Expert Reviews in Molecular Medicine

cambridge.org/erm

Efficacy of immune checkpoint inhibitor monotherapy or combined with other small molecule-targeted agents in ovarian cancer

Munawaer Muaibati[1], Abasi Abuduyilimu[1], Tao Zhang[2], Yun Dai[1], Ruyuan Li[3], Fanwei Huang[1], Kexin Li[1], Qing Tong[1], Xiaoyuan Huang[1] and Liang Zhuang[4]

[1]Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; [2]Reproductive Medicine Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; [3]Department of Gynecology and Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China and [4]Cancer Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Review

Cite this article: Muaibati M *et al* (2023). Efficacy of immune checkpoint inhibitor monotherapy or combined with other small molecule-targeted agents in ovarian cancer. *Expert Reviews in Molecular Medicine* **25**, e6, 1–15. https://doi.org/10.1017/erm.2023.3

Received: 27 September 2022
Revised: 12 December 2022
Accepted: 16 January 2023

Keywords:
Immune checkpoint inhibitors (ICIs); immune checkpoint; ovarian cancer; targeted therapy; tumour microenvironment

Author for correspondence:
Liang Zhuang,
E-mail: mrzhuangliang@126.com

Abstract

Ovarian cancer is the most lethal female reproductive system tumour. Despite the great advances in surgery and systemic chemotherapy over the past two decades, almost all patients in stages III and IV relapse and develop resistance to chemotherapy after first-line treatment. Ovarian cancer has an extraordinarily complex immunosuppressive tumour microenvironment in which immune checkpoints negatively regulate T cells activation and weaken antitumour immune responses by delivering immunosuppressive signals. Therefore, inhibition of immune checkpoints can break down the state of immunosuppression. Indeed, Immune checkpoint inhibitors (ICIs) have revolutionised the therapeutic landscape of many solid tumours. However, ICIs have yielded modest benefits in ovarian cancer. Therefore, a more comprehensive understanding of the mechanistic basis of the immune checkpoints is needed to improve the efficacy of ICIs in ovarian cancer. In this review, we systematically introduce the mechanisms and expression of immune checkpoints in ovarian cancer. Moreover, this review summarises recent updates regarding ICI monotherapy or combined with other small-molecule-targeted agents in ovarian cancer.

Introduction

Ovarian cancer is the third most frequently diagnosed gynaecological malignancy and is the most lethal of all gynaecological malignancies worldwide, being responsible for 5% of all cancer-related deaths in women each year (Refs 1, 2). Because of the lack of early clinical symptoms and screening, most patients are diagnosed with metastasis of the pelvic and peritoneal cavities (Refs 2, 3, 4). Although surgery and systemic chemotherapy have made great advances in the last two decades, almost all patients in stages III and IV will relapse and develop resistance to chemotherapy after first-line treatment. The 5-year survival rate of these patients is less than 25% (Refs 2, 5). Consequently, new treatment strategies and paradigms are of great need for these patients. Immune checkpoint inhibitors (ICIs) have attracted tremendous attention as promising new therapeutic targets with the recent improved understanding of the molecular basis of tumour immune microenvironment. Indeed, ICIs have revolutionised the therapeutic landscape of many solid tumours. However, there are currently no approved ICIs for ovarian cancer. Ovarian cancer is known to be an immunogenic disease in which peripheral tumour-infiltrating lymphocytes (TILs) actively recognise tumour antigens and generate tumour-specific T cells to destroy tumour cells. Unfortunately, even if large numbers of tumour-specific T cells are generated in patients by immunotherapy, these T cells fail to destroy tumour cells in vivo (Ref. 6). Previous studies have reported many mechanisms for this failure. For example, ovarian cancer has an extraordinarily complex immunosuppressive tumour microenvironment (TME) that is full of a large number of negative immune regulatory components, such as myeloid-derived suppressor cells (MDSCs), tumour-associated macrophages (TAMs), regulatory T cells (Tregs), cytokines, soluble factors, which have been demonstrated to be immunosuppressive functions and are associated with tumour invasiveness, spread and angiogenesis (Refs 7, 8, 9, 10, 11). Furthermore, immune checkpoint molecules have been identified as crucial regulators of the immune response. The binding of immune checkpoint receptor to ligand negatively regulates T cells activation and weakens antitumour immune responses by delivering immunosuppressive signals, ultimately leading to escape of tumour cells from immune destruction (Ref. 5). ICIs could effectively prevent this effect. However, ICIs have yielded modest benefits in ovarian cancer. Therefore, a more comprehensive understanding of the mechanistic basis of the immune checkpoints is needed to improve the efficacy of ICIs in ovarian cancer.

Immune checkpoints in ovarian cancer

Immune checkpoints are a series of inhibitory regulators that directly regulate the initiation, duration and magnitude of immune responses. Normally, when the immune response is

activated, immune checkpoints work as negative regulators, suppressing the immune responses, maintaining self-tolerance and preventing damage to normal tissues (Ref. 12). However, tumour cells selectively utilise these inhibitory regulatory mechanisms to suppress effector T cells, leading to immune escape of tumour cells (Ref. 13) (Fig. 1). Therefore, a comprehensive understanding of the immune checkpoints in ovarian cancer is needed. We summarise immune checkpoints and functions in Table 1.

PD-1

The immune checkpoint molecule programmed cell death protein 1 (PD-1) is expressed on activated T cells, B cells, natural killer (NK) cells, natural killer T (NKT) cells, dendritic cells (DCs) and macrophages and interacts with two ligands, programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), to exert inhibitory effects on both peripheral lymphocytes and the TME (Refs 32, 33). PD-1 is a type I transmembrane receptor, the cytoplasmic tail is composed of two tyrosyl residues and the N-terminal tyrosine residues constitute an immunoreceptor tyrosine-based inhibitory motif (ITIM). The C-terminal domain constitutes an immunoreceptor tyrosine-based switch motif (ITSM). When PD-1 interacts with PD-L1/PD-L2, ITIM and ITSM are phosphorylated, recruiting and activating the Src homology (SH) domains of SH-containing phosphatase (SHP), which dephosphorylates the crucial downstream intracellular signalling pathway PI3K-Akt. Ultimately, this leads to a reduction of both cytokine production and T-cell proliferation, thereby suppressing T-cell-mediated immune response (Refs 32, 33, 34). In addition, when PD-1 interacts with PD-L1/L2, it upregulates the E3 ubiquitin ligases casitas B-lineage lymphoma-b (CBL-b) and c-casitas B-lineage lymphoma (c-CBL) and triggers PD-1 pathway-mediated suppression of antitumour immune responses. Tregs are strongly associated with advanced stages of ovarian cancer and have immunosuppressive effects on tumours. Terme *et al.* claimed that PD-1 binding to ligands could regulate the differentiation of Tregs and maintain their immunosuppressive functions. The latest study illustrated that the immunosuppressive cytokine interleukin-18 produced by tumour cells upregulates PD-1 expression on activated mature NK cells, thereby inhibiting NK cell-dependent immunosurveillance in many tumours (Ref. 35). In addition, B cell receptor (BCR) induces the expression of PD-1 on the surface of B cells, which inhibits B cells function in tumours (Ref. 15). These results indicate that PD-1 inhibits the antitumour immune response through multiple pathways and that targeted PD-1 therapies play an antitumour role in part by inhibiting Treg cells and restoring B-cell and NK-cell functions.

In ovarian cancer, Matsuzaki *et al.* elaborated that compared with peripheral blood lymphocytes, tumour-derived NY-ESO-1-specific CD8(+) T cells enriched co-expression of inhibitory molecules lymphocyte activation gene 3 (LAG-3) and PD-1, dual blockade of LAG-3 and PD-1 during T-cell priming efficiently augmented proliferation and cytokine production by NY-ESO-1-specific CD8 (+) T cells (Ref. 36). Tu *et al.* used Oncomine and PrognoScan database analyses to investigate the expression levels and prognostic values of PD-1 in ovarian cancer, and found that the expression of PD-1 was closely associated with relatively poor survival in an advanced stage of ovarian cancer (Ref. 37). Moreover, Rådestad *et al.* reported that CD8+ T cells coexpressed the immune checkpoints LAG-3, PD-1 and T-cell immunoglobulin domain and mucin domain-3 (TIM-3) in tumours, the most common combination being PD-1 and TIM-3, and dual blockade of these molecules improved CD8+ T-cell response to non-specific stimulate in the TME by synthesising effector (Ref. 38). Another study has shown that CD8+ T cells that do not express LAG-3, PD-1 and TIM-3 are beneficial for OS (Ref. 39). These results provide new insights

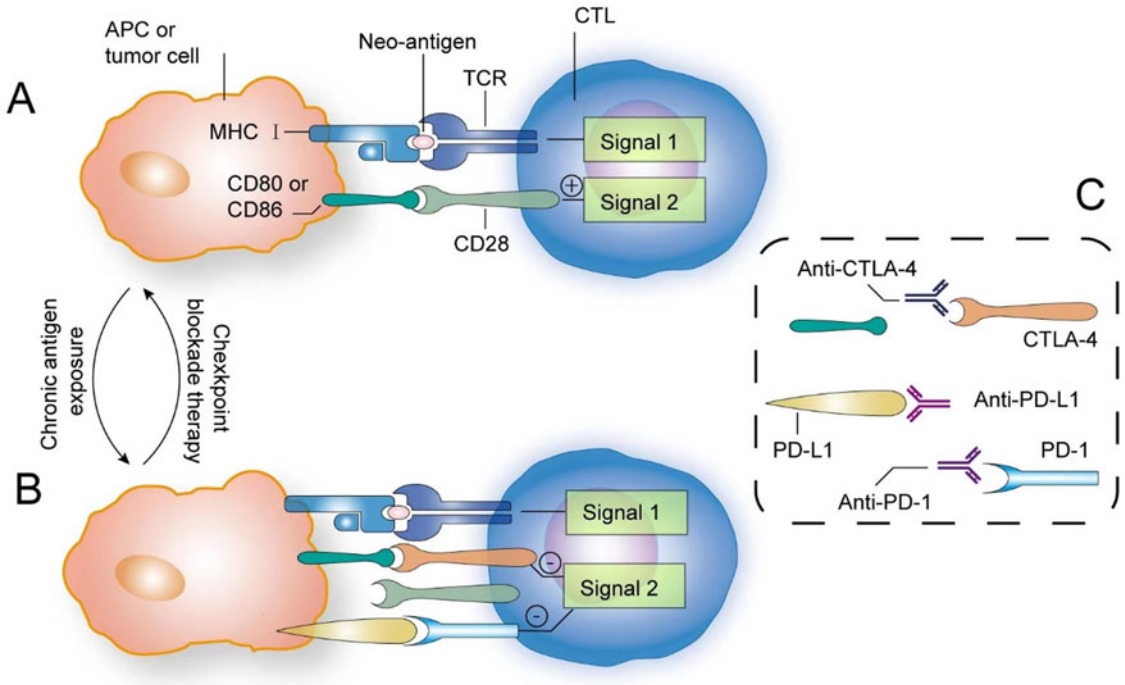

Fig. 1. Neo-antigens derived from tumour cells to CTL through MHC class I–TCRs and a co-stimulation signal of CD80 and/or CD86–CD28 interactions, CTLs are subsequently activated to destroy tumour cells. However, tumour cells often escape immune destruction through upregulation of immune checkpoint ligands, such as programmed cell death 1 ligand 1 (PD- L1), that can bind the immune checkpoint receptors programmed cell death 1 (PD-1) on the CTLs to deliver suppressing signals, finally inhibit the proliferation and activation of CTLs. Another negative-regulate immune checkpoint molecule cytotoxic T lymphocyte protein 4 (CTLA-4) that binds CD80 and CD86 and prevents their interaction with CD28, inhibit the co-stimulation signal of CD80 and/or CD86-CD28 interactions, thus inhibit the proliferation and activation of CTLs. ICIs could effectively prevent this effect. ICIs highly specifically bind to immune checkpoints, blocking this inhibitory mechanism and thereby reactivating the anti-tumour immune response.

