



HAL
open science

Basics of immunotherapy for epithelial ovarian cancer

Virginie Bund, Henri Azais, Sabrina Bibi-Triki, Lise Lecointre, Sarah B. Betrian, Martina A. Angeles, Lauriane Eberst, Emilie Faller, Thomas Boisrame, Sofiane Bendifallah, et al.

► To cite this version:

Virginie Bund, Henri Azais, Sabrina Bibi-Triki, Lise Lecointre, Sarah B. Betrian, et al.. Basics of immunotherapy for epithelial ovarian cancer. *Journal of Gynecology Obstetrics and Human Reproduction*, 2021, 51 (2), pp.102283. 10.1016/j.jogoh.2021.102283 . hal-04544620

HAL Id: hal-04544620

<https://hal.science/hal-04544620>

Submitted on 12 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Basics of immunotherapy for epithelial ovarian cancer

Virginie Bund ^{1,2}, Henri Azaïs ³, Sabrina Bibi-Triki ², Lise Lecointre ^{1,4},
Sarah Bétrian ⁵, Martina Aida Angeles ⁶, Lauriane Eberst ⁷, Emilie Faller¹,
Thomas Boisrame¹, Sofiane Bendifallah ⁸, Chérif Akladios ^{1,9}, Élise Deluche ¹⁰,
on behalf of SFOG Campus

- 1- Department of Gynecologic Surgery, Hôpitaux Universitaires de Strasbourg, 67000 Strasbourg, France: virginie.collin@chru-strasbourg.fr; lise.lecointre@chru-strasbourg.fr; Cherif.AKLADIOS@chru-strasbourg.fr
- 2- Laboratoire d'ImmunoRhumatologie Moléculaire, Institut national de la santé et de la recherche médicale (INSERM) UMR_S 1109, Institut thématique interdisciplinaire (ITI) de Médecine de Précision de Strasbourg, Transplantex NG, Faculté de Médecine, Fédération Hospitalo-Universitaire OMICARE, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, Strasbourg, France. : virginie.collin@chru-strasbourg.fr ; bibitriki@unistra.fr
- 3- Department of Gynecologic and Breast Oncological Surgery, Georges-Pompidou European Hospital, APHP. Centre, France : henri.azais@aphp.fr
- 4- IHU-Strasbourg (Institut Hospitalo-Universitaire), Strasbourg, France
- 5- Medical oncology Department, Institut Claudius Regaud, Institut Universitaire du Cancer, Toulouse, France: Bétrian.Sarah@iuct-oncopole.fr
- 6- Department of Gynecologic and Breast Oncological Surgery, European Georges-Pompidou Hospital, APHP. Centre, France : AngelesFite.Martina@iuct-oncopole.fr
- 7- Department of Oncology, Institut de Cancérologie de Strasbourg (ICANS), Strasbourg, France : l.eberst@icans.eu
- 8- Hôpital Tenon APHP, France sofiane.bendifallah@aphp.fr
- 9- I.R.C.A.D - Institut de Recherche contre les Cancers de l'Appareil Digestif. 67000 Strasbourg: Cherif.AKLADIOS@chru-strasbourg.fr
- 10- Medical oncology Department, Limoges University Hospital, France. Elise.DELUCHE@chu-limoges.fr

Corresponding author:

Virginie Bund

Department of Gynecologic Surgery, Hôpitaux Universitaires de Strasbourg, 67000 Strasbourg, France.

Tel : 0781702239

Mail: virginie.collin@chru-strasbourg.fr

Conflict of interest: The authors declare no conflict of interest in connection with this work.

Article type: review

Authors' contribution:

Conception and design: CA, VB

Administrative support: /

Provision of study materials or patients: /

Collection and assembly of data: CA, VB, ED, SBT

Data analysis and interpretation: CA, VB, ED, SBT, SB, MAA, HA, LE, SB, LL, EF, TB

Manuscript writing: All authors.

Final approval of manuscript: All authors.

Ethical statement:

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.

Abstract

Epithelial ovarian cancer (EOC) is the most lethal of all gynecological cancers.

Despite excellent responses to standard treatment in approximately 70% of patients, most of them will relapse within 5 years of initial treatment and many of them will develop chemotherapy-resistant disease. It is then important to find other means of treatment for these patients such as immunotherapy or targeted therapy. To understand immunotherapy, it is important to explain the dynamic interplay between cancer and the immune system. Compared to traditional tumor therapies, immunotherapy acts primarily on the immune system or the tumor microenvironment but not directly on the tumor cells, and it may also promote synergistic anti-tumor actions as part of a combined treatment. The aim of this narrative review is to provide a basic understanding of immunotherapy the interest of this treatment in EOC, and to present the main ongoing studies that could change patient management in the future

Keywords: immunotherapy; epithelial ovarian cancer; immune checkpoint, tumor microenvironment

1. Introduction

Epithelial ovarian cancer (EOC) affects one in 70 women in industrialized countries [1] and is the 8th most common cancer in women and the 4th most common cause of death from cancer [1]. It is the most common cause of gynecological cancer-associated death in woman [2]

In France, it was estimated that 5,193 new cases of EOC occurred during 2018 and the number of deaths was estimated at 3,479 [3]. Approximately 75% of new cases are diagnosed at International Federation of Gynecology and Obstetrics (FIGO) Stage III or IV [4]. Five-year age-standardized net survival reached only 44% for cases diagnosed in the period of 2005–2010 [5]. The standard treatment for advanced EOC is currently based on complete macroscopic cytoreductive surgery (CRS) combined with platinum-based chemotherapy [6], and targeted therapies such as bevacizumab [7] or Poly-ADP-Ribose-Polymerase (PARP) inhibitors in BRCA mutation carriers or homologous repair deficient tumors [8]. Absence of tumor residue (Completeness Cytoreduction score 0 - CC0), which means no macroscopically visible tumor at the end of CRS, is recognized as a major prognostic factor to increase progression-free survival (PFS) and overall survival (OS) [9]. Despite excellent responses to standard treatment in approximately 70% of patients, most of them relapse within 5 years of initial treatment and many of them develop chemotherapy-resistant disease [2]. Patients who relapse within 6 months of completing first-line therapy have been classified as “platinum resistant” and have typically low response rates to subsequent chemotherapy (<15%), with a PFS of 3–4 months and a median OS of less than one year [11]. In this context, it is important to find a new perspective of treatment. Immunotherapy (IO), including checkpoint blockade and adoptive T-cell transfer (ACT), has become a clinically effective treatment modality for a wide variety of cancer types [12]. However, the application of IO in EOC is still being tested in clinical trials [12] but could provide a revolution in the treatment of EOC.

To understand IO, it is important to analyze the dynamic interplay between cancer cells and the immune system. Cancer cells are genetically unstable, and it contributes to their uncontrolled proliferation and to the expression of neo-antigens that can be recognized by the immune system [13]. Tumor antigens include normal proteins overexpressed by cancer cells and novel proteins generated by mutations and gene rearrangements [14]. Compared to traditional tumor therapies, IO acts primarily on the immune system or the tumor microenvironment (TME) but not directly on tumor cells, and it may also promote synergistic anti-tumor actions as part of a combined treatment [15].

The aim of this narrative review is to provide a basic understanding of IO, to explain the interest of this treatment in EOC, and to present the main ongoing studies that could change patient management in the future.

2. Immune system generalities

The immune system is divided into 2 categories: the passive immunity and the active immunity (table 1).

