, thus opening new windows for studying immunotherapy in EOC preclinical models [135].

The location of transplanted tumors in EOC mouse models is key, as the immune microenvironment's composition is dependent on the tumor's anatomical location [16]. While mice injected subcutaneously (SC) develop tumors readily accessible for the evaluation of the response to treatment, these tumors do not constitute an immune microenvironment representative of the human disease [16]. In comparison to SC mouse models, EOC orthotopic mouse models, achieved by surgically implanting tumors in the bursa ovari (mouse counterpart of human ovary) or by injecting tumors intraperitoneally (IP), mimic human tumor histology, vasculature, metastatic biology and immune microenvironment formation [136]. Mice with deficient immunity are used for the implantation of human tumor cell lines, most frequently SK-OV-3 and A2780 cells, or patient-derived xenografts (PDX) directly harvested from EOC patients. However, these humanized mouse models lack the appropriate immune microenvironment when human tumor cells are xenografted, and probably maintain not much time the patient's immune tumor microenvironment following PDX transplantation, hence limiting their usefulness in the evaluation of immunotherapy. Nevertheless, they can be valuable in testing human adoptive T-cell therapy, or when human tumor cells are co-implanted with human immune components. For instance, an HGSC-PDX model was validated to assess the efficacy of anti-PD-1 therapy, by adoptively transferring in vitro-expanded autologous TIL into these mice [137]. Created syngeneic EOC mouse models, particularly using the ID8 cell line, established in 2000 by Roby and colleagues [138], is probably the most commonly employed method in the development of immunotherapies such as ICB [139,140] or the DC vaccines [141]. The peritoneal tumors generated by IP injection of ID8 cells (a model widely described by the Balkwill's group) develop a complex microenvironment, with SMA⁺ fibroblasts, CD3⁺ T-cells, CD68⁺ macrophages and neo-vasculature [142]. However, the ID8 model does not contain most of the EOC-associated mutations [143], including *Tp53* and *Brca2* mutations, which may be artificially introduced into the cells using CRISPR-Cas9 technology [144].

3.2. Preclinical Assessment of Immunotherapies

Immune Checkpoint Blockade: IC expressed on T-cells either enhances or suppresses T-cell activation following binding to their ligands. ICB, using monoclonal antibodies (mAb), is currently considered as the most effective immunotherapy in many cancers, with most studies assessing the inhibitory IC PD-1 or its ligand PD-L1, and CTLA-4 [145]. PD-L1 expression in ovarian cancer cells, in particular the widely used ID8 cell line, was demonstrated to repress T-cell antitumor response [146]. Used as monotherapy, neither ICB (anti-PD-1 and anti-CTLA-4) nor activating antibodies (anti-OX40 and anti-CD137) had any significant impact on ID8 tumor-bearing mouse survival [139,140], possibly due to the compensatory upregulation of additional checkpoints on T-cells, such as LAG-3 [147]. Combination ICB therapies, however, proved efficient in EOC preclinical models. When the PD1/PD-L1 pathway blockade is combined with stimulatory anti-OX40 [140], or with anti-CTLA-4 and anti-CD137 [139,148], ID8-tumor bearing mice achieve a prolonged survival, and exhibit an increased CD8⁺ and Foxp3⁺CD4⁺ T-cell-to-Treg ratio, as well as a reduction of MDSC. Similarly, combined anti-PD-1 blockade and glucocorticoid-induced TNFR related protein (GITR)-stimulating mAb induces potent antitumor immunity in the ID8 EOC mouse model, which can be further promoted by chemotherapy [149]. In addition, combinations of other ICB, such as anti-TIM-3, or activating anti-CD137, confer long-term protection on ID8 tumor-bearing mice [150]. In most studies, mAb are administered at the early stage of the disease (15 days in most ID8 models), and their efficacy in the late-stage disease, when ascites form, remains to be evaluated. ICB, including PD-1/PD-L1 blockade, can produce synergistic

antitumor effects, and significantly improve ID8 tumor-bearing mouse survival, when combined with chemotherapy, such as paclitaxel, which is able to upregulate PD-L1 expression in tumor cells [151], or trabectedin [152]. Carboplatin, however, despite its ability to increase CD4⁺ and CD8⁺ T-cell, and decrease Treg and MDSC, infiltration into tumors, does not appear to improve the effect of PD-1/PD-L1 blockades [153]. Other agents, aiming to modify the tumor immune context, were used in order to improve ICB efficacy. For instance, the stimulator of interferon genes (STING) agonists increases antigen presentation, CD8⁺ T-cell infiltration and IFN response in ID8 tumors, when combined with anti-PD-1, hence drastically improving mouse survival [154]. Decitabine, a DNA methyl transferase inhibitor, improves the antitumor effect of anti-CTLA-4 treatment, by extending survival in friend leukemia virus B (FVB) mice IP-injected with the BR5FVB1-Akt ovarian cancer cell line. Indeed, the combination triggers memory T-cell infiltration, and the production of cytokines related to effector CD8⁺ T-cells and NK cells in the peritoneal fluid [155]. PARP inhibitors (PARPi), such as veliparib [156] or niraparib [157], can increase the efficacy of anti-CTLA-4 or anti-PD-1 therapies, respectively, through the type II IFN, as well as the memory T-cell-mediated, antitumor effects in both cases.