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

Table 1. Summary of immune checkpoints and functions

	Immune checkpoints	Other names	Ligands or receptors	Expressed cells	Functions	Ref.
1	Programmed cell death protein 1 (PD-1)	CD279	PD-L1 (B7-H1, CD274, PDCD1L1, PDCD1LG1), PD-L2 (B7-H2, CD273)	Activated T cells, B cells, NK cells, NKT cells, DCs and macrophages	(1) Negatively regulates effector T cells function (2) Regulates Treg differentiation and maintains Treg tumour suppressor function (3) Inhibits NK cells function, negatively regulate B cell proliferation	14, 15
2	Cytotoxic T-lymphocyte associated antigen-4 (CTLA-4)	CD152	B7–1 (CD80) B7–2 (CD86)	Activated T cells; memory T cells; Tregs	(1) Negatively regulates T cells function (2) Down regulates CD80/CD86 on APCs by trogocytosis	16, 17
3	Lymphocyte activation gene-3 (LAG-3)	CD223	MHC-II, galectin-3 (Gal-3), LSECtin, FGL1	Activated T cells, NK cells, activated B cells and DCs	(1) Negatively regulates proliferation, activation and homoeostasis of both CD8 and CD4T cells (2) Down regulates T cells produce cytokines	18, 19, 20
4	T-cell immunoglobulin-3 (TIM-3)	HAVCR2	Galectin-9 (Gal-9), ceacam-1, HMGB1, PtdSer	Effector T cells, Tregs, B cells, macrophages, NK cells, DCs, tumour cells	(1) Promotes T cells exhaustion (2) Promotes the expansion of MDSCs in the TME	21, 22, 23, 24
5	T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT)	WUCAM, Vstm3, VSIG9	CD155 (PVR, necl-5), CD112 (PVRL2, nectin-2)	Activated T cells and NK cells, Tregs and follicular T helper cells	(1) Inhibits T-cell proliferation (2) Decreased the cytolytic capacity of NK cells (3) Inhibits degranulation of NK cells and produce cytokines (4) Enhancement of immunosuppressive function of Tregs	25, 26
6	B and T lymphocyte attenuator (BTLA)	CD272	HVEM	B cells, T cells, monocytes, macrophages, DCs, NK cells	(1) Inhibits T-cell function	27, 28
7	V-domain immunoglobulin suppressor of T-cell activation (VISTA)	Dies1, Gi24, B7-H5, SISP1, DD1α, PD-1H	PSGL-1, VSIG-3	Myeloid cells, naive CD4+ T cells, FoxP3 + Tregs, and other subsets of T cells, NK cells and tumour cells	(1) Inhibits T cells activation (2) VISTA expression on tumour cells lead to tumour development	29, 30
8	Indoleamine 2,3-dioxygenase-1 (IDO-1)		Tryptophan	Highly expressed in a variety of tumour vascular cells, macrophages, DCs, eosinophils, endothelial cells (ECs) and fibroblasts	(1) Converts tryptophan into kynurenines (2) IDO-1 promotes tumourigenesis and tolerogenic APCs formation (3) Inhibits proliferation and activation of CD8+ T effector cells and NK cells (4) Induced production of Tregs and MDSCs (5) Promotes the expansion and activation of MDSCs	31

to investigate the simultaneous blockade of multiple immune checkpoints in the treatment of ovarian cancer.

On the contrary, PD-L1 has received a great deal of attention. It has been reported that PD-L1 is not expressed in normal tissue but is increased in ovarian cancer, PD-L1 expression is significantly higher in malignant disease than in benign/borderline disease, tumour cells lysis by cytotoxic T lymphocytes (CTLs) was attenuated when PD-L1 was overexpressed and promoted when it was silenced in mouse ovarian cancer cells, and PD-L1 expression in tumour cells promotes peritoneal dissemination by repressing CTL function (Refs 39, 40, 41, 42). In addition, PD-L1 expression in tumours correlates with FIGO stage of ovarian cancer. Obviously, the PD-1/PD-L1 signalling pathway plays a crucial role in the occurrence and development of ovarian cancer. However, some studies have reported different results, with no significant correlation between PD-1 expression and infiltration of effector T cells in tumours (Refs 39, 43). In conclusion, the relationship between PD-1 and PD-L1 expression and the prognosis of ovarian cancer patients remains controversial, and more studies are needed to investigate the role of immune checkpoints in ovarian cancer.

CTLA-4

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), also known as CD152, is a leucocyte differentiation antigen and a transmembrane receptor. Its intracellular structural domain consists of 36 amino acids forming the ITIM, which plays an opposite role in the intracellular ITAM structural stimulatory molecule CD28 (Ref. 17). CTLA-4 is mainly expressed on the surface of activated CD4+ and CD8+ effector T cells and on Tregs, and is involved in early T-cell activation in secondary lymphoid organs. In ovarian cancer, CTLA-4 competitively binds to the same ligands as the costimulatory receptor CD28, namely, B7 (B7-1: other name CD80; B7-2: other name CD86), expressed on the surface of antigen-presenting cells (APCs) but with greater affinity (Refs 16, 44). CTLA-4 interacts with ligands to upregulate inhibitory signals, inhibiting the cell cycle progression of T cells from the G1 to S phase and attenuating or even terminating T-cell immune response (Ref. 45). Furthermore, another biological function of CTLA-4 is endocytosis, which induces CD80/CD86 endocytosis and downregulates CD80 and CD86 expression, thereby further inhibiting T-cell function.

Recently, an increasing number of experiments have demonstrated the important roles of CTLA-4 in ovarian cancer. Jaikumar *et al.* reported that one-third to half of CD8+ TILs coexpressed PD-1 and CTLA-4 in ovarian cancer, and PD-1 + CTLA-4 + CD8+ TILs have more severe dysfunctional features than PD-1+ or CTLA-4+ TILs. Dual blockade of PD-1 and CTLA-4 reverses CD8+ TIL dysfunction and activates antitumour immune responses in the majority of mice (Ref. 46). Furthermore, some experiments have provided evidence that TILs usually express multiple immune checkpoints in patients with ovarian cancer. In total, CTLA-4 plays a crucial role in immune escape, and dual blockade may be an effective strategy to activate antigen-specific effector T cells.

LAG-3

Lymphocyte activation gene 3 (LAG-3) is mainly expressed on the surface of activated T cells. Its extracellular molecular structure is similar to that of CD4, and it interacts stably with major histocompatibility complex (MHC)-II molecules in a non-competitive manner with a significantly higher affinity than CD4 (Ref. 47). This interaction suppresses T-cell receptor (TCR)-mediated T-cell proliferation and activation by downregulation of intracellular STAT5 phosphorylation and reducing CD3 and TCR expression (Refs 46, 48). However, several studies reported that the binding of LAG-3 to MHC-II was not the main inhibitory mechanism. Galectin-3 is the second major LAG-3 functional ligand independent of MHC-II. Interaction of LAG-3 with galectin-3 is needed for galectin-3-mediated CD8(+) T cells inhibition in vitro (Ref. 49). LSECtin, a cell surface lectin constitutively expressed in many tumour cells, is also a ligand for LAG-3, and blocking the interaction of LAG-3 with LSECtin restores interferon-γ secretion and regulates the function of CD8+ T cells and NK cells (Ref. 50). Notably, in 2019, Jun *et al.* reported another ligand, FGL1, is produced by human cancer cells and that blocking the FGL1–LAG-3 interaction preferentially stimulates T cells in tumours and can treat established mouse tumours (Ref. 51). Furthermore, LAG-3 negatively regulates T-cell proliferation by upregulating Tregs, thereby promoting the immune escape of tumour cells (Ref. 19). In ovarian cancer, researchers observed that CD8+ T cells coexpressing LAG-3 (+) PD-1 (+) have more severe dysfunction than LAG-3 (+) PD-1 (−) or LAG-3 (−) PD-1 (−) subsets. Dual blockade of LAG-3 and PD-1 significantly increased effector T-cell function and dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumours that were largely resistant to single-antibody treatment. But not by blocking either molecule alone (Refs 36, 52, 53). This suggests that dual blockade of these molecules remains one of the most promising regimens to explore immunotherapy.

TIM-3

T-cell immunoglobulin domain and mucin domain-3 (TIM-3) are expressed on T cells, Th1 cells, cytotoxic T cells, Treg cells and innate immune cells (Ref. 54). A study reported that the interaction of TIM-3 and galectin-9 secreted by tumour cells increased apoptosis of CD8+ TIL cells in colorectal cancer (Refs 22, 55). TIM-3 interacts with ligands ceacam1 to inhibit the function of effector T cells, and ligands galectin-9 and ceacam1 have a synergistic effect on the TIM-3 signalling pathway. High-mobility group box1 (HMGB1) is another ligand of TIM-3. TIM-3 interacts with HMGB1 to suppress nucleic acid-mediated innate immune responses (Ref. 21). PtdSer (PS) is a non-protein ligand for TIM-3, binds to TIM-3 and recognises apoptotic cells, resulting in clearance of apoptotic cells by resident phagocytes (Ref. 56).

In ovarian cancer, TIM-3 is involved in tumourigenesis and progression by suppressing immunity. In 2017, Xu *et al.* observed that TIM-3+ CD4T cells isolated from tumour tissue were significantly higher than those isolated from normal tissue. This phenomenon was related to tumour grade, with further increased expression of TIM-3 in T cells (CD4+ and CD8+) from high-grade tumours compared with other lower-grade tumours (Ref. 57). Another study showed that TIM-3 + Foxp3 + CD4T cells induce TIM-3 + Tregs in ovarian cancer. It is well known that TIM-3 + FoxP3 + Treg is a promoter of T-cell dysfunction in tumours, thus TIM-3-FoxP3 + Tregs may cause strong immunosuppression in ovarian cancer (Refs 58, 59). Overall, TIM-3 may negatively regulate antitumour immune responses through various T-cell subsets.

TIGIT

T-cell immunoglobulin and ITIM domain (TIGIT) is a promising new target for cancer immunotherapy. Similar to CD28 and CTLA-4, it competes with CD226 for the same ligands CD155 (PVR) and CD112 (PVRL2, nectin-2), thereby inhibiting the function of T cells and NK cells. TIGIT is upregulated by immune cells in tumours, and its ligands CD155 and CD112 are

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

overexpressed in various tumour cells, but almost absent in normal cells. Whelan *et al.* reported that ovarian cancers having the highest percentage of $PVR^{-}PVRL2^{+}$ tumour cells, and a combination of PVRIG blockade with TIGIT or PD-1 blockade further increased T-cell activation (Ref. 60). Furthermore, TIGIT was observed to suppress the antitumour immune response by enhancing the CD4 + Treg cell response (Refs 61, 62, 63). Chen *et al.* reported that anti-TIGIT treatment reduced CD4 + Tregs without affecting CD4+ or CD8+ T cells or NK cells (Ref. 64).