Table 1: Summary of immunotherapy

	Passive immunotherapy (initiator of a new immune response in the tumor)	Active immunotherapy (booster of an immune response)
Non-specific	NK cells	Cytokines
Specific	Adoptive cell transfer therapy = therapeutic use of the patient's individual T cell: TILs / CARs / TCR	Vaccines: peptides, DCs Checkpoint inhibitor (Ac anti-PD-1/PD-L1, anti-CTLA-4)
	Monoclonal antibodies	

TILs: tumor infiltrating lymphocyte; TCR: receptor T-cell; CAR: chimeric antigen receptor T-cell; DC: dendritic cell; NK cells: natural killer cells; T cell: lymphocyte T; CTLA-4: anti-cytotoxic T lymphocyte associated protein 4; PD-1/PD-L1: anti-programmed death 1 receptor and ligand

A/ Innate immunity: non-specific passive immunity.

The innate immunity is composed of dendritic cells (DCs), granulocytes (neutrophils, eosinophils, basophils, mast cells), macrophages, natural killer cells (NK) and complement system [16]. Phagocytic cells use a combination of degradation enzymes, peptides and oxygen-derived toxic molecules to kill invasive pathogens; and also secrete several signal molecules that participate in stimulating an inflammatory reaction. NK cells produce pro-inflammatory cytokines, such as interferon gamma (IFN- γ), which help guide the adaptive immune response. The complement system induces a series of inflammatory responses that fight infection by allowing activation of peptide mediators of inflammation, phagocytes recruitment and lysis of certain pathogens and cells [17]. This is the primary mechanism blocking the invasion of external pathogens, including tumor cells.

The innate response is fast but not specific. This is the primary mechanism involving in the invasion of external pathogens, including tumor cells.

B/ Adaptive immunity or specific active immunity.

The adaptive immune system is composed by T cells (cell-mediated immunity) and B cells (humoral immunity with production of antibodies). The adaptive immune response is slow but very specific [18]. B cells and T cells develop in the bone marrow and the thymus, respectively (central lymphoid organs) and respond to foreign antigens in the peripheral organs. T cells differentiate into CD4+ (helper cells) and CD8+ (cytotoxic cells). Once the meeting with the antigen occurs, B cells and T cells proliferate and undergo maturation into effector lymphocytes. B cells produce antibody and are then called plasmocytes in the medulla of the ganglia. The plasmocytes are then released into the blood circulation allowing the recognition of non-self-antigen (viral or tumoral).

A subpopulation of T and B cells named Regulatory (Tregs and Bregs respectively) are involved to suppress immune response, thereby maintaining homeostasis and self-tolerance.

It has been shown that Tregs are able to inhibit T cell proliferation and cytokine production and play a critical role in preventing autoimmunity [19]. Bregs protect against chronic inflammatory responses primarily through production of anti-inflammatory cytokines such as IL-10 [20].

The adaptive immune system cooperates with the innate immune system to protect the host from infections or tumor cells [21].

3. Recognition of tumor cell by the immune system

These mechanisms were described by Chen et al. [22] described below. Neoantigens created by oncogenesis are released and captured by DCs present in the TME for processing. The neo-antigen-active DCs then migrate to a proximal lymphoid organ, such as a lymph node, where they present antigen-Major Histocompatibility Complex [MHC] I and II to cell surface T cell receptors (TCRs) present on naive T cell. Binding of the TCR to the antigen-MHC ligand is insufficient to trigger a full activation of T cell. A co-signal between a stimulatory immune checkpoint (CD28) on T cell and its ligands CTLA4 on active DC is essential to initiate the T cell response.

Through this action, DCs establish the link between the innate and adaptive immune systems. Once activated, the T cell differentiate into effector cells and memory cells. Effector cells proliferate and migrate to the tumor where they participate in the elimination of tumor cells notably by the secretion of pro-inflammatory cytokines like tumor necrosis factor (TNF- α), interferon (IFN- γ) and interleukin 2, which have anti-tumor effects.

The most important item in the immune response is the balance between an immune response, adapted and sufficient to control tumor cells, but not excessive, to prevent damaging on the

normal cells and the generation of autoimmunity [23]. Inhibitory immune checkpoints such as PD-1 or CTLA-4 first have a physiological role in preventing the immune response from being so strong that it would destroy healthy cells in the body [24]. When the inhibitory checkpoint and partner protein bind together, they send an “off” signal to the T cell. This phenomenon is called immune-editing, and prevents the immune system from destroying the cancer [25].

Immune tolerance is normally effected by immune editing that occurs centrally in the thymus and bone marrow for T cell and B cell, respectively, with deletion of autoreactive lymphocyte clones by apoptosis (negative selection), or induction of anergy [18]. Vital fundamental discoveries made over the last few decades have unequivocally shown that the immune system plays a critical role in maintaining an equilibrium between immune recognition and tumor development with a dual capacity to both promote and suppress tumor growth [26]. These discoveries collectively support the concept of “immunoediting” and help to explain why tumors can sometimes lie dormant in patients for years before re-emerging, and why tumors grow despite the host having a fully functional immune system [27].

4. Tumor microenvironment (TME)

The recognition of the tumor cell by the immune system is highly dependent on the TME (figure 1).