Adoptive T-cell therapy (ACT): ACT involves the ex vivo selection of naturally-arising autologous antigen-specific T-cells, or the in vitro generation of specific T-cells, by transducing bulk autologous T-cells with viruses encoding modified TCR, specific for tumor Ag-derived epitopes. These cells are then expanded and re-infused in patients in order to achieve tumor targeting. In the ID8 model, the transfer of naïve T-cells, primed in vitro against ID8 Ag, combined with the depletion of tumor-associated immunosuppressive DC, results in durable rejection of EOC [158]. In this study, the therapeutic activity required the expression of perforin and CCL5 by adoptively-transferred T-cells [158]. T-cells can also be genetically modified to express a chimeric antigen receptor (CAR), encoding the tumor Ag-binding domain of an immunoglobulin linked to T-cell costimulatory molecules [159]. Preclinical studies, using humanized xenografted mouse models, assessed the activity of CAR T-cells against several human EOC Ags. For instance, Brentjens's group used human EOC-bearing SCID-Beige mice to demonstrate the therapeutic efficacy of adoptively transferred CAR T-cells, targeting the extracellular conserved domain of MUC16 (MUC16^{ecto}) [160]. More recently, the preclinical antitumor efficacy of MUC16^{ecto}-targeting CAR T-cells was improved by genetically modifying them to produce IL-12 [161]. Other proteins highly expressed in EOC were recently targeted by CAR T-cells, including mesothelin [162], folate receptor (FR) [163], 5T4 oncofetal Ag [164] and B7-H3 [165], thus effectively controlling tumor growth in ID8 or human EOC-grafted mice. Other preclinical studies demonstrated the antitumor efficacy of CAR T-cells directed against adhesion molecules-expressing cells, including EpCAM [166], $\alpha v \beta 6$ integrin [167] and L1-CAR [168], in human EOC-xenografted mice, which reported tumor regression and significantly prolonged survival.

Immunosuppressive microenvironment targeting: Targeting ovarian tumor-infiltrating immunosuppressive cell subsets is a potential strategy for opposing EOC tumor progression. For instance, immunosuppressive TAM limit the efficacy of antitumorigenic thymoquinone therapy, and their combination with the macrophage-depleting drug liposomal clodronate restores treatment efficacy in the ID8 model [169]. Targeting the CSF-1 receptor (CSF-1R) pathway, which is central to macrophage differentiation and survival, reduces TAM infiltration in ascites [170], and overcomes treatment resistance when combined with anti-VEGF [171]. Monocyte recruitment can be prevented through the targeting of chemokines, such as CCL2. Trabectedin, a DNA-damaging alkaloid, was found to inhibit CCL2 and IL-6 production, exerting selective toxicity for TAM in an EOC mouse model [172]. Another strategy to deplete TAM consists of exploiting their phenotype, which potentially includes the elevated expression levels of folate receptor-2 (FR2) in human and murine EOC. Indeed, FOLR2⁺ TAM can be effectively depleted, in preclinical ovarian tumors and ascites, using G5-methotrexate nanoparticles [173]. Vascular leukocytes and Tie2⁺ monocytes express high levels of CD52, and can be targeted using the anti-CD52 mAb Alemtuzumab. This therapy exhibits potent anti-myeloid and anti-angiogenic properties, thus restricting EOC growth in the ID8 model [174]. TAM can also be re-polarized, from regulatory M2 to antitumor M1, through NF- κ B targeting, thus favoring Th1

cytokine productions and inhibiting tumor growth in mice [175]. Zhang et al. described nanoparticles that can deliver an in vitro-transcribed mRNA, encoding M1-polarizing transcription factors, IFN regulatory factor 5, and activating kinase IKK β . In an ID8 model, it was observed that infusion of the nanoparticles reprograms TAM to an antitumor phenotype, which induces antitumor immunity and promotes tumor regression [176]. Natural plant-derived products, such as neferine, also inhibit M2 polarization in the EOC xenograft mouse model [177]. Finally, epigenetic modulators, such as bromodomain inhibitor JQ1, were demonstrated to prevent myeloid cell-related immunosuppression, by significantly reducing PD-L1 expression in TAM and DC, thus inducing increased T-cell cytotoxic activity and reducing ovarian tumor growth [178]. Zahnow's group observed that combining DNA methyltransferase inhibitors with histone deacetylase inhibitors, or with an ornithine decarboxylase inhibitor, can reduce M2 infiltration in tumors, while increasing tumor-killing M1, T- and NK cell activation, thus delaying EOC progression in an ID8 VEGF-expressing mouse model [179,180]. Other immunosuppressive cells, such as Treg, that significantly infiltrate the EOC microenvironment, have been targeted in preclinical models. For instance, CCR4⁺ Treg recruitment was targeted by Chang et al., who administrated anti-CCR4, in a NOD scid gamma (NSG) humanized mouse model bearing human CCL22-secreting EOC, and engendered the potent restoration of antitumor immunity [181]. Righi et al. proposed the modulation of the CXCL12–CXCR4 axis, involved in Treg and MDSC recruitment, through the use of a selective CXCR4 antagonist. They were able to increase tumor apoptosis and necrosis, and reduce intratumoral Treg, in a syngeneic EOC mouse model [182]. The same group demonstrated that combining the CXCL12–CXCR4 axis blockade with anti-PD-1 further improves the antitumor effect of the CXCR4 antagonist [183].