BTLA

B and T lymphocyte attenuator (BTLA) is the third coinhibitory molecule observed from the CD28 family and is structurally similar to CTLA-4 and PD-1. BTLA is constitutively expressed on resting T cells and upon activation continues to be expressed. Herpesvirus entry mediator (HVEM), a ligand for BTLA, binds to BTLA, induces its phosphorylation and binds to the tyrosine phosphatase SHP-2, suppressing the immune responses and leading to tumour immune tolerance (Refs 27, 65).

An early study elucidated that BTLA is overexpressed on the surface of CD4+ and CD8+ T cells in patients with various tumours. In addition, HVEM expression was elevated in ovarian cancer cells compared with benign tissues, and T cells numbers and secretion of anti-tumour cytokines were increased in HVEM (−) ovarian cancer (Ref. 66). Chen *et al.* reported that BTLA is mainly expressed in B lymphocytes and its detection in cancer tissues predicts poor outcome of epithelial ovarian cancer (EOC) patients. Preclinical experiments showed that blocking BTLA in combination with chemotherapy significantly reduced peritoneal tumour volume in tumour-bearing mice (Ref. 67).

VISTA

V-domain immunoglobulin suppressor of T-cell activation (VISTA) is a recently discovered negative regulator that is persistently expressed on naive T cells. VISTA acts as a ligand, receptor or both in the TME. VISTA is overexpressed in a variety of tumours, and blocking the VISTA signalling pathway can enhance the antitumour immune response in mice (Refs 68, 69). Some studies found that VISTA was almost absent in normal ovarian epithelial cells but was overexpressed in ovarian cancer, and anti-VISTA therapy markedly prolonged the survival of mice bearing tumours that expressed high VISTA (Ref. 70). Notably, Zong *et al.* gave the opposite conclusion that VISTA expression has been associated with favourable clinical outcomes in patients with high-grade serous ovarian cancer (Ref. 71). The differences in these results were related to the variability of the study samples, the complex immunosuppressive microenvironment of ovarian cancer and the weak immunosuppressive functions of VISTA. Targeting VISTA might be a way to enhance antitumour immune responses. However, more studies are still needed to investigate the effects of NISTA on humans.

IDO-1

Tryptophan is involved in multiple catabolic processes and is required for T-cell activation. Indoleamine 2,3-dioxygenases (IDO-1) are tryptophan-degrading enzymes that degrade tryptophan to kynurenine, and the depletion of tryptophan and generation of kynurenine play important immunosuppressive functions by activating Tregs and MDSCs, suppressing the functions of effector T and NK cells. Moreover, IDO-1 modulates the downstream effector pathway, promoting neovascularisation of solid tumours, which promotes tumour growth (Refs 72, 73, 74). Several studies claimed that upregulation of IDO-1 expression in ovarian cancer suppresses T-cell expansion and reduces the number of CD8 + TILs, resulting in a poor prognosis in patients. Another study described that IDO-1 induced PD-1 expression in T-cell ovarian cancer, which was positively associated with paclitaxel resistance (Refs 75, 76, 77, 78). Importantly, these results demonstrate that IDO-1 plays an important role in ovarian cancer.

Clinical trials of ICI monotherapy in ovarian cancer

In the second part, we describe the mechanisms of immune checkpoints and their crucial roles in ovarian cancer. Therefore, we believe that immune checkpoints are the most promising targets for ovarian cancer therapy. ICIs are small-molecule agents that target immune checkpoints and specifically recognise and bind immune checkpoint molecules, reducing immunesuppression and thus enhancing antitumour immune responses. Currently, several ICIs have been approved by the U.S. Food and Drug Administration (FDA) for cancer treatment (Refs 79, 80, 81). Although none have been approved for ovarian cancer, several clinical trials are currently underway to evaluate the clinical activity of ICIs in ovarian cancer. Table 2 lists the completed clinical trials of ICI monotherapy in ovarian cancer.

PD-1 inhibitors

Nivolumab

Nivolumab is an immunoglobulin G4 (IgG4) monoclonal antibody that targets PD-1 receptors. Nivolumab binds to PD-1 block negative/suppressing signal delivery to the T cell, activating them and enhancing host anti-tumour immunity. To date, nivolumab has been approved by the FDA for treatment of various tumours.

In 2014, Hamanishi *et al.* evaluated the efficacy of nivolumab in ovarian cancer in a phase II clinical trial that enrolled 20 patients with platinum-resistant ovarian cancer. In this trial, patients were sequentially assigned to the high-dose group (nivolumab 3 mg/kg; $n = 10$) and the low-dose group (nivolumab 1 mg/kg; $n = 10$) and received nivolumab monotherapy. A better objective response ratio (ORR) [20%; 95% confidence interval (CI), 2.5–55.6] was found in the 3 mg/kg cohort compared with an ORR of 10% (95% CI, 0.3–44.5) in the 1 mg/kg cohort. The incidence of treatment-related adverse events (TRAEs) did not differ between the two groups. Consequently, it can be concluded that ovarian cancer patients may benefit more from nivolumab 3 mg/kg (Ref. 83). Subsequently, in 2021, Hamanishi *et al.* compared the efficacy of nivolumab alone or chemotherapy in patients with platinum-resistant ovarian cancer, demonstrating that the nivolumab group was more well tolerated than the chemotherapy group. However, no remarkable clinical benefit was observed in this study, with a median overall survival (OS) of 10.1 months (95% CI, 8.3–14.1) in the nivolumab group and 12.1 months (95% CI, 9.3–15.3) in the chemotherapy group, and there was no significant difference in OS between groups (Ref. 84). Normann *et al.* also evaluated the efficacy of nivolumab in patients with platinum-resistant ovarian cancer and reported that the disease control rate (DCR) was 44% (95% CI, 19–87), the median OS was 30 weeks (95% CI, 14–42) and the progression free survival (PFS) was 15 weeks (95% CI, 13–17) (Ref. 101). This study reported similar DCR and PFS to the trial reported by Hamanishi in 2014.

In conclusion, nivolumab monotherapy has limited clinical efficacy in patients with advanced or platinum-resistant ovarian cancer. However, nivolumab showed an acceptable safety profile, suggesting that more investigations would be valuable to elucidate the clinical efficacy of nivolumab in ovarian cancer.

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

Table 2. Clinical trials of ICI monotherapy in ovarian cancer

Immune checkpoints	Agents	NCT number	Phase	Interventions	Conditions	Results	Ref.
PD-1	Nivolumab	NCT02498600	2	Nivolumab+/ipilimumab	Persistent or recurrent EOC	(1) Six (12.2%) responses occurred within 6 months in the nivolumab group and 16 (31.4%) in the nivolumab + ipilimumab group (2) PFS: nivolumab: 2 months; nivolumab + ipilimumab: 3.9 months (3) Grade ≥ 3 TRAEs: nivolumab: 33%; nivolumab + ipilimumab: 49%, with no treatment-related deaths.	82
		UMIN000005714	2	Nivolumab	Platinum-resistant ovarian cancer	(1) Grade 3 or 4 TRAEs occurred in 8 (40%) of 20 patients. Two patients had severe TRAEs. (2) OR: 15%; DCR: 45%; median PFS: 3.5 months (95% CI, 1.7–3.9 months); median OS: 20.0 months (95% CI, 7.0 months to not reached)	83
		ONO-4538-23	3	Nivolumab/gemcitabine (GEM)/ pegylated liposomal doxorubicin (PLD)	Platinum-resistant ovarian cancer	(1) Median OS was 10.1 (95% CI, 8.3–14.1) and 12.1 (95% CI, 9.3–15.3) months with nivolumab and GEM or PLD, respectively. (2) Median PFS was 2.0 (95% CI, 1.9–2.2) and 3.8 (95% CI, 3.6–4.2) months with nivolumab and GEM or PLD, respectively. (3) Median duration of response was (18.7 versus 7.4 months) nivolumab and GEM or PLD. Fewer TRAEs were observed with nivolumab versus GEM or PLD (61.5 versus 98.1%).	84
	Pembrolizumab	NCT02674061	2	Pembrolizumab	Advanced recurrent ovarian cancer (ROC)	(1) ORR was 7.4% for cohort A (received one to three prior lines of treatment with a platinum-free interval (PFI) or treatment-free interval (TFI) between 3 and 12 months) and 9.9% for cohort B (received four to six prior lines with a PFI/TFI of ⩾3 months). (2) Median DOR was 8.2 months for cohort A and not reached for cohort B. (3) DCR was 37.2 and 37.4%, respectively, in cohorts A and B.	85
		NCT02608684	2	Pembrolizumab, cisplatin and gemcitabine	Platinum-resistant ovarian cancer	(1) ORR was 60%, duration of response was 4.9 months and time to progression was 5.2 months. (2) PFS at 6 and 12 months was 43 and 5%. (3) Median PFS was 6.2 months and median OS was 11.3 months.	86
		NCT02865811	2	Pembrolizumab and pegylated liposomal doxorubicin	Platinum resistant ovarian cancer	(1) 12 patients achieving clinical benefit for a CBR of 52.2% (95% CI, 30.6–73.2), 5 PRs (21.7%) and 1 CR (4.3%), for an ORR of 26.1%. 6 patients had SD lasting at least 24 weeks. (2) Combination therapy was well tolerated without unexpected toxicities.	87
		NCT02054806	2	Pembrolizumab	PD-L1-expressing advanced ovarian epithelial, fallopian tube or primary peritoneal carcinoma	(1) TRAEs occurred in 19 (73.1%) patients, most commonly arthralgia (19.2%), nausea (15.4%) and pruritus (15.4%). One grade 3 TRAEs occurred. (2) ORR was 11.5% (1 CR, 2 PR); 7 patients (26.9%) achieved SD. Median PFS and OS were 1.9 (95% CI, 1.8–3.5) and 13.8 (95% CI, 6.7–18.8) months, respectively.	88
		NCT02674061	2	Pembrolizumab	Advanced ovarian cancer	(1) Previously treated advanced ROC showed ORR of 8.0%. (2) The relationship between PD-L1 expression and ORR was assessed. ORR was 19.0% (95% CI, 5.4–41.9) and seemed to increase with increasing PD-L1 expression. (3) A total of 13 (61.9%) patients had TRAEs, and 5 (23.8%) had grade 3–4 TRAEs.	89
		NCT02298959	1b	Ziv-aflibercept + pembrolizumab	Advanced solid tumours	Median OS was 12.5 months (90% CI, 3.8–13.6) in ovarian cancer.	90
PD-L1		NCT00729664	1	Anti-PD-L1 antibody	Ovarian cancer	Objective response was observed in 1 of 17 with ovarian cancer.	91
	Durvalumab	NCT02811497	2	Azacitidine + durvalumab	Advanced solid tumours	The combination of CC-486 and durvalumab was tolerable.	92