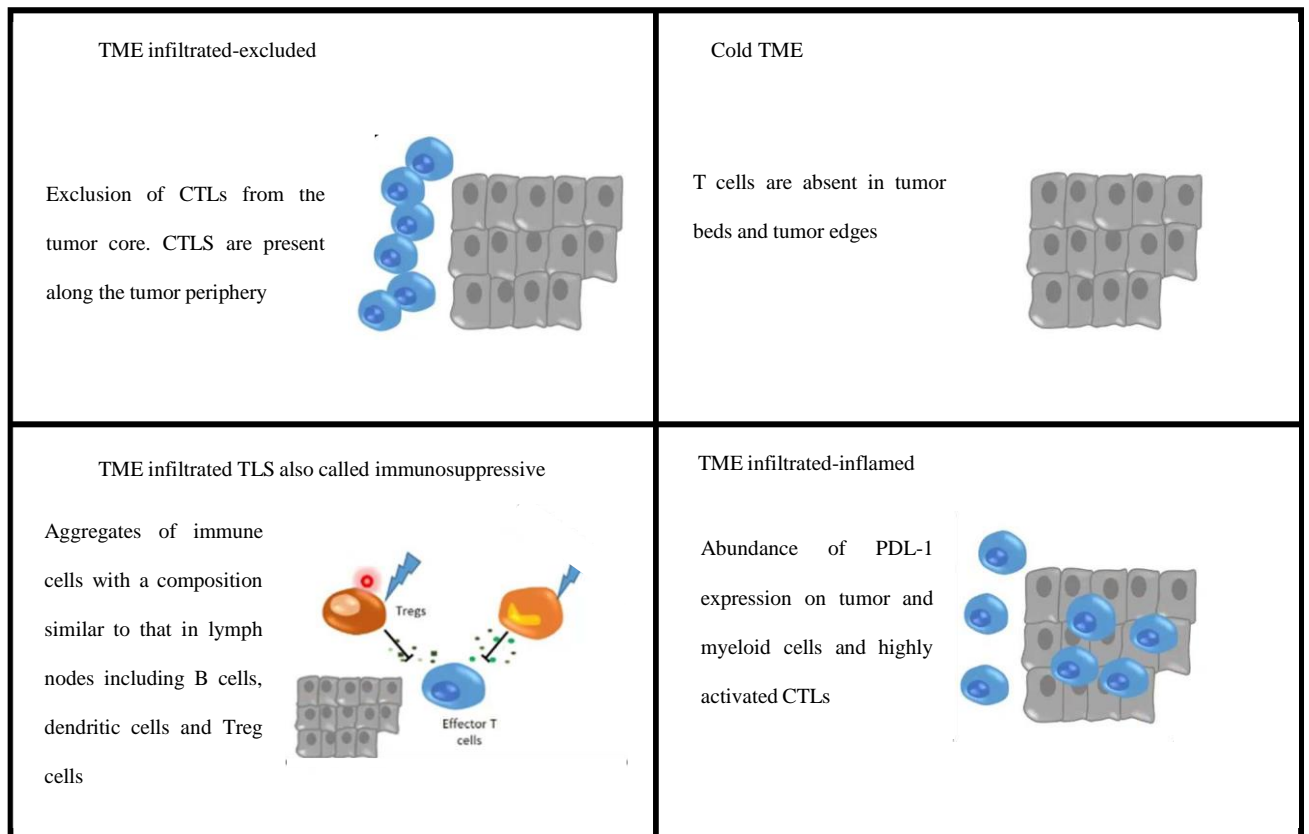


Figure 1: The different spectrum of immune microenvironment

*The grey cells represent the tumor cells. The blue cells represent the immune cells of the TME
TME: tumor microenvironment / TLS: tertiary lymphoid structure, CTLs: cytotoxic T lymphocyte; PDL-1: programmed death 1 ligand; Treg: regulatory T-cell*

A/ General concept

The TME refers to the cellular environment in which tumors or cancer stem cells co-exist [28].

Cancer stem cells are tumor cells with the abilities to self-renew and drive tumorigenesis [29].

The TME encompasses blood vessels, extracellular matrix (ECM), fibroblasts, lymphocytes, bone marrow-derived inflammatory cells, and signaling molecules [30].

The TME differs from a "normal" microenvironment by the biochemical composition of the extracellular matrix and especially by the fact that stromal cell populations (fibroblasts,

endothelial cells, immune cells, etc.), although not transformed, are subverted and controlled by the tumor cells to meet their own needs [31]. The TME takes into account different parameters such as the composition of the immune infiltrate and the characteristics of the inflammatory response [32] that have an influence on tumor initiation and response to therapy [32].

There are four types of TME divided into two main groups: tumor tissues with immune infiltration and tumor tissues without immune infiltration known as "cold" TME [33] (figure 1). Tumors with immune infiltration are divided into three subgroups: TME infiltrated-excluded, infiltrated-inflamed and infiltrated-tertiary lymphoid structure (TLS) [32].

TME is largely involved in tumorigenesis because it contains tumor cells that interact with surrounding cells through the circulatory and lymphatic systems to influence the development and progression of cancer in particular by modulating the existing activated antitumor T cell [22]. In addition, nonmalignant cells in the TME play critical roles in all the stages of carcinogenesis by stimulating and facilitating uncontrolled cell proliferation [28].

Thus, targeting TME can help enhance acquired resistance, improve therapeutic efficacy, and prevent metastasis [34] and so, TME plays a major role in the clinical outcome [35].

B/ Immune system escape mechanism

Initially, CD8+ and CD4+ T helper cells can limit cancer development by producing IFN and cytotoxins. There are different ways for the tumor to escape its microenvironment [22,26].

Concerning tumor mechanisms

Various mechanisms, such as rapid growth through mutations that promote replication, immunoediting which consists of a selection of tumor clones be able of escaping immune recognition [36] and weak immunogenicity of tumor cells [37] lead to immune escape.

Concerning the immunosuppressive environment of the TME

The immunosuppressive environment does not allow an effective antitumor immunity by various mechanisms: T cell may not properly home to tumors training reduction of infiltrating the tumor or secretion of factors inhibiting the production of effector cells [26].

In this immunosuppressive TME, there is a chronic inflammation [38] and a downregulation or even an absence of MHC expression [39] resulting in a poor presentation of antigens or a lack of maintenance of the T cell response for a sufficient time period to eliminate the cancer [18].

Impact of ascite fluids

It is well documented that the ascites fluid from patients with advanced stage EOC suppress the function of otherwise normal immune effectors, including NK cells [40]. The ascites contains large numbers of growth factors and cytokines that promote the proliferation of tumor cells [41].

5. Immunotherapy generalities

In recent years, tumor IO has attracted increasing attention. The goal of IO is to restart a sufficient immune response to fight against cancer cells without initiating an autoimmune response [42]. This therapy can eliminate cancer cells by strengthening the body's immune function [43]. Strategies for cancer IO (active or passive immunotherapies [33]) may be aim to either stimulate the immune system with immune effectors or to modulate the immune system to delete the inhibitors of the immune system [44]. Moreover, IO is only effective when

competent immune cells are present in the TME. Thus, one of the challenges in IO is to transform "cold TMEs" into "inflamed TMEs" to make IO effective, a strategy called immunomodulation [45]. In this review, we will not develop anti-angiogenesis drugs or PARP inhibitors [46] even there are included in specific and passive IO. Monoclonal antibodies (mAbs) promote the recognition of tumor cells by the immune system by targeting tumor cell surface proteins. Monoclonal antibodies were introduced as targets in cancer IO [47]. Examples of these include trastuzumab and bevacizumab which block human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor (VEGF), respectively.

6. Immunotherapy in ovarian cancer

The different actors are summarized in Table 1 and the non-exhaustive list of clinical trials in Table 2.

A/ Nonspecific and passive immunotherapies: NK cell

1. NK cells

Most of the published studies document limited infiltration of NK cells within the primary ovarian tumor and cells that suppress immune response and support tumor growth dominate [48–54]. The presence of infiltrating NK cells impact on OS is also controversial [55]. Infiltrating NK cells have largely not been associated with better outcomes, and in one case, predicted worse OS [56]. However, it was recently shown that CD103⁺ tumor-infiltrating NK cells were almost always found with CD8⁺ T cells and were the second best predictor of positive outcomes in primary EOC [57].

2. Tumor-Associated Macrophages (TAMs)

TAMs constitute the main population of immune cells present in the ovarian tumor microenvironment [58].

The main pro-tumoral function of M2-like TAMs is the secretion of a variety of cytokines, chemokines, enzymes and exosomes that reach microRNAs, directly inducing the invasion potential and chemoresistance of EOC cells by triggering their pro-survival signaling pathways. The M2-like TAMs are also important players in the metastasis of EOC cells in the peritoneum through their assistance in spheroid formation and attachment of cancer cells to the metastatic area particularly the omentum [58]. Moreover, TAMs interplay with other immune cells, such as lymphocytes, natural killer cells, and dendritic cells, to inhibit their responsiveness, resulting in the development of immunosuppression. The detrimental character of the M2-like type of TAMs in ovarian tumors has been confirmed by a number of studies, demonstrating the positive correlation between their high level in tumors and low overall survival of patients [58].

B/ Specific and passive immunotherapies

Agents used for the various strategies of passive immunotherapies have included adoptive transfer of cells : TILs, T cell receptor (TCRs), antigen specific chimeric antigen receptors (CARs) [18].

1. TILS and ovarian carcinoma:

TIL therapy has been shown to induce complete regression of metastatic tumor in patients with melanoma [59] with response rates can be from 47 to 72% [60].

By definition, TILs are white blood cells, for example, T-cells, B-cells, macrophages or natural killer cells, which have left the vasculature and have localized in tumor stroma or intraepithelium [61]. The absence of CTL infiltration (CTL) also predicts platinum resistance [62].