Cytokines-based therapies: Potent immunomodulatory cytokines, including IL-12, IL-2, IFN- α and IFN- γ , are known to enhance antitumor immune responses, and some can exert direct cytotoxicity in EOC [184]. Initial studies in EOC mouse models highlighted an in vivo antitumor effect following the direct repeated injection of recombinant IL-12 [185], and underlined that IL-12 potently induces INF- γ , which stimulates tumor infiltration by lymphoid cells [186]. Later, liposomal delivery of IL-12 [187], and gene-based therapy delivery of IL-12 [188], proved efficient in EOC preclinical models. Other strategies of IL-12 delivery were validated as being able to induce strong antitumor effects, such as through IL-12-secreting transformed fibroblasts in the ID8 model [189], or through an armed-oncolytic herpes simplex virus in a GEMM developing spontaneous EOC [190]. The in vivo transduction of IL-12- and CCL27-encoding genes into preexisting murine EOC induced tumor regression and the development of long-term specific immunity [191]. Bankert et al. developed a humanized PDX-NSG mouse model, and evaluated the efficacy of human IL-12-loaded liposomes as a potential immunotherapy for EOC. Following treatment, they observed activation of T- and NK cells among TIL, leading to increased IFN- γ production [192]. IFN-based therapies were also initially tested via direct intraperitoneal injection in EOC preclinical models [193]. IFN- α is able to boost the antitumor effect of paclitaxel [194]. In addition, IFN- γ - and IFN- α 2a-based therapy synergizes with monocyte adoptive transfer, mediating a profound antitumor effect in EOC-xenografted immunodeficient mice [195]. Nonetheless, caution may be necessary when using IFN- γ in particular, as it is known to upregulate suppressive PD-L1 in EOC cells [146], thus potentially promoting OC progression [196].

Vaccines: As inducers of specific adaptive immune responses, vaccines are promising for antitumor immunotherapy [197]. Therapeutic anticancer vaccines aim to boost or prime adaptive immune responses by delivering tumor Ag, and can be classified in different categories, such as cell-based, peptide/protein, epigenetic and genetic vaccines [197]. Despite its low mutational burden, the ID8-EOC mouse model was used to design neoantigen-targeting peptide vaccines. In this model, however, although vaccination with 17 synthetic peptides, covering the potential neoantigens, induced CD4⁺ or CD8⁺ T-cell responses to 7 mutated peptides, no survival benefit was observed [198]. This could be due to the lack of appropriate processing and presentation of these epitopes in tumor cells, or to the low avidity of the vaccine-induced T-cells, that were, as shown by the authors, not able to recognize tumor cells. Cell-based vaccines can use DC pulsed with whole tumor lysates, thus covering the complete

repertoire of tumor Ag. Coukos' group demonstrated the preclinical efficacy of DC, pulsed with hypochlorous acid (HOCl)-oxidized ID8-OVA whole tumor lysate, in eliciting an IFN- γ -dependent specific antitumor response, and in controlling tumor progression [141]. GEMM mice are useful in assessing vaccine efficacy using human tumor Ag. For instance, mice expressing human MUC1, and exhibiting *Pten* deletion and an activating *Kras* mutation, spontaneously develop ovarian tumors highly infiltrated by FOXP3⁺ Treg and dysfunctional DC [199]. In this model, vaccination with type 1-polarized DC loaded with MUC1 peptides reduces Treg infiltration and extends survival [199]. In another study, Chang et al. assessed the efficacy of a cell-based vaccine targeting mesothelin, an EOC Ag, in combination with an IL-12-encoding virus, and demonstrated enhanced specific CD4⁺ and CD8⁺ T-cells, and prolonged survival [200]. Other types of vaccines, such as DNA or RNA vaccines, used to induce the in vivo expression of selected Ag in cells, such as DC, infiltrating the vaccination site, proved efficient in preclinical cancer models (mainly in tumor types other than ovarian cancer) [197,201,202]. However, vaccines are currently being tested in clinical trials for the treatment of EOC patients [203].