		NCT03405454		Durvalumab + chemotherapy	Recurrent ovarian clear cell adenocarcinomas	No result available.	93
		NCT03899610	2	Neoadjuvant chemotherapy + durvalumab + tremelimumab	Ovarian cancer stages IIIC, IV	No result available.	94
	Atezolizumab	NCT01375842	1	Atezolizumab	Advanced/recurrent epithelial ovarian and uterine cancers	Atezolizumab was generally well tolerated with no new safety signals identified.	95
	Avelumab	NCT02580058	3	Avelumab + chemotherapy (PLD)	Platinum-resistant or platinum-refractory ovarian cancer	Median PFS was 3.7 months (95% CI, 3.3–5.1) in the combination group, 3.5 months (2.1–4.0) in the PLD group, and 1.9 months (1.8–1.9) in the avelumab group. Median OS was 15.7 months (95% CI, 12.7–18.7) in the combination group, 13.1 months (11.8–15.5) in the PLD group, and 11.8 months (8.9–14.1) in the avelumab group. Serious TRAEs occurred in 32 (18%) patients in the combination group, 19 (11%) in the PLD group, and 14 (7%) in the avelumab group.	96, 97
		NCT02718417	3	Chemotherapy + avelumab	Previously untreated EOC	PFS: (chemotherapy followed by avelumab: 16.8 (13.5 to NA)) (chemotherapy + avelumab followed by avelumab: 18.1 (14.8 to NA)) (chemotherapy followed by observation: NA (18.2 to NA))	98
		NCT01772004	1	Avelumab	Metastatic or locally advanced solid tumours	Avelumab demonstrated antitumour activity and acceptable safety, patients received avelumab for a median of 2.8 months, with a median follow-up of 26.6 months. A confirmed OR occurred in 12 patients, including a CR in 1 patient (0.8%) and a PR in 11 patients (8.8%). The 1-year PFS rate was 10.2% and median OS was 11.2 months. Infusion-related reactions occurred in 25 patients (20.0%).	99
CTLA-4	Ipilimumab		1b	Ipilimumab	Relapsed and refractory B-cell non-Hodgkin lymphoma	Ipilimumab was generally well tolerated.	100

Pembrolizumab

Pembrolizumab (Keytruda) is a humanised monoclonal IgG4 antibody that blocks the PD-1 pathway and has been extensively investigated in a variety of malignancies.

In a phase Ib trial (NCT02054806), the clinical efficacy and safety of pembrolizumab monotherapy in patients with PD-L1-expressing advanced ovarian cancer was evaluated, TRAEs occurred in 19 (73.1%) patients. One grade 3 TRAEs (increased plasma transaminase level) occurred. No deaths and no treatment discontinuations because of TRAEs occurred. The ORR was 11.5%, with seven patients (26.9%) having stable disease, and the median PFS and OS were 1.9 (95% CI, 1.8–3.5) and 13.8 (95% CI, 6.7–18.8) months, respectively (Ref. 88). Matulonis *et al.* reported a phase II clinical trial of 376 patients with advanced recurrent ovarian cancer in which pembrolizumab monotherapy; ORR was 8%, DCR was 37% and PFS was 2.1 months. The study also found that high levels of PD-L1 were related to an increased clinical efficacy of pembrolizumab. Nishio *et al.* also reported in advanced ovarian cancer pembrolizumab monotherapy had an ORR of 19.0% (95% CI, 5.4–41.9) and seemed to increase with increasing PD-L1 expression. A total of 13 (61.9%) patients had TRAEs, and five (23.8%) had grade 3–4 TRAEs (Refs 85, 89). These results indicated that the levels of PD-L1 expression in tumour cells may be a valid predictor of disease prognosis. However, a variety of trials have also reported that patients can benefit from the combination of ICIs with other therapies regardless of their PD-L1 expression levels.

Overall, these trials demonstrated an ORR of 5–20% with manageable toxicities in patients with advanced ovarian cancer with pembrolizumab monotherapy. Further studies are needed to identify appropriate predictors to facilitate pembrolizumab efficacy.

Dostarlimab

Dostarlimab (TSR-042) is another anti-PD-1 inhibitor that interacts with the PD-1 receptor with high affinity. Currently, no clinical trials have reported the clinical activity of dostarlimab in ovarian cancer. However, multiple phase III clinical trials (NCT04679064; NCT03602859; NCT03806049) are being performed to test dostarlimab as a monotherapy or in combination with other agents in ovarian cancer, and we expect promising outcomes from these treatments.

PD-L1 inhibitors

Atezolizumab

Atezolizumab is a fully humanised monoclonal antibody that selectively targets PD-L1 to prevent interaction with PD-1. Liu *et al.* investigated single-agent atezolizumab in 12 patients with recurrent EOC in a first-in-human phase 1 study. Antitumour activity of atezolizumab was observed in two patients with mostly grade ≤ 2 TRAEs and no grade ≥ 4 TRAEs were reported (Ref. 95). Overall, atezolizumab monotherapy was generally well tolerated in patients with recurrent EOC, and its clinical efficacy warrants further investigation.

Avelumab

Avelumab is a fully humanised IgG1 monoclonal antibody against PD-L1. It is the only agent that kills cancer cells using both antibody-dependent cell-mediated cytotoxicity and immune checkpoint inhibition simultaneously. Disis *et al.* first investigated the clinical activity of ipilimumab in previously treated patients with recurrent or refractory ovarian cancer in a phase Ib trial (NCT01772004). The ORR was 9.6% (95% CI, 5.1–16.2), the 1-year PFS rate was 10.2% (95% CI, 5.4–16.7) and the median OS was 11.2 months (95% CI, 8.7–15.4 months). Other frequent TRAEs were fatigue (17 [13.6%]), diarrhoea (15 [12.0%]) and nausea (14 [11.2%]). Grade 3 or higher TRAEs occurred in nine patients (7.2%). Twenty-one patients (16.8%) had TRAEs of any grade (Ref. 99). Another phase 3 trial evaluated avelumab alone or avelumab plus chemotherapy compared with chemotherapy alone in patients with platinum-resistant or platinum-refractory ovarian cancer. The results showed that the median OS was 15.7 months (95% CI, 12.7–18.7), 13.1 months (11.8–15.5) and 11.8 months (8.9–14.1) in the combination group, chemotherapy group and avelumab group, respectively. Here, we found no significant clinical benefit of avelumab alone or in combination with chemotherapy compared with chemotherapy, and worse PFS and OS were observed in the avelumab group (Ref. 96). Overall, avelumab showed limited clinical activity in recurrent or refractory ovarian cancer. Monk *et al.* compared chemotherapy plus avelumab, chemotherapy followed by avelumab maintenance and chemotherapy alone in stage III–IV epithelial ovarian, fallopian tube or peritoneal cancer. The median PFS was 18·1 months [14.8 to not estimable (NE)] with avelumab combination treatment and 16.8 months (95% CI, 13·5 to not estimable) with avelumab maintenance. No significant clinical benefit was observed with either avelumab maintenance therapy or chemotherapy plus avelumab in this trial. More studies are needed to evaluate the clinical efficacy of avelumab as a first-line therapy (Ref. 98).

CTLA-4 inhibitors

Ipilimumab is the first FDA-approved ICI that effectively blocks the CTLA-4 pathway. A phase II study (NCT01611558) in 40 patients evaluated the safety and efficiency of ipilimumab monotherapy in recurrent platinum-sensitive ovarian cancer. This trial found that the incidence of grade ≥ 3 TRAEs was 50%, and the best ORR was 15% (5.7–29.8). However, studies on ipilimumab are limited. Randomised phase 2 or 3 clinical trials of CTLA-4-targeted agents in ovarian cancer patients have not reported a clear overall survival benefit, either alone or in combination with available agents.

In conclusion, ICIs have yielded only modest responses as monotherapy for advanced or recurrent ovarian cancer. There are extensive challenges for further clinical applications of ICIs alone in ovarian cancer, such as the limited effectiveness of monotherapy, the lack of investigation of identified biomarkers to predict prognosis and serious TRAEs and primary and acquired resistance. Therefore, further research is needed to develop combination approaches to allow more patients to benefit from ICIs.

Clinical trials of ICIs combined with other small-molecule-targeted agents in ovarian cancer

The antitumour function of ICIs depends on TILs, and the activation of TILs requires immunogenic tumour-specific antigens (Refs 102, 103). The standard treatment for ovarian cancer includes surgery followed by platinum-based chemotherapy. Chemotherapy can lead to the destruction of cancer cells and the release of immunogenic molecules (Ref. 104). Combining gemcitabine chemotherapy drugs with a CTLA-4 blockade could induce a potent CD4+ and CD8+ T-cell-dependent antitumour immune response. Furthermore, small-molecule-targeted agents induce tumour cell death and lead to the release of large amounts of neoantigens, thereby enhancing the infiltration and activation of effector T cells in the TME. Therefore, the combination of ICIs with other small-molecule-targeted agents achieves cumulative or synergistic therapy to show the greatest antitumour immune responses. Clinical trials of ICIs combined with other small-molecule-targeted agents in ovarian cancer are listed in Table 3.

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

Table 3. Clinical trials of ICIs combined with other small-molecule-targeted agents in ovarian cancer

Targets	Agents	NCT number	Phase	Interventions	Conditions	Study results	Ref.
VEGFR	Cediranib	NCT02681237	2	Cediranib + olaparib	Progression on a PARPi. Women with HGSOC and radiographic evidence of disease progression	(1) OR were observed in 0 of 11 (0%) platinum-sensitive patients, 2 of 10 (20%) platinum-resistant patients and 1 of 13 (8%) in the exploratory cohort. Sixteen-week PFS rates were 55, 50 and 39%, respectively. The most common grade 3 toxicities were diarrhoea (12%) and anaemia (9%).	105
	Bevacizumab	NCT02873962	2	Bevacizumab + nivolumab	Relapsed EOC.	(1) Nivolumab + bevacizumab: 11 patients (ORR, 28.9%; 95% CI, 15.4–45.9), with 1 additional unconfirmed response. (2) ORR was 40.0% (19.1–64.0%) in platinum-sensitive and 16.7% (95% CI, 3.6–41.4) in platinum-resistant participants. (3) Thirty-four participants (89.5%) experienced at least 1 TRAEs; 9 participants (23.7%) experienced a grade 3 or higher TRAEs.	106
		NCT02853318	2	Pembrolizuma + bevacizumab + cyclophosphamide	Recurrent platinum-sensitive, platinum-resistant or refractory epithelial ovarian, fallopian tube or primary peritoneal cancer.	(1) 3 women (7.5%) had CR, 16 (40.0%) had PR and 19 (47.5%) had SD, ORR: 47.5%, clinical benefit in 38 (95.0%), and durable response in 10 (25.0%). (2) Median PFS was 10.0 (90% CI, 6.5–17.4) months. (3) The most common grade 3 to 4 TRAEs were hypertension (6 [15.0%]) and lymphopoenia (3 [7.5%]).	107
		NCT03038100	3	Bevacizumab + atezolizumab + chemotherapy	Newly diagnosed untreated stage III or IV OC who either had undergone primary cytoreductive surgery with macroscopic residual disease or were planned to receive neoadjuvant chemotherapy and interval surgery.	(1) Median PSF was 19.5 versus 18.4 months with atezolizumab versus placebo, respectively. (2) The most common grade 3 or 4 TRAEs were neutropenia (21% with atezolizumab versus 21% with placebo), hypertension (18 versus 20%, respectively) and anaemia (12 versus 12%).	108
		NCT01633970	1b	Bevacizumab + atezolizumab	Platinum-resistant ovarian cancer.	(1) TRAEs occurred in 19 patients (95%); seven (35%) had grade 3/4 events. (2) 3 patients had PR of 11.3–18.9 months' duration; the ORR was 15%. 8 patients (40%) had SD, hence the DCR was 55%. Median PFS was 4.9 months (range, 1.2–20.2); median OS was 10.2 months (range, 1.2–26.6).	109
PARP	Niraparib	NCT03598270	3	Niraparib + chemotherapy + atezolizumab	Recurrent ovarian, tubal or peritoneal cancer and platinum treatment-free interval of more than 6 months.	Not yet recruiting.	110
	Olaparib	NCT04361370	2	Pembrolizumab + bevacizumab + olaparib	RCA non-mutated patients with platinum-sensitive recurrent ovarian cancer (OPEB-01).	Not yet recruiting.	111
		NCT02734004	2	Olaparib + durvalumab	Recurrent ovarian cancer.	ORR was 14% (5/35; 95% CI, 4.8–30.3). DCR (PR + SD) was 71% (25/35; 95% CI, 53.7–85.4).	112