Zhang et al. performed analysis on 186 samples of advanced stage EOC and found that there were significant differences in the distributions of progression-free survival and overall survival according to the presence or absence of intratumoral T cells ($P < 0.001$ for both comparisons) [48]. That 5-year survival benefit jumps to 73.9% when considering patients who had a complete clinical response after debulking and platinum based chemotherapy, compared to just 11.9% of patients without TILs ($p < 0.001$) [48].

Sato et al. [63] conclude that intraepithelial CD8⁺ TILs (median = 55 versus 26 months; hazard ratio = 0.33; confidence interval (C.I.) = 0.18–0.60; $P = 0.0003$) and a high CD8⁺/Treg ratio are associated with favorable prognosis in EOC (median = 58 versus 23 months; hazard ratio = 0.31; C.I. = 0.17–0.58; $P = 0.0002$). Hao et al. [64] compared TIL-positive and TIL-negative patients by a meta-analysis of patients with HGSOC by. However, the multivariate analysis revealed that PD-1⁺ TILs were not associated with the OS of patients with HGSOC (HR 0.97, 95% CI 0.90–1.04) [64]. The multivariate analysis revealed that intraepithelial CD8⁺ TILs were positively correlated with progression-free survival (PFS, HR 0.46, 95% CI 0.25–0.67) and overall survival (OS, HR 0.90, 95% CI 0.86–0.9); stromal CD8⁺ TILs were positively correlated with OS (HR 0.61, 95% CI 0.36–0.87) [64].

In the pilot study of Pedersen et al. [65] they tested TIL based Adoptive cell therapy (ACT) in patients with metastatic EOC and discovered that ACT with TIL in combination with decrescendo IL-2 is feasible in patients with metastatic ovarian cancer but the efficacy was incomplete with possible involvement of the inhibitory immune checkpoint pathways like LAG3/MHCII or PD1/PD-L1.

2. CAR-T cells in EOC.

CAR-T cell are T cell that have been genetically engineered to produce an artificial T cell receptor to use in IO [66]. Adoptive cell transfer can be used to induce an immune response in tumors that are “COLD” or refractory to immune checkpoint inhibitors.

CAR-T cell technology as novel IO has made breakthrough progress in the treatment of hematologic malignancies, and there were also benefits shown in a partial solid tumor in previous research [67]. It may be a promising candidate as an immunotherapeutic tool against EOC. Initial studies of CAR T cell therapy have shown promising results in EOC first in vitro and mouse model studies [68,69]. There are some obstacles like impaired T cell trafficking, lack of antigenic targets, cytokine release syndrome and most important immunosuppressive tumor microenvironment [70].

C/ Active immunotherapy.

Active IO relies on chemical agents that specifically stimulates the patient’s own immune responses, such as the production of antibodies or T cell directed against tumor cells [71].

1. Cancer vaccines

A therapeutic vaccine induces cell mediated immunity in which immune cells are activated to recognize and destroy their cellular targets in affected tissue [72]. Generally, therapeutic cancer vaccines has few side effects, but they have shown consistently lower efficacy [72] than other types of IO.

Cancer vaccines include in particular: whole tumor cell vaccines, cancer cell lysates, peptide-based vaccines and direct delivery of recombinant proteins or epitopes in combination with immunological adjuvants for example [18].

A promising recent pre-clinical study has found that administration of a vaccine without adjuvant against seemingly irrelevant viruses could be an effective cancer IO by converting

immunologically “cold” tumors into hot tumors [73]. A seasonal influenza vaccine administered intratumorally within the TME stimulated systemic CD8+ T-cell-mediated immunity and infiltration of CD8+ T cell into the tumors, while decreasing intra-tumoral B-regs [18]. Other clinical trials for EOC employ oncolytic viruses from the vaccinia, adenovirus, and reovirus families [74].

In EOC, many clinical studies have revealed induced antigen-specific T cell response and improved survival in different degrees by using different vaccines, including recombinant protein or peptide vaccines and whole tumor lysate or dendritic cell (DC)-based autologous vaccines [12].

The Dafni et al. meta-analysis, no statistically significant differences were detected by vaccine type or treatment schema [75]. In fact, median PFS was 13.0 months (95%CI[8.5,16.3]) for ovarian cancer, while corresponding median OS was 39.0 months (95%CI[31.0,49.0]) with a moderate toxicity [75].

The recent clinical and biological observations provide promising data that DC vaccines pulsed with autologous whole-tumor antigen as personalized combinatorial IO will be an important future strategy. This approach is able to mobilize broad antitumor immunity and neo-epitope-specific T cells causing clinical benefit for the patients with EOC [76].

2. The immune checkpoint inhibitors

Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the “off” signal from being sent, allowing the T cell to kill cancer cells [24]. Three candidate immune checkpoint inhibitors are potentially interesting in EOC: anti-cytotoxic T lymphocyte associated protein 4 (CTLA-4) (Ipilimumab), anti-programmed death 1 receptor and ligand (PD-1 (nivolumab) /PD-L1)

(Atezolizumab) and LAG-3 [42] have been tested in monotherapy of EOC as monotherapy in clinical trials.

The most important peripheral checkpoint inhibitor pathway exploited by tumor cells within the TME from a clinical perspective to date is the interaction between the PD-1 receptor on T cell with its ligands PD-L1 and PD-L2 on tumor cells [77]. PD-1 is highly expressed on TILs [78], particularly CD8+ immune effector cells [79]. Both PD-1 and CTLA-4 blockades were more effective in tumors that are infiltrated by T cell [80–82]

In EOC, objective response rates to these checkpoint inhibitors as single agents in clinical trials was estimated to be only 10–15% [83,84], or 6–22% [85,86]. So, immune checkpoint inhibitors monotherapy did not produce favorable results in clinical trials [87].

Many trials are currently studying the associations between immune checkpoint inhibitor and anti-angiogenic agents (VEGF/VEGF), anti-PARP, chemotherapy, other immune-checkpoint inhibitors or other IO [33].

Combination with chemotherapy

Chemotherapy is the cornerstone of the treatment of EOC, and leads to the destruction of cancer cells [88]. In addition to direct cytotoxic effects on tumor cells, a proportion of chemotherapy agents may induce immunogenic cell death, expand neoantigen repertoire, increase antigen presentation, change the inflammatory milieu of tumor microenvironment and/or decrease the numbers of immunosuppressive cells, thereby inducing or enhancing the anti-tumoral immune response [89,90]. Based on the published results, combinational therapy including PD-1/PD-L1 inhibitors and chemotherapy certainly has the potential to be superior to chemotherapy alone [91,92]. Moreover, recent studies demonstrated that certain chemotherapy agents might attenuate the anti-tumor immune response [93,94]. Therefore, to thoroughly assess the

combination with chemotherapy, selection of chemotherapy agents, optimization of the sequencing, timing, dose, and management of concurrent toxicities will be required [12].

The JAVELIN Ovarian 200 [95] study compared Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory EOC. This study shows no significant improvement in progression-free survival or overall survival when chemotherapy is combined with immune checkpoint inhibitors versus chemotherapy alone in platinum-resistant or refractory EOC.

Combination with radiotherapy

EOC is sensitive to radiation therapy, but abdominal radiotherapy-induced side effects, such as intestinal obstruction and ureteral stenosis or fistulae, highlighting the need of paying close attention to dosimetry [96]. Radiation therapy can enhance IO efficacy via inducing *in-situ* vaccination and immune reprogramming [97].