4. Clinical Status of Immunotherapy Efficacy in Ovarian Cancer

4.1. Immune Checkpoint Blockade Monotherapy

The results from several ICB phase I/II clinical trials in ovarian cancer showed overall response rates (ORR) of 10–15% for recurrent ovarian cancer, including heavily treated and platinum-resistant patients, in most studies (Table 1). Complete and durable responses have been found in a minority of patients, partial responses in up to 10%, and stable disease in approximately 30% of cases. Median progression free survival (PFS) varies between 2 and 3.5 months, and OS between 17 and 20 months [204–209]. Grades 3 and 4 toxicity are observed in 7–40% of patients, and immune-related events in 16.8–22.6%. It is unclear whether PD-L1 expression is associated with improved response rates in ovarian cancer. In one study, assessment of PD-L1 expression using a combined positive score (CPS), i.e., the determination of PD-L1 expression in tumor and immune cells, showed that such expression was significantly associated with response rate, with ORR of 4.1% for CPS < 1.5, and ORR of 10% for CPS \geq 10 [204]. The ORR and survival outcome are significantly increased in patients with a longer platinum-free interval, treated with less than three lines of chemotherapy [204]. Improved patient selection and a combination with other approaches, in particular combinations with chemotherapy, PARPi and angiogenic inhibitors, aim to optimize ICB activity.

Table 1. Published results from selected ICB clinical trials for recurrent EOC.

Study	Phase	Drug	Population	N	ORR (%)	Stable Disease	PFS Months	OS Months	Grade 3/4 Toxicity (%)
Anti-PD-1									
Matulonis et al. [204]	II	Pembrolizumab	Refractory/recurrent OC Cohort A	376	8	29.3	2.1		19.7
			<3 lines, PFI 3–12 months Cohort B	285	7.4	10.5	2.1	NR	
			4–6 lines, PFI > 3 months	100	9.9	27.5	2.1	17.6 months	
Hamanishi et al. [206]	II	Nivolumab	Recurrent/persistent OC 1 to 3 lines PFI < 12 months	20	15	30	3.5	20	40
Zamarin et al. [207]	II	Nivolumab	Recurrent/persistent OC 1 to 3 lines	100	12	29	2	21.8	33
		Nivolumab and Ipilimumab	PFI < 12 months		31.4	39	3.9	28.1	49
Anti-PD-L1									
Disis et al. [205]	Ib	Avelumab	Recurrent OC >3 lines (64.8%)	125	9.6	42.4	10.2% at 12 months	11.2	7.2
Brahmer et al. [208]	I	BMS-936559	>1line	17	6	18	22% at 24 weeks		9
Anti-CTAL4									
Hodi et al. [209]	I	Ipilimumab	>1 line and GVAX vaccination (GM-CSF)	9	10	33			22

N: number of patients; ORR: overall response rate; PFS: progression-free survival; OS: overall survival; OC: ovarian cancer.

Of interest, a mAb specific to carcinoembryonic Ag (CEA), that leads to tumor opsonization and elimination by antibody dependent cell-mediated cytotoxicity (ADCC) or complement-mediated cytotoxicity (CDC) [210], could actually have an innate ICB activity through the blockade of CEA's interaction with carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), the latter of which enacts an inhibitory activity in NK cells [211]. NEO-201 enhances NK cell function, including cytokine production and ADCC in vitro. NEO-201 has been shown to decrease tumor growth in human pancreatic cancer xenograft models. A phase I dose escalation trial is currently underway, to assess safety in patients with solid tumors, including mucinous ovarian carcinoma (NCT03476681).

4.2. Immune Checkpoint Blockade Combination Strategies

PARP inhibitors and ICB: Maintenance treatment with PARPi has significantly improved the prognostic outcome of patients with platinum-sensitive ovarian cancer [212–216]. Homologous recombination deficiencies (HRD), including *BRCA1/BRCA2* and other DNA damage repair (DDR) gene mutations, occur in approximately half of HGSC patients, and motivate the use of non-conservative DNA repair mechanisms in altered cells, thus increasing the mutational load [217]. PARPi lead to synthetic lethality, whereby cell death results from the functional loss of two DDR proteins, one due to the germline or somatic tumor mutation responsible for HRD, and one to PARP inhibition [218]. In addition to the mutational burden, HRD is correlated with high TIL infiltration and PD-1 expression in EOC [219]. In addition, PARPi induce PD-L1 upregulation through increased IFN- γ expression [220]. Based on this rationale, several ongoing phase III trials are assessing the combination of ICB and PARPi in the frontline and recurrent settings (Table 2).

Table 2. Ongoing Phase III ICB, PARPi and/or Anti-VEGF trials.