(*Continued*)

Table 3. (*Continued.*)

Targets	Agents	NCT number	Phase	Interventions	Conditions	Study results	Ref.
		NCT04169841	2	Olaparib + tremelimumab + durvalumab	Solid cancers (breast cancer, ovarian cancer, pancreatic cancer, endometrial cancer, prostate cancer and others).	Not yet recruiting.	113
		NCT02484404	1	Olaparib + durvalumab + cediranib	Recurrent women's cancers.	Grade 3/4 adverse events include hypertension (1/9), anaemia (1/9) and lymphopoenia (3/9).	114
		NCT03699449	2	Olaparib; cediranib; durvalumab; durvalumab; pegylated liposomal doxorubicin (PLD); topotecan; paclitaxel; tremelimumab	Platinum-resistant ovarian cancer.	Overall ORR was 37.1%; 2 achieved CR. ORR was 50, 42.9, 20, 33.3 and 29.4%, respectively. Grade 3/4 TRAEs were reported in 37.5, 35.7, 20, 66.7 and 35.3% of patients, respectively.	115
	Rucaparib	NCT03522246	3	Nivolumab + rucaparib	Newly diagnosed ovarian, fallopian tube or peritoneal cancer.	No result available.	116
IDO-1	Navoximod	NCT02471846	1	Navoximod + atezolizumab	Advanced solid tumours (melanoma, pancreatic, prostate, ovarian, head and neck squamous cell carcinoma, cervical, neural sheath, non-small cell lung cancer, triple-negative breast cancer, renal cell carcinoma, urothelial bladder cancer).	The most common treatment-related AEs were fatigue (22%), rash (22%) and chromaturia (20%).	117
DNMT	Guadecitabine	NCT02901899	2	Guadecitabine + pembrolizumab	Platinum-resistant ovarian cancer.	(1) The primary endpoint was the RR. 3 patients had PR (8.6%), 8 (22.9%) patients had SD, resulting in an ORR of 31.4% (95% CI, 16.9–49.3).	118
Folate receptor alpha vaccine	TPIV200	NCT02764333	2	Durvalumab + TPIV200	Advanced ovarian cancer.	(1) Treatment was well tolerated, grade 3 TRAEs of 18.5%. (2) There was 1 unconfirmed partial response (3.7%) and 9 patients had stable disease (33.3%). The median OS was 21 months (13.5 to infinity).	119
CFS-1R	LY3022855	NCT02718911	1a/1b	LY3022855 in combination with durvalumab or tremelimumab	Advanced solid tumours.	No result available.	120
Vaccine	Vigil®	NCT03073525	1,2	Vigil® + atezolizumab	Relapsed ovarian cancer.	(1) Safety assessment of Vigil + atezolizumab. (2) Grade 3/4 TRAEs of Atezo-1st versus Vigil-1st were 17.2 versus 5.1%. Median OS was not reached (NR) (Vigil-1st) versus 10.8 months (Atezo-1st). The exploratory subset analysis of BRCAwt suggested improved OS benefit (NR in Vigil-1st versus 5.2 months in Atezo-1st, HR 0.16, *P* 0.027).	121
Anti-CD38 antibody	Isatuximab	NCT03637764	1,2	Isatuximab + atezolizumab	EOC, glioblastoma (GBM), hepatocellular carcinoma (HCC) and squamous cell carcinoma of the head and neck (SCCHN).	(1) In phase I, Isa + Atezo showed an acceptable safety profile, no dose-limiting toxicities were observed, and RP2D was confirmed. Most patients experienced ≥1 TRAEs, with ≤48.5% being grade ≥3.	122

Multiple ICIs in combination

Several preclinical studies have demonstrated that 33–50% of CD8 (+) TILs coexpress more than one immune checkpoints, and that blocking any of these immune checkpoints compensatively increase the expression of other immune checkpoints, and that tumour cells may choose this replacement immunosuppressive molecule to continue evading attack from the immune system (Refs 38, 123). Tumour cells also overexpress several immune checkpoints ligands, to synergistically exploit coexpression of immune checkpoints at the T-cell surface as an immune escape mechanism (Ref. 124). Huang *et al.* observed that dual blockade of PD-1 with CTLA-4 or LAG-3 synergistically enhanced effector T-cell function and led to tumour rejection in mouse ovarian tumours (Ref. 125). Therefore, blocking multiple immune checkpoints could improve the efficacy of ICIs in ovarian cancer.

A phase 1, 2 trial NCT03287674 evaluated ipilimumab and nivolumab in metastatic ovarian cancer and showed that the ORR was 16.7%, and the stable disease rate was 83.3%. Although it had limited efficacy, the combination strategy showed better efficacy than monotherapy. Subsequently, Zamarin *et al.* reported results from the phase II trial NCT02498600, which evaluated ipilimumab plus nivolumab compared with nivolumab alone in patients with persistent or recurrent EOC. Grade ≥3 TRAEs occurred in 33 and 49% of patients in the nivolumab and combination groups, respectively. Within 6 months of treatment responses occurred in six (12.2%) patients in the nivolumab group and 16 (31.4%) patients in the nivolumab plus ipilimumab group (OR, 3.28; 85% CI, 1.54 to infinity), and the median PFS was 2 and 3.9 months in the nivolumab and combination groups, respectively. These results demonstrated that combination therapy for persistent or recurrent EOC improved response rates and prolonged PFS compared with nivolumab alone (Ref. 82). Overall, the combination regimens showed superior efficacy in patients with persistent or recurrent EOC.

Combination of ICIs and PARP inhibitors

In tumours, the rapid expansion of cancer cells is prone to DNA damage, which requires rapid DNA damage repair (DDR). There are two most common modalities of DDR: DNA single-strand break (SSB) repair involving poly (ADP-ribose) polymerase (PARP) enzymes and homologous recombination repair in which BRCA1/2 plays an important role (Ref. 126). During DNA replication, when SSB repair is blocked, the replication fork collides with the unrepaired SSBs, forming a double-strand break (DSB). Therefore, if only the SSB repair pathway is blocked, cells can still rely on HR to repair DSBs. However, in HR deficiency (HRD) cancer cells, PARPi impairs the repair of DNA SSBs, rendering DSBs ineffective and leading to the accumulation of damage, chromosomal rearrangements, genomic instability and synthetic lethality (Refs 126, 127, 128), which means, patients with BRCA1/2 mutations are particularly sensitive to PARPi (Refs 129, 130). It has been reported that HRD-related DDR was observed in approximately 40–50% of patients with ovarian cancer (Ref. 131), and the majority of them are strongly associated with BRCA1/2 mutation. BRCA1/2 mutation EOC showed higher neoantigen load and PD-L1 expression compared with BRCA1/2 wild type and HR proficient. Ding *et al.* described the results from preclinical studies; PARPi drives powerful local and systemic antitumour immunity in mice bearing BRCA1-deficient ovarian tumours, and this antitumour effect is further enhanced when PARPi is combined with a PD-1 inhibitor (Refs 132, 133, 134). Therefore, these results provide a powerful molecular basis for PARPi in combination with ICIs playing a synergic role in ovarian cancer.

A phase 2 clinical trial NCT02484404 enrolled 35 ovarian cancer patients and evaluated the efficacy of olaparib and durvalumab; the ORR was 14% (5/35; 95% CI, 4.8–30.3), and the DCR was 71% (25/35; 95% CI, 53.7–85.4) (Ref. 112). In addition, Konstantinopoulos *et al.* reported results from an open-label, single-arm, phase 1 and 2 trial that evaluated niraparib in combination with pembrolizumab in patients with recurrent ovarian carcinoma. The ORR was 18% (90% CI, 11–29), and the DCR was 65% (90% CI, 54–75). Overall, these results suggested that niraparib combined with pembrolizumab has a favourable safety profile tolerable and showed promising antitumour activity in patients with recurrent ovarian cancer, and this combination strategy may represent a new choice for these individuals (Ref. 135). In addition, several ongoing trials (NCT02657889, NCT04169841) are also investigating the efficacy of ICIs in combination with PARPi therapy in patients with solid tumours and expect promising results.

Combination of ICIs and VEGF/VEGFR inhibitors

Vascular endothelial growth factor (VEGF) is a highly biologically active glycoprotein, and its ligand vascular endothelial growth factor receptor (VEGFR) is expressed on endothelial cells, thereby triggering angiogenesis signals. Neovascularisation in the TME plays a key role in tumour progression, invasion and metastasis. Recently, several studies have found that VEGF/VEGFR expression is significantly higher in tumour vascular cells than in normal vascular cells, and the highest levels of VEGF were observed in patients diagnosed with advanced tumours (Refs 136, 137, 138, 139). VEGF inhibitors exert antitumour effects by targeting the blocking of VEGF signalling pathways, inhibiting tumour neovascularisation and causing tumour vascular regression. Currently, VEGF inhibitors have shown therapeutic efficacy in an increasing number of human cancers (Refs 140, 141). Moreover, some researchers reported that PD-L1 inhibitors plus antiangiogenic agents can inhibit angiogenesis and tumour progression induced by the direct interaction of PD-L1 and VEGFR2, and this combination therapy can also overcome single-drug resistance (Ref. 142). Furthermore, antiangiogenic therapy attempts to normalise the tumour vasculature and improve the efficiency of anticancer drug delivery, and better efficacy can be achieved with a lower dose of ICIs, which can decrease TRAEs. Combining PD-L1 antiangiogenic agents may be a potential therapeutic strategy for ovarian cancer patients.

A single-arm, phase 2 trial evaluated the combination of nivolumab and bevacizumab in 38 patients (18 had platinum-resistant and 20 had platinum-sensitive disease) with relapsed EOC. In this trial, the ORR was 40.0% (19.1–64.0%) in platinum-sensitive participants and 16.7% (95% CI, 3.6–41.4) in platinum-resistant participants. Nivolumab combined with bevacizumab has significant clinical activity in relapsed ovarian cancer patients, with greater activity in the platinum-sensitive setting (Ref. 106). Moroney also reported similar safety and clinical activity in a platinum-resistant ovarian cancer setting, with an ORR of 15% and stable disease in eight patients (40%) (Ref. 109). In conclusion, ICIs combined with VEGF inhibitors have a better benefit in platinum-sensitive ovarian cancer, but their clinical efficacy in platinum-resistant ovarian cancer is still limited.

Combination of ICIs and DNMT inhibitors

In normal cells, DNA methylation is crucial for regulating gene expression and is required for the maintenance of genome stability. Aberrant DNA methylation leads to alterations in chromatin structure and silencing of tumour suppressor genes, ultimately leading to tumourigenesis (Ref. 143).