A preclinical study demonstrated that mice treated with radiotherapy in combination with IO had increased survival compared to those treated with radiotherapy alone. In this study, IO efficacy was enhanced by radiotherapy, as this last can function as an *in-situ* vaccination and accelerate T cell arrival to the tumor site [46].

Combination with VEGF inhibitor

A promising approach is to combine vascular endothelial growth factor (VEGF) inhibitor and checkpoint blockade [12]. VEGF is primarily known as a mediator of angiogenesis; however, emerging studies have also recognized VEGF as a critical mediator of immune suppression in the tumor microenvironment [98]. Inhibitors targeting VEGF or VEGF receptors (VEGFR)

have been shown to decrease the numbers of regulatory T cells and myeloid-derived suppressor cells (MDSC) and enhance the infiltration of effector T cells [98,99].

Several clinical trials are currently ongoing to evaluate the safety and efficacy of the combination of bevacizumab (anti-VEGF) and checkpoint blockade in melanoma and renal cell cancer [12].

Table 2 : Clinical trials in progress (<https://clinicaltrials.gov/>)

	Therapeutic target	Name of the study	NCT (Clinical Trial)	Phase
Non specific and passive immunotherapies	NK cells	Intraperitoneal Infusion of ex Vivo-cultured Allogeneic NK Cells in Recurrent Ovarian Carcinoma Patients (INTRO)	NCT03539406	Phase 1
	Tumor-Associated macrophages (TAMs)	A Trial of BI 765063 Monotherapy and in Combination With BI 754091 in Patients With Advanced Solid Tumour	NCT03990233	Phase 1
<u>Specific and passive immunotherapies</u>	TILs and ovarian carcinoma:	OVSTAR TIL Trial (OVarian Cancer Co-STimulatory Antigen Receptor TIL Trial) (OVSTAR)	NCT04389229	Phase 2
		"Re-Stimulated" Tumor-Infiltrating Lymphocytes And Low-Dose Interleukin-2 Therapy in Patients With Platinum Resistant High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	NCT01883297	Phase 1
	CAR-T cells in EOC.	Adoptive T Cell Therapy in Patients With Recurrent Ovarian Cancer (OVACURE)	NCT04072263	Phase 2
		Adoptive Cell Therapy Following a Reduced Intensity, Non-myeloablative, Lymphodepleting Induction Regimen in Metastatic Ovarian	NCT03412526	Phase 2
		T-cell Therapy in Combination With Nivolumab, Relatlimab and Ipilimumab for Patients With Metastatic Ovarian Cancer	NCT04611126	Phase 2
<u>Active immunotherapy.</u>	Cancer vaccines	Ovarian Cancer Treatment With a Liposome Formulated mRNA Vaccine in Combination With (Neo-)Adjuvant Chemotherapy (OLIVIA)	NCT04163094	Phase 1
		A Phase I Study of WT1 or NY-ESO-1 Vaccine and Nivolumab For Recurrent Ovarian Cancer	NCT02737787	Phase 1
		Phase 2 Study of Pembrolizumab, DPX-Survivac Vaccine and Cyclophosphamide in Advanced Ovarian, Primary Peritoneal or Fallopian Tube Cancer	NCT03029403	Phase 2
		P53MVA and Pembrolizumab in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	NCT03113487	Phase 2
		OSE2101 Alone or in Combination With Pembrolizumab vs BSC in Patient With Platinum-sensitive Recurrent OC (TEDOVA)	NCT04713514	Phase 2
	The immune checkpoint inhibitors	Anti-programmed Cell Death-1 Ligand 1 (aPDL-1) Antibody Atezolizumab, Bevacizumab and Acetylsalicylic Acid in Recurrent Platinum Resistant Ovarian Cancer	NCT02659384	Phase 2
		A Study of Atezolizumab Versus Placebo in Combination With Paclitaxel, Carboplatin, and Bevacizumab in Participants With Newly-Diagnosed Stage III or Stage IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (IMagyn050)	NCT03038100	Phase 3
		PEMBRO With Chemo in Neo Adj Treatment of Ovarian Cancer . (NEOPEMBROV)	NCT03275506	Phase 2
		A Phase 3 Comparison of Platinum-based Therapy With TSR-042 and Niraparib Versus Standard of Care (SOC) Platinum-based Therapy as First-line Treatment of Stage III or IV Nonmucinous Epithelial Ovarian Cancer (FIRST)	NCT03602859	Phase 3
		Durvalumab Treatment in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib Treatment in Advanced Ovarian Cancer Patients (DUO-O)	NCT03737643	Phase 3
		Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (MK-7339-001/KEYLYNK-001/ENGOT-ov43/GOG-3036)	NCT03740165	Active, not recruiting

Conclusion

This narrative review of IO in EOC provides a better understanding of the mechanisms of this therapy. The evolution of knowledge and the appearance of new treatments in the therapeutic arsenal of EOC could improve the prognosis of patients. It is important to know their mechanisms in order to be able to select the compounds that could be beneficial as well as to predict their side effects. Predicting responsiveness to immune checkpoint blockade on the basis of the presence and the quality of tumor immune infiltrates is a critical next step in improving the success of current immune checkpoint blockade and developing next-generation immunotherapies.