Study	N	Arms	Primary Endpoint	Recruitment Status
Frontline setting				
GINECO FIRST-ENGOT Ov44 (NCT03740165)	912	Arm 1: CT + Bev + Placebo followed by Placebo Arm 2: CT + Placebo Followed by Placebo + Niraparib Arm 3: CT + Dostarlimab followed by Dostarlimab+Niraparib	PFS	Recruiting
AGO DUO-ENGOT (NCT03737643)	1056	Arm 1: CT + Bev + Placebo followed by Bev + Placebo Arm2: CT + Bev + Durvalumab followed by Bev + Durvalumab+Placebo Arm3: CT + Bev + Durvalumab followed by Bev + Durvalumab + Olaparib	PFS in non tBRCAmut	Recruiting
KELYNK-001 EBOGT-Ov43 (NCT03740165)	1086	Arm 1: CT + Placebo followed by Placebo +/- Bev Arm 2: CT + Pembrolizumab followed by Placebo +/- Bev Arm 3: CT+Pembrolizumab followed by Pembrolizumab + Olaparib +/- Bev	PFS and OS	Recruiting
ATHENA (NCT03522246)	1012	Arm 1: CT followed by Placebo Arm 2: CT followed by Rucaparib + Placebo Arm 3: CT followed by Nivolumab + Placebo Arm 4: CT followed by Rucaparib + Nivolumab	PFS	Recruiting
IMagyn 50 GOG3015-ENGOT Ov39 (NCT 03038100)	1300	Arm 1: CT + Bev + Placebo Arm 2: CT+ Bev+ Atezolizumab	PFS, OS PSF and OS assessed by PD-L1	Active Not recruiting
Recurrent platinum-sensitive disease				
ATALANTE/ENGOT Ov29 (NCT02891824)	405	Arm1: Placebo + Bev + platinum-based chemotherapy. Arm 2: Atezolizumab + Bev + platinum-based chemotherapy	PFS	Active, not recruiting
ANITA/GEICO 69/ENGOT Ov41 (NCT03598270)	414	Arm 1: Carboplatin + Niraparib Arm 2: Carboplatin + Niraparib + Atezolizumab	PFS	Recruiting

Table 2. Cont.

Study	N	Arms	Primary Endpoint	Recruitment Status
Recurrent platinum resistant				
EORTC -1508 (NCT02659384)	160	Arm 1: Bev + Atezolizumab Arm 2: Bev + Atezolizumab + aspirin	PFS at 6 months	Recruiting

CT: Carboplatin-taxol; Bev: Bevacizumab; PFS: progression-free survival; OS: overall survival.

In platinum-sensitive recurrent disease, the phase II basket trial, MEDIOLA, evaluated the safety and efficacy of using Durvalumab (anti-PD-L1) and Olaparib (PARPi) in patients with germline *BRCA* mutations. The preliminary results show an ORR of 63%, including 19% complete responses (CR) and 44% partial responses (PR), and a low rate of adverse events (AEs) [221]. A phase I escalation study of Durvalumab and Olaparib, or Cediranib (anti-VEGFR), in recurrent EOC also showed improved disease control rates, compared to monotherapy strategies. Authors reported 17% and 50% PR rates, in the Olaparib and Cediranib arms, respectively [222]. In platinum-resistant disease, the phase I/II trial, TOPACIO/KEYNOTE-162, assessed Niraparib (PARPi) with Pembrolizumab (anti-PD-1) in 62 patients with recurrent EOC, irrespective of *BRCA* status. The ORR was 18%, with 5% CR, 13% PR, and 28% stable disease (SD). Median PFS was 3.4 months, and OS was not reached. High-grade immune-related AEs occurred in 6% of patients, anemia being the most common AE [223]. Results from both trails showed increased response rates to ICB using combination strategies with PARPi, even in *BRCA* non-mutated patients.

ICB and VEGF inhibitors: Antiangiogenic agents can promote normal vessel architecture, reduce hypoxia and improve antitumor immunity, by increasing CD8⁺ T-cell tumor infiltration, enhancing antigen presentation, or inducing TAM polarization to M1-subtype [224]. A dose-escalation phase I trial of Olaparib, Durvalumab and an anti-VEGF1-3, in the platinum-resistant recurrent setting, showed 44% PR [225]. As stated above, a dose-escalation phase I trial of Durvalumab showed the safety profile and activity for a combination with Olaparib or Cediranib [222]. Several ongoing phase III trials are assessing the efficacy of combination strategies using ICB and antiangiogenic agents in the frontline and recurrent settings (Table 2).

4.3. Vaccine Strategies

Targeting shared antigens: Aberrant overexpression of the folate binding protein or folate receptor alpha (FR α) is observed in more than 80% of ovarian cancers. FR α contributes to carcinogenesis through cell growth regulation and signaling functions, and has also been associated with chemotherapy resistance and poor prognosis [226]. Phase I/II FR α vaccine trials have demonstrated the low toxicity profile, and increased T-cell immunity, in small cohorts of recurrent ovarian cancer patients [227,228]. The best ORR were obtained after frontline treatment or in patients treated with less than 3 lines of chemotherapy [229,230]. Based on these results, a phase III trial has been conducted to assess PFS in platinum-resistant ovarian cancer patients with FR α expression, randomized to Mirvetuximab soravtansine (IMGN853) or standard chemotherapy (FORWARD I trial, NCT02631876).