DNA methyltransferase (DNMT) is an important epigenetic molecule for DNA methylation that can catalyse DNA methylation

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

and inhibit gene transcription. Therefore, DNMT inhibitors can block abnormal DNA methylation during tumourigenesis, promoting the activation of tumour suppressor genes and achieving antitumour effects. Some studies have elaborated that DNMT is expressed at levels three times higher in ovarian cancer cells than in normal ovarian epithelial cells (Ref. 144).

Guadecitabine is a second-generation hypomethylating agent, phase I/II randomised trial (NCT02901899) evaluating the clinical efficacy of guadecitabine and pembrolizumab in recurrent ovarian, peritoneal and fallopian tube carcinomas. Final results have not yet been available.

Combination of ICIs and IDO-1 inhibitors

The immunosuppressive enzyme IDO-1 catalyses the cleavage of L-tryptophan to produce a series of kynurenine metabolites that inhibit the action of CD8+ T lymphocytes (Refs 145, 146). IDO-1 inhibitors have been reported to be synergistic with ICIs and may increase the effectiveness of ICIs in cancer patients. Several studies are evaluating the efficacy and safety of IDO-1 inhibitors plus ICIs in ovarian cancer.

Combination of ICIs and FRα inhibitors

Folate is an important regulator of cell growth and survival. The binding of folate to folate receptor α (FRα) is one of the main methods by which folate enters cells. Several studies found that FRα was selectively overexpressed in ovarian cancers, whereas expression was not detectable in normal ovarian surface epithelium (Refs 147, 148, 149). Furthermore, FRα can be transferred into the nucleus, where it acts as a transcription factor to regulate the expression of key developmental genes in tumour cells. At the same time, folate regulates tumour growth and development by participating in a variety of intracellular signalling pathways and downregulating cell adhesion molecules (Ref. 150).

A phase II trial of durvalumab in combination with the multiepitope FRα vaccine TPIV200 in 27 ovarian cancer patients observed a treatment-related grade 3 toxicity rate of 18.5%. Although the ORR in this trial was only 3.7%, all patients had increased T-cell responses at 6 weeks with a median OS of 21 months (13.5 to infinity). These observations demonstrated that a combination therapeutic strategy of ICIs and FRα inhibitors or FRα vaccines is extremely valuable (Ref. 119).

Combination of ICIs and HDAC inhibitors

Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are involved in transcription, cell cycle regulation and cell transformation. Normally, histones are in a dynamic balance between acetylation and deacetylation and are coregulated by HAT and HDAC. In human cells, increased levels of histone deacetylation result in alterations of the normal cell cycle and metabolic behaviour, which ultimately induce tumours (Ref. 151). Anti-HDAC therapy can activate histone acetylation, promote the expression of antitumour transcription factors and inhibit tumourigenesis. Furthermore, HDAC inhibitors promote the degradation of the proto-oncoprotein (Ref. 152). Several studies have observed that HDACs are frequently overexpressed in ovarian cancer and are often associated with poor prognosis (Refs 153, 154, 155). ICIs combined with HDAC inhibitors may be a new treatment strategy for ovarian cancer patients. The phase II trial NCT02915523 is testing in combination with entinostat and avelumab in ovarian, fallopian tube, or primary peritoneal cancer, and we expect good outcomes from this treatment.

Combination of ICIs and RAF/MEK/ERK pathway inhibitors

Ras has been identified as an oncogene, and the RAF–MEK–ERK pathway is an important downstream effector of Ras. Ras mutation activates the RAF–MEK–ERK signalling pathway, which plays a key role in cancer cell expansion, invasion and metastasis. Hence, each component of the RAS/RAF/MEK/ERK pathway has become an important target of antitumour therapy (Refs 156, 157). Currently, RAF and MEK inhibitors are being developed as cancer treatments. Some studies have demonstrated that MEK inhibitors show good treatment effects in ovarian cancer patients (Ref. 158). Clinical trials NCT03363867 and NCT03363867 for the treatment of patients with ovarian cancer are ongoing.

Conclusion

The development of ICIs has revolutionised the management of many types of solid tumours, particularly advanced-stage cancers. Herein, we describe the mechanisms and expression of immune checkpoints and summarise recent updates regarding ICIs monotherapy or combined with other small-molecule-targeted agents in ovarian cancer. It is worth noting that the ICIs monotherapy have limited efficacy in ovarian cancer. Although synergistic therapies exhibit superior efficacy in patients with persistent or recurrent ovarian cancer compared with monotherapy, fundamental research and clinical use of combination therapy still encounters many obstacles, such as treatments with ICIs have limited response rates, no identified predictive biomarkers to select patients suited for ICIs, cannot effectively avoid the immune-related adverse events and the number of clinical trials of ICIs in ovarian cancer is relatively limited. Therefore, a more comprehensive understanding of immune checkpoints and immunosuppressive TME is crucial to improve the efficacy of ICIs in ovarian cancer.

Acknowledgements. We thank all authors who contributed to this article.

Conflict of interest. The authors have no other conflicts of interest to declare.

Ethical standards. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. **Siegel RL *et al.*** (2018) Cancer statistics. *CA: A Cancer Journal for Clinicians* **68**, 7–30.
2. **Torre LA *et al.*** (2018) Ovarian cancer statistics. *CA: A Cancer Journal for Clinicians* **68**, 284–296.
3. **Hennessy BT *et al.*** (2009) Ovarian cancer. *Lancet* **374**, 1371–1382.
4. **Siegel RL *et al.*** (2017) Cancer statistics. *CA: A Cancer Journal for Clinicians* **67**, 7–30.
5. **Odunsi K** (2017) Immunotherapy in ovarian cancer. *Annals of Oncology* **28**, viii1–viii7.
6. **Anadon CM *et al.*** (2022) Ovarian cancer immunogenicity is governed by a narrow subset of progenitor tissue-resident memory T cells. *Cancer Cell* **40**, 545–557.e513.
7. **Maiorano BA *et al.*** (2021) Ovarian cancer in the era of immune checkpoint inhibitors: state of the art and future perspectives. *Cancers (Basel)* **13**, 4438.
8. **Yin M *et al.*** (2016) Tumor-associated macrophages drive spheroid formation during early transcoelomic metastasis of ovarian cancer. *Journal of Clinical Investigation* **126**, 4157–4173.
9. **Kolomeyevskaya N *et al.*** (2015) Cytokine profiling of ascites at primary surgery identifies an interaction of tumor necrosis factor-α and interleukin-6 in predicting reduced progression-free survival in epithelial ovarian cancer. *Gynecologic Oncology* **138**, 352–357.
10. **Yuan X *et al.*** (2017) Prognostic significance of tumor-associated macrophages in ovarian cancer: a meta-analysis. *Gynecologic Oncology* **147**, 181–187.

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

11. **Curiel TJ *et al.*** (2004) Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nature Medicine* **10**, 942–949.
12. **Edner NM *et al.*** (2020) Targeting co-stimulatory molecules in autoimmune disease. *Nature Reviews. Drug Discovery* **19**, 860–883.
13. **Jiang X *et al.*** (2019) Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. *Molecular Cancer* **18**, 10.
14. **Hirano F *et al.*** (2005) Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Research* **65**, 1089–1096.
15. **Okazaki T *et al.*** (2001) PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting Src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proceedings of the National Academy of Sciences of the USA* **98**, 13866–13871.
16. **Egen JG *et al.*** (2002) CTLA-4: new insights into its biological function and use in tumor immunotherapy. *Nature Immunology* **3**, 611–618.
17. **Lingel H *et al.*** (2019) CTLA-4 (CD152): a versatile receptor for immune-based therapy. *Seminars in Immunology* **42**, 101298.
18. **Goldberg MV *et al.*** (2011) LAG-3 in cancer immunotherapy. *Current Topics in Microbiology and Immunology* **344**, 269–278.
19. **Workman CJ *et al.*** (2004) Lymphocyte activation gene-3 (CD223) regulates the size of the expanding T cell population following antigen activation in vivo. *Journal of Immunology* **172**, 5450–5455.
20. **Workman CJ *et al.*** (2002) Cutting edge: molecular analysis of the negative regulatory function of lymphocyte activation gene-3. *Journal of Immunology* **169**, 5392–5395.
21. **Chiba S *et al.*** (2012) Tumor-infiltrating DCs suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1. *Nature Immunology* **13**, 832–842.
22. **Kang CW *et al.*** (2015) Apoptosis of tumor infiltrating effector TIM-3 +CD8+ T cells in colon cancer. *Scientific Reports* **5**, 15659.
23. **Murga-Zamalloa CA *et al.*** (2020) Expression of the checkpoint receptors LAG-3, TIM-3 and VISTA in peripheral T cell lymphomas. *Journal of Clinical Pathology* **73**, 197–203.
24. **Zhao L *et al.*** (2021) TIM-3: an update on immunotherapy. *International Immunopharmacology* **99**, 107933.
25. **Chauvin JM *et al.*** (2020) TIGIT in cancer immunotherapy. *Journal for Immunotherapy of Cancer* **8**, e000957.
26. **Dougall WC *et al.*** (2017) TIGIT and CD96: new checkpoint receptor targets for cancer immunotherapy. *Immunological Reviews* **276**, 112–120.
27. **Han P *et al.*** (2004) An inhibitory Ig superfamily protein expressed by lymphocytes and APCs is also an early marker of thymocyte positive selection. *Journal of Immunology* **172**, 5931–5939.
28. **Sedy JR *et al.*** (2005) B and T lymphocyte attenuator regulates T cell activation through interaction with herpesvirus entry mediator. *Nature Immunology* **6**, 90–98.
29. **Hosseinkhani N *et al.*** (2021) The role of V-domain Ig suppressor of T cell activation (VISTA) in cancer therapy: lessons learned and the road ahead. *Frontiers in Immunology* **12**, 676181.
30. **Johnston RJ *et al.*** (2019) VISTA is an acidic pH-selective ligand for PSGL-1. *Nature* **574**, 565–570.
31. **Tang K *et al.*** (2021) Indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors in clinical trials for cancer immunotherapy. *Journal of Hematology & Oncology* **14**, 68.
32. **Ishida Y *et al.*** (1992) Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO Journal* **11**, 3887–3895.
33. **Nishimura H *et al.*** (1999) Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* **11**, 141–151.
34. **Marasco M *et al.*** (2020) Molecular mechanism of SHP2 activation by PD-1 stimulation. *Science Advances* **6**, eaay4458.
35. **Terme M *et al.*** (2011) IL-18 induces PD-1-dependent immunosuppression in cancer. *Cancer Research* **71**, 5393–5399.
36. **Matsuzaki J *et al.*** (2010) Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. *Proceedings of the National Academy of Sciences of the USA* **107**, 7875–7880.
37. **Tu L *et al.*** (2020) Assessment of the expression of the immune checkpoint molecules PD-1, CTLA4, TIM-3 and LAG-3 across different cancers in relation to treatment response, tumor-infiltrating immune cells and survival. *International Journal of Cancer* **147**, 423–439.
38. **Rådestad E *et al.*** (2019) Immune profiling and identification of prognostic immune-related risk factors in human ovarian cancer. *Oncoimmunology* **8**, e1535730.
39. **Hensler M *et al.*** (2020) M2-like macrophages dictate clinically relevant immunosuppression in metastatic ovarian cancer. *Journal for Immunotherapy of Cancer* **8**, e000979.
40. **Maine CJ *et al.*** (2014) Programmed death ligand-1 over-expression correlates with malignancy and contributes to immune regulation in ovarian cancer. *Cancer Immunology Immunotherapy* **63**, 215–224.
41. **Abiko K *et al.*** (2013) PD-L1 on tumor cells is induced in ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction. *Clinical Cancer Research* **19**, 1363–1374.
42. **Parvathareddy SK *et al.*** (2021) Differential expression of PD-L1 between primary and metastatic epithelial ovarian cancer and its clinicopathological correlation. *Scientific Reports* **11**, 3750.
43. **Darb-Esfahani S *et al.*** (2016) Prognostic impact of programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) expression in cancer cells and tumor-infiltrating lymphocytes in ovarian high grade serous carcinoma. *Oncotarget* **7**, 1486–1499.
44. **Linsley PS *et al.*** (1991) CTLA-4 is a second receptor for the B cell activation antigen B7. *Journal of Experimental Medicine* **174**, 561–569.
45. **Krummel MF *et al.*** (1995) CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *Journal of Experimental Medicine* **182**, 459–465.
46. **Duraiswamy J *et al.*** (2013) Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors. *Cancer Research* **73**, 3591–3603.
47. **Huard B *et al.*** (1995) CD4/major histocompatibility complex class II interaction analyzed with CD4- and lymphocyte activation gene-3 (LAG-3)-Ig fusion proteins. *European Journal of Immunology* **25**, 2718–2721.
48. **Grosso JF *et al.*** (2007) LAG-3 regulates CD8+ T cell accumulation and effector function in murine self- and tumor-tolerance systems. *Journal of Clinical Investigation* **117**, 3383–3392.
49. **Kouo T *et al.*** (2015) Galectin-3 shapes antitumor immune responses by suppressing CD8+ T cells via LAG-3 and inhibiting expansion of plasmacytoid dendritic cells. *Cancer Immunology Research* **3**, 412–423.
50. **Xu F *et al.*** (2014) LSECTin expressed on melanoma cells promotes tumor progression by inhibiting antitumor T-cell responses. *Cancer Research* **74**, 3418–3428.
51. **Wang J *et al.*** (2019) Fibrinogen-like protein 1 is a major immune inhibitory ligand of LAG-3. *Cell* **176**, 334–347.e312.
52. **Woo SR *et al.*** (2012) Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Research* **72**, 917–927.
53. **Huang RY *et al.*** (2015) LAG3 and PD1 co-inhibitory molecules collaborate to limit CD8+ T cell signaling and dampen antitumor immunity in a murine ovarian cancer model. *Oncotarget* **6**, 27359–27377.
54. **Das M *et al.*** (2017) TIM-3 and its role in regulating anti-tumor immunity. *Immunological Reviews* **276**, 97–111.
55. **Zhu C *et al.*** (2005) The TIM-3 ligand galectin-9 negatively regulates T helper type 1 immunity. *Nature Immunology* **6**, 1245–1252.
56. **Santiago C *et al.*** (2007) Structures of T cell immunoglobulin mucin protein 4 show a metal-ion-dependent ligand binding site where phosphatidylserine binds. *Immunity* **27**, 941–951.
57. **Xu Y *et al.*** (2017) Role of TIM-3 in ovarian cancer. *Clinical & Translational Oncology* **19**, 1079–1083.
58. **Yan J *et al.*** (2013) TIM-3 expression defines regulatory T cells in human tumors. *PLoS ONE* **8**, e58006.
59. **Sakuishi K *et al.*** (2013) TIM3(+)FOXP3(+) regulatory T cells are tissue-specific promoters of T-cell dysfunction in cancer. *Oncoimmunology* **2**, e23849.
60. **Whelan S *et al.*** (2019) PVRIG and PVRL2 are induced in cancer and inhibit CD8(+) T-cell function. *Cancer Immunology Research* **7**, 257–268.
61. **Li YC *et al.*** (2020) Overexpression of an immune checkpoint (CD155) in breast cancer associated with prognostic significance and exhausted tumor-infiltrating lymphocytes: a cohort study. *Journal of Immunology Research* **2020**, 3948928.
62. **Harjunpää H *et al.*** (2020) TIGIT as an emerging immune checkpoint. *Clinical and Experimental Immunology* **200**, 108–119.
63. **Maas RJ *et al.*** (2020) TIGIT blockade enhances functionality of peritoneal NK cells with altered expression of DNAM-1/TIGIT/CD96 checkpoint molecules in ovarian cancer. *Oncoimmunology* **9**, 1843247.