References

1. Institut National du Cancer Thésaurus - Conduites à Tenir Initiales Devant Des Patientes Atteintes d'un Cancer Épithélial de l'ovaire - Ref : RECOKOVAIRETHES18 Available online: <https://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Thesaurus-Conduites-a-tenir-initiales-devant-des-patientes-atteintes-d-un-cancer-epithelial-de-l-ovaire> (accessed on 4 November 2019).
2. Jayson, G.C.; Kohn, E.C.; Kitchener, H.C.; Ledermann, J.A. Ovarian Cancer. *Lancet Lond. Engl.* **2014**, *384*, 1376–1388, doi:10.1016/S0140-6736(13)62146-7.
3. Defossez, G.; Le Guyader-Peyrou, S.; Uhry, Z.; Grosclaude, P.; Remontet, L.; Colonna, M. Estimations Nationales de l'incidence et de La Mortalité Par Cancer En France Métropolitaine Entre 1990 et 2018. Étude à Partir Des Registres Des Cancers Du Réseau Francim. Résultats Préliminaires. Synthèse. Saint Maurice : Santé Publique France, 2019. 20 p. Disponible à Partir de : [Www. Santepubliquefrance.Fr](http://www.santepubliquefrance.fr) et [Https://Www.Ecancer.Fr](https://www.ecancer.fr).
4. Jemal, A.; Tiwari, R.C.; Murray, T.; Ghafour, A.; Samuels, A.; Ward, E.; Feuer, E.J.; Thun, M.J.; American Cancer Society Cancer Statistics, 2004. *CA. Cancer J. Clin.* **2004**, *54*, 8–29, doi:10.3322/canjclin.54.1.8.
5. Cowppli-Bony, A. *Survie Des Personnes Atteintes de Cancer En France Métropolitaine 1989-2013 - Partie 1 - Tumeurs Solides. Partenariat Francim/HCL/ InVS/INCa ; 2016 Févr p. 274.*;
6. du Bois, A.; Quinn, M.; Thigpen, T.; Vermorken, J.; Avall-Lundqvist, E.; Bookman, M.; Bowtell, D.; Brady, M.; Casado, A.; Cervantes, A.; et al. 2004 Consensus Statements on the Management of Ovarian Cancer: Final Document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIg OCCC 2004). *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2005**, *16 Suppl 8*, viii7–viii12, doi:10.1093/annonc/mdi961.
7. Perren, T.J.; Swart, A.M.; Pfisterer, J.; Ledermann, J.A.; Pujade-Lauraine, E.; Kristensen, G.; Carey, M.S.; Beale, P.; Cervantes, A.; Kurzeder, C.; et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *N. Engl. J. Med.* **2011**, *365*, 2484–2496, doi:10.1056/NEJMoa1103799.
8. Banerjee, S.; Moore, K.N.; Colombo, N.; Scambia, G.; Kim, B.-G.; Oaknin, A.; Friedlander, M.; Lisyanskaya, A.; Floquet, A.; Leary, A.; et al. 811MO Maintenance Olaparib for Patients (Pts) with Newly Diagnosed, Advanced Ovarian Cancer (OC) and a BRCA Mutation (BRCAm): 5-Year (y) Follow-up (f/u) from SOLO1. *Ann. Oncol.* **2020**, *31*, S613, doi:10.1016/j.annonc.2020.08.950.
9. Bristow, R.E.; Tomacruz, R.S.; Armstrong, D.K.; Trimble, E.L.; Montz, F.J. Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma during the Platinum Era: A Meta-Analysis. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2002**, *20*, 1248–1259, doi:10.1200/JCO.2002.20.5.1248.
10. Stoeckle, E.; Paravis, P.; Floquet, A.; Thomas, L.; Lara, C.T.D.; Bussièrès, E.; Macgrogan, G.; Picot, V.; Avril, A. Number of Residual Nodules, Better than Size, Defines Optimal Surgery in Advanced Epithelial Ovarian Cancer. *Int. J. Gynecol. Cancer* **2004**, *14*, 779–787, doi:10.1111/j.1048-891X.2004.014508.x.
11. Davis, A.; Tinker, A.V.; Friedlander, M. “Platinum Resistant” Ovarian Cancer: What Is It, Who to Treat and How to Measure Benefit? *Gynecol. Oncol.* **2014**, *133*, 624–631, doi:10.1016/j.ygyno.2014.02.038.
12. Wang, W.; Liu, J.R.; Zou, W. Immunotherapy in Ovarian Cancer. *Surg. Oncol. Clin. N. Am.* **2019**, *28*, 447–464, doi:10.1016/j.soc.2019.02.002.
13. Seidel, J.A.; Otsuka, A.; Kabashima, K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. *Front. Oncol.* **2018**, *8*, 86,

doi:10.3389/fonc.2018.00086.

14. Lawrence, M.S.; Stojanov, P.; Polak, P.; Kryukov, G.V.; Cibulskis, K.; Sivachenko, A.; Carter, S.L.; Stewart, C.; Mermel, C.H.; Roberts, S.A.; et al. Mutational Heterogeneity in Cancer and the Search for New Cancer-Associated Genes. *Nature* **2013**, *499*, 214–218, doi:10.1038/nature12213.
15. Li, Y.; Li, F.; Jiang, F.; Lv, X.; Zhang, R.; Lu, A.; Zhang, G. A Mini-Review for Cancer Immunotherapy: Molecular Understanding of PD-1/PD-L1 Pathway & Translational Blockade of Immune Checkpoints. *Int. J. Mol. Sci.* **2016**, *17*, doi:10.3390/ijms17071151.
16. Zhang, H.; Chen, J. Current Status and Future Directions of Cancer Immunotherapy. *J. Cancer* **2018**, *9*, 1773–1781, doi:10.7150/jca.24577.
17. Charles A Janeway, J.; Travers, P.; Walport, M.; Shlomchik, M.J. The Complement System and Innate Immunity. *Immunobiol. Immune Syst. Health Dis. 5th Ed.* **2001**.
18. Macpherson, A.M.; Barry, S.C.; Ricciardelli, C.; Oehler, M.K. Epithelial Ovarian Cancer and the Immune System: Biology, Interactions, Challenges and Potential Advances for Immunotherapy. *J. Clin. Med.* **2020**, *9*, 2967, doi:10.3390/jcm9092967.
19. Kondělková, K.; Vokurková, D.; Krejsek, J.; Borská, L.; Fiala, Z.; Ctírad, A. Regulatory T Cells (TREG) and Their Roles in Immune System with Respect to Immunopathological Disorders. *Acta Medica (Hradec Kralove)* **2010**, *53*, 73–77, doi:10.14712/18059694.2016.63.
20. van de Veen, W. The Role of Regulatory B Cells in Allergen Immunotherapy. *Curr. Opin. Allergy Clin. Immunol.* **2017**, *17*, 447–452, doi:10.1097/ACI.0000000000000400.
21. Bayersdorf, R.; Fruscalzo, A.; Catania, F. Linking Autoimmunity to the Origin of the Adaptive Immune System. *Evol. Med. Public Health* **2018**, *2018*, 2–12, doi:10.1093/emph/eoy001.
22. Chen, D.S.; Mellman, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* **2013**, *39*, 1–10, doi:10.1016/j.immuni.2013.07.012.
23. Gonzalez, S.; González-Rodríguez, A.P.; Suárez-Álvarez, B.; López-Soto, A.; Huergo-Zapico, L.; Lopez-Larrea, C. Conceptual Aspects of Self and Nonself Discrimination. *Self Nonself* **2011**, *2*, 19–25, doi:10.4161/self.2.1.15094.
24. Immune Checkpoint Inhibitors - National Cancer Institute Available online: <https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors> (accessed on 26 October 2020).
25. Messerschmidt, J.L.; Prendergast, G.C.; Messerschmidt, G.L. How Cancers Escape Immune Destruction and Mechanisms of Action for the New Significantly Active Immune Therapies: Helping Nonimmunologists Decipher Recent Advances. *The Oncologist* **2016**, *21*, 233–243, doi:10.1634/theoncologist.2015-0282.
26. Motz, G.T.; Coukos, G. Deciphering and Reversing Tumor Immune Suppression. *Immunity* **2013**, *39*, 61–73, doi:10.1016/j.immuni.2013.07.005.
27. Dunn, G.P.; Bruce, A.T.; Ikeda, H.; Old, L.J.; Schreiber, R.D. Cancer Immunoediting: From Immunosurveillance to Tumor Escape. *Nat. Immunol.* **2002**, *3*, 991–998, doi:10.1038/ni1102-991.
28. Arneth, B. Tumor Microenvironment. *Medicina (Mex.)* **2019**, *56*, doi:10.3390/medicina56010015.
29. Grivennikov, S.I.; Greten, F.R.; Karin, M. Immunity, Inflammation, and Cancer. *Cell* **2010**, *140*, 883–899, doi:10.1016/j.cell.2010.01.025.
30. Del Prete, A.; Schioppa, T.; Tiberio, L.; Stabile, H.; Sozzani, S. Leukocyte Trafficking in Tumor Microenvironment. *Curr. Opin. Pharmacol.* **2017**, *35*, 40–47, doi:10.1016/j.coph.2017.05.004.
31. Rôle Du Microenvironnement Dans La Tumorigenèse et La Progression Tumorale.
32. Binnewies, M.; Roberts, E.W.; Kersten, K.; Chan, V.; Fearon, D.F.; Merad, M.; Coussens, L.M.; Gaborilovich, D.I.; Ostrand-Rosenberg, S.; Hedrick, C.C.; et al. Understanding

the Tumor Immune Microenvironment (TIME) for Effective Therapy. *Nat. Med.* **2018**, *24*, 541–550, doi:10.1038/s41591-018-0014-x.