In addition, several phase I trials have assessed vaccination strategies targeting P53, mutated in over 95% of HGSC, in platinum-resistant patients, and yielded rather unsatisfactory results [231–233]. A single study, nonetheless, using a modified recombinant vaccinia ankara vaccine, delivering wild type human p53 (p53MVA), in combination with gemcitabine chemotherapy found a significant association between P53-specific vaccine-induced CD4⁺ and CD8⁺ T-cell responses and PFS [233].

Cancer-testis Ag (CTA): Vaccination strategies targeting the CTA NY-ESO-1 have been developed in the clinic, using long peptides combined with adjuvants, recombinant viruses, or epigenetic modifiers. Published I/II trials have demonstrated the immunogenicity of long peptide/adjuvant and viral vector vaccines, which induced humoral and T-cell responses. However, most clinical trials included small numbers of patients, and were not initially designed to evaluate clinical efficacy [69,234,235]. A review, including a large cohort of cases, demonstrated the increased clinical responses of, and significant OS

advantages for, patients with NY-ESO-1⁺ tumors treated with immunotherapy strategies targeting the Ag [236] (Table 3).

Table 3. Selected ongoing vaccination trials.

Study (NCT)	Phase	Type of Vaccine	N	Population	Primary Objective	Recruitment Status
NCT01536054	I	ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine with sirolimus	42	Stage II–IV ovarian, FT or primary peritoneal cancer	Safety	Completed
NCT00616941	I	NY-ESO-1 OLP4 + Montanide + Poly-ICLC	28	Stage II–IV and recurrent disease ovarian, FT or primary peritoneal cancer	Safety	Completed
NCT00112957	I/II	Recombinant vaccinia-NY-ESO-1 (rV-NY-ESO-1) and recombinant fowlpox-NY-ESO-1 (rF-NY-ESO-1)	23	Ovarian, FT or primary peritoneal cancer with NY-ESO-1 or LAGE-1 expression	12 months DFS	Completed
NCT02166905	I	IDO1 inhibitor INCB024360 in combination with DEC-205/NY-ESO-1 fusion protein CDX-1401 and poly ICLC	62	Ovarian, FT or primary peritoneal cancer in remission after CT for primary or recurrent disease	Safety Toxicity PFS	Recruiting
NCT00948961	I/II	CDX-1401 in combination with Resiquimod and/or Poly-ICLC	70	Ovarian cancer and other solid tumors with NY-ESO-1 expression	Safety	Completed
NCT01673217	I	Decitabine, NYESO-I protein mixed with montanide and (GM-CSF)	18	Recurrent ovarian, FT or primary peritoneal cancer	Safety	Completed
NCT02432378	I/II	Cisplatin + CKM + Celecoxib + DC intranodal vaccine	25	Recurrent platinum-sensitive ovarian cancer	Safety, CD8 in the peritoneal cavity	Recruiting
NCT03029403	II	DPX-Survivac Vaccine+pembrolizumab + cyclophosphamide	42	Ovarian, FT or primary peritoneal cancer after first line	ORR	Recruiting
NCT02759588	I/II	GL-ONC1 +/- chemotherapy +/- Bevacizumab	64	Resistant/refractory	Safety, PFS, Ca125, ORR	Recruiting

FT: fallopian tube; DFS: Disease-free survival; IDO1: Indoleamine-pyrrole 2,3-dioxygenase; polyICLC: Polyinosinic-Polycytidylic acid with Polylysine and Carboxymethylcellulose; CT: chemotherapy; ORR: overall response rate; Ca125: carbohydrate antigen 125.

Targeting neoantigens: Recent early-phase clinical studies, performed in various cancer types, have demonstrated the possibility of enhancing neoantigen-specific T-cell responses with personalized vaccines [237,238]. However, only a small proportion of non-synonymous mutations will lead to antigenic peptides and tumor recognition by T-cells specific for these peptides [237]. Approaches to target neoantigens include vaccination with long peptides encompassing the mutation-encoded amino acid combined with adjuvants, and adoptive T-cell transfer.

Although neoantigen vaccines have been preferentially developed in tumor types with a high mutational burden [237], neoantigen-specific T-cells are found in patients with low mutation load tumors, including EOC [66], and personalized neoantigen-based vaccines have been used in such tumor types [239]. Recently, personalized vaccination, using oxidized autologous whole-tumor lysates, was

administered alone, in combination with bevacizumab, or with cyclophosphamide and bevacizumab, and was tested in a cohort of 25 patients with recurrent EOC until progression. The vaccine induced specific CD8⁺ and CD4⁺ polyfunctional T-cell responses, which were correlated to PFS. The vaccine amplified preexisting neo-epitope T-cell responses, and induced new responses to peptides harboring amino acids encoded by non-synonymous somatic mutations [240].