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

64. **Chen F *et al.*** (2020) TIGIT enhances CD4(+) regulatory T-cell response and mediates immune suppression in a murine ovarian cancer model. *Cancer Medicine* **9**, 3584–3591.
65. **Yu X *et al.*** (2019) BTLA/HVEM signaling: milestones in research and role in chronic hepatitis B virus infection. *Frontiers in Immunology* **10**, 617.
66. **Zhang T *et al.*** (2016) Knockdown of HVEM, a lymphocyte regulator gene, in ovarian cancer cells increases sensitivity to activated T cells. *Oncology Research* **24**, 189–196.
67. **Chen YL *et al.*** (2019) BTLA blockade enhances cancer therapy by inhibiting IL-6/IL-10-induced CD19(high) B lymphocytes. *Journal for Immunotherapy of Cancer* **7**, 313.
68. **Lines JL *et al.*** (2014) VISTA is an immune checkpoint molecule for human T cells. *Cancer Research* **74**, 1924–1932.
69. **ElTanbouly MA *et al.*** (2020) VISTA: coming of age as a multi-lineage immune checkpoint. *Clinical and Experimental Immunology* **200**, 120–130.
70. **Mulati K *et al.*** (2019) VISTA expressed in tumour cells regulates T cell function. *British Journal of Cancer* **120**, 115–127.
71. **Zong L *et al.*** (2020) VISTA expression is associated with a favorable prognosis in patients with high-grade serous ovarian cancer. *Cancer Immunology Immunotherapy* **69**, 33–42.
72. **Liu M *et al.*** (2018) Targeting the IDO1 pathway in cancer: from bench to bedside. *Journal of Hematology & Oncology* **11**, 100.
73. **Wainwright DA *et al.*** (2012) IDO expression in brain tumors increases the recruitment of regulatory T cells and negatively impacts survival. *Clinical Cancer Research* **18**, 6110–6121.
74. **Mellor AL *et al.*** (2002) Cells expressing indoleamine 2,3-dioxygenase inhibit T cell responses. *Journal of Immunology* **168**, 3771–3776.
75. **Qian F *et al.*** (2009) Efficacy of levo-1-methyl tryptophan and dextro-1-methyl tryptophan in reversing indoleamine-2,3-dioxygenase-mediated arrest of T-cell proliferation in human epithelial ovarian cancer. *Cancer Research* **69**, 5498–5504.
76. **Okamoto A *et al.*** (2005) Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. *Clinical Cancer Research* **11**, 6030–6039.
77. **Takao M *et al.*** (2007) Increased synthesis of indoleamine-2,3-dioxygenase protein is positively associated with impaired survival in patients with serous-type, but not with other types of, ovarian cancer. *Oncology Reports* **17**, 1333–1339.
78. **Amobi-McCloud A *et al.*** (2021) IDO1 expression in ovarian cancer induces PD-1 in T cells via aryl hydrocarbon receptor activation. *Frontiers in Immunology* **12**, 678999.
79. **Boland JL *et al.*** (2019) Early disease progression and treatment discontinuation in patients with advanced ovarian cancer receiving immune checkpoint blockade. *Gynecologic Oncology* **152**, 251–258.
80. **Wolchok JD *et al.*** (2010) Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *The Lancet. Oncology* **11**, 155–164.
81. **Hodi FS *et al.*** (2010) Improved survival with ipilimumab in patients with metastatic melanoma. *New England Journal of Medicine* **363**, 711–723.
82. **Zamarin D *et al.*** (2020) Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG oncology study. *Journal of Clinical Oncology* **38**, 1814–1823.
83. **Hamanishi J *et al.*** (2015) Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. *Journal of Clinical Oncology* **33**, 4015–4022.
84. **Hamanishi J *et al.*** (2021) Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant ovarian cancer: open-label, randomized trial in Japan (NINJA). *Journal of Clinical Oncology* **39**, 3671–3681.
85. **Matulonis UA *et al.*** (2019) Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Annals of Oncology* **30**, 1080–1087.
86. **Walsh CS *et al.*** (2021) Phase II trial of cisplatin, gemcitabine and pembrolizumab for platinum-resistant ovarian cancer. *PLoS ONE* **16**, e0252665.
87. **Lee EK *et al.*** (2020) Combined pembrolizumab and pegylated liposomal doxorubicin in platinum resistant ovarian cancer: a phase 2 clinical trial. *Gynecologic Oncology* **159**, 72–78.
88. **Varga A *et al.*** (2019) Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: analysis of KEYNOTE-028. *Gynecologic Oncology* **152**, 243–250.
89. **Nishio S *et al.*** (2020) Pembrolizumab monotherapy in Japanese patients with advanced ovarian cancer: subgroup analysis from the KEYNOTE-100. *Cancer Science* **111**, 1324–1332.
90. **Rahma OE *et al.*** (2022) Phase IB study of ziv-aflibercept plus pembrolizumab in patients with advanced solid tumors. *Journal for Immunotherapy of Cancer* **10**, e003569.
91. **Brahmer JR *et al.*** (2012) Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *New England Journal of Medicine* **366**, 2455–2465.
92. **Taylor K *et al.*** (2020) An open-label, phase II multicohort study of an oral hypomethylating agent CC-486 and durvalumab in advanced solid tumors. *Journal for Immunotherapy of Cancer* **8**, e000883.
93. **Ngoi NY *et al.*** (2020) A multicenter phase II randomized trial of durvalumab (MEDI-4736) versus physician's choice chemotherapy in recurrent ovarian clear cell adenocarcinoma (MOCCA). *International Journal of Gynecological Cancer* **30**, 1239–1242.
94. **Lee JY *et al.*** (2019) A phase II study of neoadjuvant chemotherapy plus durvalumab and tremelimumab in advanced-stage ovarian cancer: a Korean gynecologic oncology group study (KGOG 3046), TRU-D. *Journal of Gynecologic Oncology* **30**, e112.
95. **Liu JF *et al.*** (2019) Safety, clinical activity and biomarker assessments of atezolizumab from a phase I study in advanced/recurrent ovarian and uterine cancers. *Gynecologic Oncology* **154**, 314–322.
96. **Pujade-Lauraine E *et al.*** (2021) Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN ovarian 200): an open-label, three-arm, randomised, phase 3 study. *The Lancet. Oncology* **22**, 1034–1046.
97. **Pujade-Lauraine E *et al.*** (2018) Avelumab (anti-PD-L1) in platinum-resistant/refractory ovarian cancer: JAVELIN ovarian 200 phase III study design. *Future Oncology* **14**, 2103–2113.
98. **Monk BJ *et al.*** (2021) Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN ovarian 100): an open-label, randomised, phase 3 trial. *The Lancet. Oncology* **22**, 1275–1289.
99. **Disis ML *et al.*** (2019) Efficacy and safety of avelumab for patients with recurrent or refractory ovarian cancer: phase 1b results from the JAVELIN solid tumor trial. *JAMA Oncology* **5**, 393–401.
100. **Ansell SM *et al.*** (2009) Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. *Clinical Cancer Research* **15**, 6446–6453.
101. **Normann MC *et al.*** (2019) Early experiences with PD-1 inhibitor treatment of platinum resistant epithelial ovarian cancer. *Journal of Gynecologic Oncology* **30**, e56.
102. **Linette GP *et al.*** (2019) Tumor-infiltrating lymphocytes in the checkpoint inhibitor era. *Current Hematologic Malignancy Reports* **14**, 286–291.
103. **Cheng WC *et al.*** (2019) Firing up cold tumors. *Trends in Cancer* **5**, 528–530.
104. **Bezu L *et al.*** (2015) Combinatorial strategies for the induction of immunogenic cell death. *Frontiers in Immunology* **6**, 187.
105. **Lheureux S *et al.*** (2020) EVOLVE: a multicenter open-label single-arm clinical and translational phase II trial of cediranib plus olaparib for ovarian cancer after PARP inhibition progression. *Clinical Cancer Research* **26**, 4206–4215.
106. **Liu JF *et al.*** (2019) Assessment of combined nivolumab and bevacizumab in relapsed ovarian cancer: a phase 2 clinical trial. *JAMA Oncology* **5**, 1731–1738.
107. **Zsiros E *et al.*** (2021) Efficacy and safety of pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide in the treatment of recurrent ovarian cancer: a phase 2 nonrandomized clinical trial. *JAMA Oncology* **7**, 78–85.
108. **Moore KN *et al.*** (2021) Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). *Journal of Clinical Oncology* **39**, 1842–1855.
109. **Moroney JW *et al.*** (2020) Safety and clinical activity of atezolizumab plus bevacizumab in patients with ovarian cancer: a phase Ib study. *Clinical Cancer Research* **26**, 5631–5637.
110. **Gonzalez Martin A *et al.*** (2021) A phase III, randomized, double blinded trial of platinum based chemotherapy with or without atezolizumab followed by niraparib maintenance with or without atezolizumab in patients with recurrent ovarian, tubal, or peritoneal cancer and platinum