33. Palaia, I.; Tomao, F.; Sassu, C.M.; Musacchio, L.; Benedetti Panici, P. Immunotherapy For Ovarian Cancer: Recent Advances And Combination Therapeutic Approaches. *OncoTargets Ther.* **2020**, *13*, 6109–6129, doi:10.2147/OTT.S205950.

34. Chen, F.; Zhuang, X.; Lin, L.; Yu, P.; Wang, Y.; Shi, Y.; Hu, G.; Sun, Y. New Horizons in Tumor Microenvironment Biology: Challenges and Opportunities. *BMC Med.* **2015**, *13*, doi:10.1186/s12916-015-0278-7.

35. Bösmüller, H.-C.; Wagner, P.; Peper, J.K.; Schuster, H.; Pham, D.L.; Greif, K.; Beschoner, C.; Rammensee, H.-G.; Stevanović, S.; Fend, F.; et al. Combined Immunoscore of CD103 and CD3 Identifies Long-Term Survivors in High-Grade Serous Ovarian Cancer. *Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc.* **2016**, *26*, 671–679, doi:10.1097/IGC.0000000000000672.

36. Teng, M.W.L.; Galon, J.; Fridman, W.-H.; Smyth, M.J. From Mice to Humans: Developments in Cancer Immunoediting. *J. Clin. Invest.* **2015**, *125*, 3338–3346, doi:10.1172/JCI80004.

37. D'Aloia, M.M.; Zizzari, I.G.; Sacchetti, B.; Pierelli, L.; Alimandi, M. CAR-T Cells: The Long and Winding Road to Solid Tumors. *Cell Death Dis.* **2018**, *9*, 1–12, doi:10.1038/s41419-018-0278-6.

38. Vinay, D.S.; Ryan, E.P.; Pawelec, G.; Talib, W.H.; Stagg, J.; Elkord, E.; Lichtor, T.; Decker, W.K.; Whelan, R.L.; Kumara, H.M.C.S.; et al. Immune Evasion in Cancer: Mechanistic Basis and Therapeutic Strategies. *Semin. Cancer Biol.* **2015**, *35 Suppl*, S185–S198, doi:10.1016/j.semcancer.2015.03.004.

39. Jm, Z.; A, G.-D.; Ds, S.; H, E.-O.; W, H.; S, H.-L.; Dy, T.; G, A.-R.; S, S.; L, B.; et al. Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma. *N. Engl. J. Med.* **2016**, *375*, 819–829, doi:10.1056/nejmoa1604958.

40. Felices, M.; Chu, S.; Kodal, B.; Bendzick, L.; Ryan, C.; Lenvik, A.J.; Boylan, K.L.M.; Wong, H.C.; Skubitz, A.P.N.; Miller, J.S.; et al. IL-15 Super-Agonist (ALT-803) Enhances Natural Killer (NK) Cell Function against Ovarian Cancer. *Gynecol. Oncol.* **2017**, *145*, 453–461, doi:10.1016/j.ygyno.2017.02.028.

41. Westermann, A.M.; Beijnen, J.H.; Moolenaar, W.H.; Rodenhuis, S. Growth Factors in Human Ovarian Cancer. *Cancer Treat. Rev.* **1997**, *23*, 113–131, doi:10.1016/s0305-7372(97)90024-4.

42. Mellman, I.; Coukos, G.; Dranoff, G. Cancer Immunotherapy Comes of Age. *Nature* **2011**, *480*, 480–489, doi:10.1038/nature10673.

43. Quail, D.; Joyce, J. Microenvironmental Regulation of Tumor Progression and Metastasis. *Nat. Med.* **2013**, *19*, 1423–1437, doi:10.1038/nm.3394.

44. Releasing the Brakes on Cancer Immunotherapy | NEJM Available online: <https://www.nejm.org/doi/10.1056/NEJMp1510079> (accessed on 28 October 2020).

45. Locy, H.; de Mey, S.; de Mey, W.; De Ridder, M.; Thielemans, K.; Maenhout, S.K. Immunomodulation of the Tumor Microenvironment: Turn Foe Into Friend. *Front. Immunol.* **2018**, *9*, doi:10.3389/fimmu.2018.02909.

46. Yang, C.; Xia, B.-R.; Zhang, Z.-C.; Zhang, Y.-J.; Lou, G.; Jin, W.-L. Immunotherapy for Ovarian Cancer: Adjuvant, Combination, and Neoadjuvant. *Front. Immunol.* **2020**, *11*, 577869, doi:10.3389/fimmu.2020.577869.

47. Scott, A.M.; Wolchok, J.D.; Old, L.J. Antibody Therapy of Cancer. *Nat. Rev. Cancer* **2012**, *12*, 278–287, doi:10.1038/nrc3236.

48. Zhang, L.; Conejo-Garcia, J.R.; Katsaros, D.; Gimotty, P.A.; Massobrio, M.; Regnani, G.; Makrigiannakis, A.; Gray, H.; Schlienger, K.; Liebman, M.N.; et al. Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer. *N. Engl. J. Med.* **2003**, *348*, 203–213,

doi:10.1056/NEJMoa020177.