4.4. Adoptive T-Cell Transfer

ACT trials have shown the objective and durable responses of several patients affected with various malignancies, in particular melanoma [241]. The efficacy of ACT has been explored in early-phase clinical trials for 20 years. Initial studies proposed a combination of IL-2-expanded TIL infusion or intraperitoneal administration with chemotherapy, resulting in variable response rates [242–245]. Later, studies in the clinic used targets, through TCR transgenic or CAR T-cell transfer approaches, in EOC, including CTA, FR α , MUC16, HER2, WT1 and p53 (Table 4). Multiple preclinical studies and some early-phase clinical trials have demonstrated the feasibility of this approach, and T-cell reactivity to targeted tumor antigens, with short-lived clinical responses. Possible explanations for this include the exhaustion of infused T-cells, antigen loss, MHC downregulation or loss, abnormal antigen presentation mechanisms, and immunosuppressive cytokines and cellular microenvironment [246]. The other limitations of ACT strategies include the ability to produce TCR transgenic or CAR T-cells, the lack of optimal targets, and high-grade toxicities. Cytokine release syndrome (CRS) can be associated with ACT secondary to T-cell activation and cytokine release, producing fever and major toxicity. In particular, one heavily treated patient with recurrent EOC received autologous mesothelin-directed CAR T-cells. The patient experienced a compartmental CRS in the pleural cavity, requiring treatment with an IL-6 receptor antagonist [247]. The first CAR T-cell experiment in EOC used autologous T-cells transduced to express an anti-FR α CAR. This phase I trial showed detectable gene-modified T-cells that nearly disappeared one month after infusion, and no tumor rejection was observed [248]. Due to the unique pattern of growth in the peritoneal cavity, and in order to reduce systemic toxicity, intraperitoneal perfusion has emerged as an alternative to systemic administration in ovarian cancer. The preliminary results of a dose escalation phase I trial demonstrate the feasibility of autologous IL-12-secreting, MUC-16-specific CAR T-cell administration through the intraperitoneal route [249].

Table 4. Selected ongoing adoptive T-cell trials.

Target	Study (NCT)	Phase	N	Population	Protocol	Primary objective	Recruitment Status
MUC-16	NCT02498912	I	30	Recurrent MUC16 + solid tumors	Cyclophosphamide followed by Iv ip infusion of MUC16 specific T-cells secreting IL-12	Safety	Recruiting
	NCT00194714	I/II	26	HLA2 Stage IV HER2 + breast/OC	HER2 peptide vaccination	Safety	Active, not recruiting
HER2	NCT00228358	I	8	Metastatic HER2 tumors previously vaccinated	Cyclophosphamide or denileukin diftitox followed by Expanded HER2-specific T-cells	Feasibility Safety	Completed
WT1	NCT00562640	I	21	Recurrent WT + OC, FT, PPC	WT-1 specific T-cells	Safety and tolerability	Active, not recruiting
Mesothelin	NCT02580747	II	20	Refractory recurrent mesothelin+ OC	Anti-meso-CAR T-cells	Safety, feasibility. Duration meso-	Unknown
	NCT03054298	I	30	Recurrent mesothelin+ OC	huCART-meso cells	CAR T-cells Safety, feasibility	Active, not recruiting Terminated
	NCT01583686	I	136	Metastatic mesothelin + cancer	Lymphodepletion followed by Anti-meso-CAR T-cells	Safety, ORR	Completed
	NCT02159716	I	24	Metastatic mesothelin + cancer	Anti-meso-CAR T-cells +/-cyclophosphamide	Safety and feasibility	
CD133	NCT02541370	I	20	CD-33 + Refractory Cancers	Anti-CD133-CAR T-cells	Safety	Completed

Table 4. Cont.

Target	Study (NCT)	Phase	N	Population	Protocol	Primary objective	Recruitment Status
MAGE-A4	NCT03132922	I	42	HLA2+ with MAGE-A4 cancer Persistent disease	Anti-MAGE-A4 ^{c1o32} T-cells	Safety, duration of Anti-MAGE4 T-cells	Recruiting
	NCT03159585	I	20	HLA-A 0201+ patients with solid tumors NYESO-1+	NY-ESO-1- T-cells (TAEST16001)	Safety	Completed
NY-ESO-1	NCT01567891	I/II	9	HLA A 0201, HLA-A 0205, and/or HLA-A 0206 recurrent OC < 2lines	NYESO-1c259 T-cells	Safety	Completed
	NCT03017131	I	12	Recurrent/refractory OC	Autologous NY-ESO-1 T-cell + decitabine + IL-2	Safety and tolerability	Recruiting
	NCT00101257	I	18	HLA DPB 0401, DPB1 0201, DRB1 07 with Stage III/IV	Autologous CD4-positive antigen-specific T-cells	Safety, toxicity, duration in vivo infused T-cells	Recruiting
	NCT02166905	I/Iib	64	NYESO-1+OC NY-ESO-1 or LAGE-1 + primary or recurrent OC	EC-205/NY-ESO-1 Fusion Protein CDX-1401, Poly ICLC, and IDO1 Inhibitor INCB024360	Safety, PFS	Recruiting
Neoantigens	NCT03412877	I/II	210	Metastatic/refractory solid cancer with measurable disease	Autologous T-cells engineered to express TCR Anti-Neoantigens	ORR	Recruiting

MUC: mucin; HER2: human epidermal growth factor receptor 2; OC: ovarian cancer; FT; fallopian tube; PPC: primary peritoneal cancer; WT1: Wilms Tumor; MAGE-A4: melanoma antigen gene family; NY-ESO-1: New York esophageal carcinoma.