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press

treatment free interval of more than 6 months: ENGOT-Ov41/GEICO 69-O/ANITA trial. *International Journal of Gynecological Cancer* **31**, 617–622.
111. **Lee YJ *et al.*** (2021) A single-arm phase II study of olaparib maintenance with pembrolizumab and bevacizumab in BRCA non-mutated patients with platinum-sensitive recurrent ovarian cancer (OPEB-01). *Journal of Gynecologic Oncology* **32**, e31.
112. **Lampert EJ *et al.*** (2020) Combination of PARP inhibitor olaparib, and PD-L1 inhibitor durvalumab, in recurrent ovarian cancer: a proof-of-concept phase II study. *Clinical Cancer Research* **26**, 4268–4279.
113. **Fumet JD *et al.*** (2020) Precision medicine phase II study evaluating the efficacy of a double immunotherapy by durvalumab and tremelimumab combined with olaparib in patients with solid cancers and carriers of homologous recombination repair genes mutation in response or stable after olaparib treatment. *BMC Cancer* **20**, 748.
114. **Zimmer AS *et al.*** (2019) A phase I study of the PD-L1 inhibitor, durvalumab, in combination with a PARP inhibitor, olaparib, and a VEGFR1-3 inhibitor, cediranib, in recurrent women's cancers with biomarker analyses. *Journal for Immunotherapy of Cancer* **7**, 197.
115. **Lee JY *et al.*** (2022) Biomarker-guided targeted therapy in platinum-resistant ovarian cancer (AMBITION; KGOG 3045): a multicentre, open-label, five-arm, uncontrolled, umbrella trial. *Journal of Gynecologic Oncology* **33**, e45.
116. **Monk BJ *et al.*** (2021) ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. *International Journal of Gynecological Cancer* **31**, 1589–1594.
117. **Jung KH *et al.*** (2019) Phase I study of the indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor navoximod (GDC-0919) administered with PD-L1 inhibitor (atezolizumab) in advanced solid tumors. *Clinical Cancer Research* **25**, 3220–3228.
118. **Chen S *et al.*** (2022) Epigenetic priming enhances antitumor immunity in platinum-resistant ovarian cancer. *Journal of Clinical Investigation* **132**, e158800.
119. **Zamarin D *et al.*** (2020) Safety, immunogenicity, and clinical efficacy of durvalumab in combination with folate receptor alpha vaccine TPIV200 in patients with advanced ovarian cancer: a phase II trial. *Journal for Immunotherapy of Cancer* **8**, e000829.
120. **Falchook GS *et al.*** (2021) A phase 1a/1b trial of CSF-1R inhibitor LY3022855 in combination with durvalumab or tremelimumab in patients with advanced solid tumors. *Investigational New Drugs* **39**, 1284–1297.
121. **Rocconi RP *et al.*** (2022) Proof of principle study of sequential combination atezolizumab and Vigil in relapsed ovarian cancer. *Cancer Gene Therapy* **29**, 369–382.
122. **Simonelli M *et al.*** (2022) Isatuximab plus atezolizumab in patients with advanced solid tumors: results from a phase I/II, open-label, multicenter study. *ESMO Open* **7**, 100562.
123. **Li J *et al.*** (2019) Expanding the role of STING in cellular homeostasis and transformation. *Trends in Cancer* **5**, 195–197.
124. **Curdy N *et al.*** (2019) Regulatory mechanisms of inhibitory immune checkpoint receptors expression. *Trends in Cell Biology* **29**, 777–790.
125. **Huang RY *et al.*** (2017) Compensatory upregulation of PD-1, LAG-3, and CTLA-4 limits the efficacy of single-agent checkpoint blockade in metastatic ovarian cancer. *Oncoimmunology* **6**, e1249561.
126. **Venkitaraman AR** (2002) Cancer susceptibility and the functions of BRCA1 and BRCA2. *Cell* **108**, 171–182.
127. **Konstantinopoulos PA *et al.*** (2015) Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. *Cancer Discovery* **5**, 1137–1154.
128. **Pilié PG *et al.*** (2019) State-of-the-art strategies for targeting the DNA damage response in cancer. *Nature Reviews. Clinical Oncology* **16**, 81–104.
129. **Foo T *et al.*** (2021) PARP inhibitors in ovarian cancer: an overview of the practice-changing trials. *Genes Chromosomes & Cancer* **60**, 385–397.
130. **Zheng F *et al.*** (2020) Mechanism and current progress of poly ADP-ribose polymerase (PARP) inhibitors in the treatment of ovarian cancer. *Biomedicine & Pharmacotherapy* **123**, 109661.
131. **da Cunha Colombo Bonadio RR *et al.*** (2018) Homologous recombination deficiency in ovarian cancer: a review of its epidemiology and management. *Clinics (Sao Paulo)* **73**, e450s.
132. **Ding L *et al.*** (2018) PARP inhibition elicits STING-dependent antitumor immunity in BRCA1-deficient ovarian cancer. *Cell Reports* **25**, 2972–2980.e2975.
133. **Wang Z *et al.*** (2019) Niraparib activates interferon signaling and potentiates anti-PD-1 antibody efficacy in tumor models. *Scientific Reports* **9**, 1853.
134. **Shen J *et al.*** (2019) PARPi triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness. *Cancer Research* **79**, 311–319.
135. **Konstantinopoulos PA *et al.*** (2019) Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma. *JAMA Oncology* **5**, 1141–1149.
136. **Bekes I *et al.*** (2016) Does VEGF facilitate local tumor growth and spread into the abdominal cavity by suppressing endothelial cell adhesion, thus increasing vascular peritoneal permeability followed by ascites production in ovarian cancer? *Molecular Cancer* **15**, 13.
137. **Nagy JA *et al.*** (1995) Pathogenesis of ascites tumor growth: vascular permeability factor, vascular hyperpermeability, and ascites fluid accumulation. *Cancer Research* **55**, 360–368.
138. **Luo JC *et al.*** (1998) Significant expression of vascular endothelial growth factor/vascular permeability factor in mouse ascites tumors. *Cancer Research* **58**, 2652–2660.
139. **Mahner S *et al.*** (2010) TIMP-1 and VEGF-165 serum concentration during first-line therapy of ovarian cancer patients. *BMC Cancer* **10**, 139.
140. **Azam F *et al.*** (2010) Mechanisms of resistance to antiangiogenesis therapy. *European Journal of Cancer* **46**, 1323–1332.
141. **Bergers G *et al.*** (2008) Modes of resistance to anti-angiogenic therapy. *Nature Reviews Cancer* **8**, 592–603.
142. **Yang Y *et al.*** (2021) Programmed death ligand-1 regulates angiogenesis and metastasis by participating in the c-JUN/VEGFR2 signaling axis in ovarian cancer. *Cancer Communications* **41**, 511–527.
143. **Klose RJ *et al.*** (2006) Genomic DNA methylation: the mark and its mediators. *Trends in Biochemical Sciences* **31**, 89–97.
144. **Ahluwalia A *et al.*** (2001) DNA methylation in ovarian cancer. II. Expression of DNA methyltransferases in ovarian cancer cell lines and normal ovarian epithelial cells. *Gynecologic Oncology* **82**, 299–304.
145. **Stone TW *et al.*** (2013) An expanding range of targets for kynurenine metabolites of tryptophan. *Trends in Pharmacological Sciences* **34**, 136–143.
146. **Li F *et al.*** (2017) IDO1: an important immunotherapy target in cancer treatment. *International Immunopharmacology* **47**, 70–77.
147. **Choi SW *et al.*** (2000) Folate and carcinogenesis: an integrated scheme. *Journal of Nutrition* **130**, 129–132.
148. **Scaranti M *et al.*** (2020) Exploiting the folate receptor α in oncology. *Nature Reviews. Clinical Oncology* **17**, 349–359.
149. **Figini M *et al.*** (2003) Reversion of transformed phenotype in ovarian cancer cells by intracellular expression of anti folate receptor antibodies. *Gene Therapy* **10**, 1018–1025.
150. **Nawaz FZ *et al.*** (2022) Emerging roles for folate receptor FOLR1 in signaling and cancer. *Trends in Endocrinology and Metabolism* **33**, 159–174.
151. **Wade PA *et al.*** (1997) Histone acetylation: chromatin in action. *Trends in Biochemical Sciences* **22**, 128–132.
152. **Eckschlager T *et al.*** (2017) Histone deacetylase inhibitors as anticancer drugs. *International Journal of Molecular Sciences* **18**, 1414.
153. **Li Y *et al.*** (2016) HDACs and HDAC inhibitors in cancer development and therapy. *Cold Spring Harbor Perspectives in Medicine* **6**, a026831.
154. **Weichert W *et al.*** (2008) Expression of class I histone deacetylases indicates poor prognosis in endometrioid subtypes of ovarian and endometrial carcinomas. *Neoplasia (New York, N.Y.)* **10**, 1021–1027.
155. **Yano M *et al.*** (2018) Association of histone deacetylase expression with histology and prognosis of ovarian cancer. *Oncology Letters* **15**, 3524–3531.
156. **Roberts PJ *et al.*** (2007) Targeting the Raf–MEK–ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene* **26**, 3291–3310.
157. **De Luca A *et al.*** (2012) The RAS/RAF/MEK/ERK and the PI3K/AKT signalling pathways: role in cancer pathogenesis and implications for therapeutic approaches. *Expert Opinion on Therapeutic Targets* **16** (suppl. 2), S17–S27.
158. **Shrestha R *et al.*** (2021) Multiomics characterization of low-grade serous ovarian carcinoma identifies potential biomarkers of MEK inhibitor sensitivity and therapeutic vulnerability. *Cancer Research* **81**, 1681–1694.

https://doi.org/10.1017/erm.2023.3 Published online by Cambridge University Press