4.5. Agents Targeting the Epigenome

Epigenome instability, including anomalies in DNA methylation (DNMT) and histone ubiquitination patterns, are related to ovarian cancer progression and platinum resistance [250]. The epigenetic silencing of genes involved in T helper responses, antigen presentation and processing have been reported. DNMT inhibitors have been shown to upregulate type I interferon signaling and apoptosis, through the viral response pathway and the endogenous retroviral gene transcripts in ovarian cancer [251]. DNMT and histone deacetylase inhibitors can reverse the immunosuppressive microenvironment by inducing MHC class I expression and CD8 T-cell responses [252]. DNA methylation of effector T-cell genes may be acquired in TILs, and can promote T-cell exhaustion by decreasing T-cell effector function, activation and proliferation. These exhaustion-associated DNA methylation alterations persist during ICB treatment, and are related to resistance [253]. DNMT inhibitors used in combination with ICB have been proven to reverse T-cell exhaustion-associated epigenetic patterns [253]. Agents targeting the epigenome have also been shown to induce platinum re-sensitization in resistant patients, via upregulation of tumor suppressor genes [254,255]. Early-phase trials using epigenetic approaches are presented in Table 5.

Table 5. Clinical trials with agents targeting epigenome.

Target	Study (NCT)	Phase	N	Population	Protocol	Primary Objective	Results
Decitabine	NCT00887796	I	12	Recurrent OC	Decitabine+ NYESO-1 protein with montanide + GM-CSF+ liposomal doxorubicin	Safety	Well-tolerated DNA Hypomethylation/ blood, circulating DNAs NY-ESO-1 Ab and T-cell responses SD 50%, PR 10%
Entinostat	NCT02915523	I/II	140	Recurrent OC >2 lines CT	Avelumab With or Without Entinostat	Dose Efficacy (PFS)	NR
Guadecitabine	NCT02901899	II	38	Recurrent OC > 1 ≤ 3 lines	Guadecitabine + Pembrolizumab	ORR	NR
Guadecitabine	NCT03206047	I/IIb	75	Platinum-resistant recurrent OC	Atezolizumab, Guadecitabine, and CDX-1401 Vaccine	Safety Efficacy (PFS)	NR
Guadecitabine SGI-110-02	NCT01696032	I/II	100	Platinum-resistant recurrent OC	SGI-110-02 + Carboplatin or CT	Efficacy (PFS)	6-month PFS rate increased in the Guadecitabine group (37% vs. 11%)

OC: ovarian cancer; CT: chemotherapy; GM-CSF: granulocyte-macrophage colony stimulating factor; SD: stable disease; PR: partial response; NR: not reported

5. Conclusions

Since the introduction of paclitaxel into first-line treatment, no dramatic advances have been attained in EOC patient progression-free survival, eliciting high expectations in new therapeutic strategies, such as immunotherapy. Recent and increasing evidence demonstrates that EOC tumors are infiltrated by cytotoxic T lymphocytes, key actors of the antitumor immune response and predictors of patient outcome. Nonetheless, so far, the most promising immunotherapies, targeting immune checkpoints expressed by exhausted T-cells, have failed to prove effective in EOC. Their limitations are possibly due to a myriad of mechanisms, likely related to the microenvironment complexity, and including strong tumor immune evasion mechanisms. While EOC tumor microenvironment (TME) was examined in both preclinical and human contexts, more work is required to clarify EOC immune complexity, in order to guide immunotherapeutic options.

Preclinical studies in EOC mouse models have helped us to understand the interactions between multiple cell subsets, including tumor cells and immune cells. In addition to tumor intrinsic qualities, such as immunogenicity, mutational burden, stage, and patient overall performance status and age,

all components of the TME and their crosstalk need to be taken into account for the development of immunotherapy. Besides, a recent innovative concept involves the tumor's anatomical location, including primary tumors, ascites and metastases, in determining the TME constitution, and thus in the global picture of treatment design. This concept appears particularly relevant in the context of EOC, considering the characteristic multi-location feature of the primary disease.

Preclinical evidence has been paving the way to numerous immunotherapy trials in EOC patients, with many of them currently ongoing. To improve the clinical benefits, future trials should optimize patient selection, and future challenges will include evaluating synergistic combinations, that concomitantly increase antitumor response and dampen immunosuppressive pathways through the targeting of crucial TME components.

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