49. Haskill, S.; Becker, S.; Fowler, W.; Walton, L. Mononuclear-Cell Infiltration in Ovarian Cancer. I. Inflammatory-Cell Infiltrates from Tumour and Ascites Material. *Br. J. Cancer* **1982**, *45*, 728–736, doi:10.1038/bjc.1982.114.
50. Introna, M.; Allavena, P.; Biondi, A.; Colombo, N.; Villa, A.; Mantovani, A. Defective Natural Killer Activity within Human Ovarian Tumors: Low Numbers of Morphologically Defined Effectors Present in Situ. *J. Natl. Cancer Inst.* **1983**, *70*, 21–26.
51. Kabawat, S.E.; Bast, R.C.; Welch, W.R.; Knapp, R.C.; Bhan, A.K. Expression of Major Histocompatibility Antigens and Nature of Inflammatory Cellular Infiltrate in Ovarian Neoplasms. *Int. J. Cancer* **1983**, *32*, 547–554, doi:10.1002/ijc.2910320505.
52. Ferguson, A.; Moore, M.; Fox, H. Expression of MHC Products and Leucocyte Differentiation Antigens in Gynaecological Neoplasms: An Immunohistological Analysis of the Tumour Cells and Infiltrating Leucocytes. *Br. J. Cancer* **1985**, *52*, 551–563, doi:10.1038/bjc.1985.227.
53. Negus, R.P.; Stamp, G.W.; Hadley, J.; Balkwill, F.R. Quantitative Assessment of the Leukocyte Infiltrate in Ovarian Cancer and Its Relationship to the Expression of C-C Chemokines. *Am. J. Pathol.* **1997**, *150*, 1723–1734.
54. Santin, A.D.; Hermonat, P.L.; Ravaggi, A.; Bellone, S.; Roman, J.J.; Smith, C.V.; Pecorelli, S.; Radominska-Pandya, A.; Cannon, M.J.; Parham, G.P. Phenotypic and Functional Analysis of Tumor-Infiltrating Lymphocytes Compared with Tumor-Associated Lymphocytes from Ascitic Fluid and Peripheral Blood Lymphocytes in Patients with Advanced Ovarian Cancer. *Gynecol. Obstet. Invest.* **2001**, *51*, 254–261, doi:10.1159/000058060.
55. Uppendahl, L.D.; Dahl, C.M.; Miller, J.S.; Felices, M.; Geller, M.A. Natural Killer Cell-Based Immunotherapy in Gynecologic Malignancy: A Review. *Front. Immunol.* **2018**, *8*, 1825, doi:10.3389/fimmu.2017.01825.
56. Dong, H.P.; Elstrand, M.B.; Holth, A.; Silins, I.; Berner, A.; Trope, C.G.; Davidson, B.; Risberg, B. NK- and B-Cell Infiltration Correlates with Worse Outcome in Metastatic Ovarian Carcinoma. *Am. J. Clin. Pathol.* **2006**, *125*, 451–458.
57. Webb, J.R.; Milne, K.; Watson, P.; Deleeuw, R.J.; Nelson, B.H. Tumor-Infiltrating Lymphocytes Expressing the Tissue Resident Memory Marker CD103 Are Associated with Increased Survival in High-Grade Serous Ovarian Cancer. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2014**, *20*, 434–444, doi:10.1158/1078-0432.CCR-13-1877.
58. Nowak, M.; Klink, M. The Role of Tumor-Associated Macrophages in the Progression and Chemoresistance of Ovarian Cancer. *Cells* **2020**, *9*, E1299, doi:10.3390/cells9051299.
59. Kelderman, S.; Heemskerk, B.; Fanchi, L.; Philips, D.; Toebes, M.; Kvistborg, P.; van Buuren, M.M.; van Rooij, N.; Michels, S.; Germeroth, L.; et al. Antigen-Specific TIL Therapy for Melanoma: A Flexible Platform for Personalized Cancer Immunotherapy. *Eur. J. Immunol.* **2016**, *46*, 1351–1360, doi:10.1002/eji.201545849.
60. Rosenberg, S.A.; Yang, J.C.; Sherry, R.M.; Kammula, U.S.; Hughes, M.S.; Phan, G.Q.; Citrin, D.E.; Restifo, N.P.; Robbins, P.F.; Wunderlich, J.R.; et al. Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2011**, *17*, 4550–4557, doi:10.1158/1078-0432.CCR-11-0116.
61. Santoiemma, P.P.; Powell, D.J. Tumor Infiltrating Lymphocytes in Ovarian Cancer. *Cancer Biol. Ther.* **2015**, *16*, 807–820, doi:10.1080/15384047.2015.1040960.
62. Mariya, T.; Hirohashi, Y.; Torigoe, T.; Asano, T.; Kuroda, T.; Yasuda, K.; Mizuuchi, M.; Sonoda, T.; Saito, T.; Sato, N. Prognostic Impact of Human Leukocyte Antigen Class I Expression and Association of Platinum Resistance with Immunologic Profiles in Epithelial Ovarian Cancer. *Cancer Immunol. Res.* **2014**, *2*, 1220–1229, doi:10.1158/2326-6066.CIR-14-0101.

63. Sato, E.; Olson, S.H.; Ahn, J.; Bundy, B.; Nishikawa, H.; Qian, F.; Jungbluth, A.A.; Frosina, D.; Gnjjatic, S.; Ambrosone, C.; et al. Intraepithelial CD8+ Tumor-Infiltrating Lymphocytes and a High CD8+/Regulatory T Cell Ratio Are Associated with Favorable Prognosis in Ovarian Cancer. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 18538–18543, doi:10.1073/pnas.0509182102.
64. Hao, J.; Yu, H.; Zhang, T.; An, R.; Xue, Y. Prognostic Impact of Tumor-Infiltrating Lymphocytes in High Grade Serous Ovarian Cancer: A Systematic Review and Meta-Analysis. *Ther. Adv. Med. Oncol.* **2020**, *12*, 1758835920967241, doi:10.1177/1758835920967241.
65. Pedersen, M.; Westergaard, M.C.W.; Milne, K.; Nielsen, M.; Borch, T.H.; Poulsen, L.G.; Hendel, H.W.; Kennedy, M.; Briggs, G.; Ledoux, S.; et al. Adoptive Cell Therapy with Tumor-Infiltrating Lymphocytes in Patients with Metastatic Ovarian Cancer: A Pilot Study. *Oncoimmunology* **2018**, *7*, e1502905, doi:10.1080/2162402X.2018.1502905.
66. Therapeutic Gene Editing in Haematological Disorders with CRISPR/Cas9 - Jensen - 2019 - British Journal of Haematology - Wiley Online Library Available online: <https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.15851> (accessed on 28 October 2020).
67. Li, T.; Wang, J. Therapeutic Effect of Dual CAR-T Targeting PDL1 and MUC16 Antigens on Ovarian Cancer Cells in Mice. *BMC Cancer* **2020**, *20*, 678, doi:10.1186/s12885-020-07180-x.
68. Anderson, K.G.; Voillet, V.; Bates, B.M.; Chiu, E.Y.; Burnett, M.G.; Garcia, N.M.; Oda, S.K.; Morse, C.B.; Stromnes, I.M.; Drescher, C.W.; et al. Engineered Adoptive T-Cell Therapy Prolongs Survival in a Preclinical Model of Advanced-Stage Ovarian Cancer. *Cancer Immunol. Res.* **2019**, *7*, 1412–1425, doi:10.1158/2326-6066.CIR-19-0258.
69. Rodriguez-Garcia, A.; Sharma, P.; Poussin, M.; Boesteanu, A.C.; Minutolo, N.G.; Gitto, S.B.; Omran, D.K.; Robinson, M.K.; Adams, G.P.; Simpkins, F.; et al. CAR T Cells Targeting MISIR for the Treatment of Ovarian Cancer and Other Gynecologic Malignancies. *Mol. Ther. J. Am. Soc. Gene Ther.* **2020**, *28*, 548–560, doi:10.1016/j.ymthe.2019.11.028.
70. Jindal, V.; Arora, E.; Gupta, S.; Lal, A.; Masab, M.; Potdar, R. Prospects of Chimeric Antigen Receptor T Cell Therapy in Ovarian Cancer. *Med. Oncol. Northwood Lond. Engl.* **2018**, *35*, 70, doi:10.1007/s12032-018-1131-6.
71. Frankel, T.; Lanfranca, M.P.; Zou, W. The Role of Tumor Microenvironment in Cancer Immunotherapy. In *Tumor Immune Microenvironment in Cancer Progression and Cancer Therapy*; Kalinski, P., Ed.; Advances in Experimental Medicine and Biology; Springer International Publishing: Cham, 2017; pp. 51–64 ISBN 978-3-319-67577-0.
72. Martin Lluesma, S.; Wolfer, A.; Harari, A.; Kandalaf, L.E. Cancer Vaccines in Ovarian Cancer: How Can We Improve? *Biomedicines* **2016**, *4*, 10, doi:10.3390/biomedicines4020010.
73. Newman, J.H.; Chesson, C.B.; Herzog, N.L.; Bommareddy, P.K.; Aspromonte, S.M.; Pepe, R.; Estupinian, R.; Aboelatta, M.M.; Buddhadev, S.; Tarabichi, S.; et al. Intratumoral Injection of the Seasonal Flu Shot Converts Immunologically Cold Tumors to Hot and Serves as an Immunotherapy for Cancer. *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 1119–1128, doi:10.1073/pnas.1904022116.
74. Orzechowska, B.U.; Jędryka, M.; Zwolińska, K.; Matkowski, R. VSV Based Virotherapy in Ovarian Cancer: The Past, the Present and ...future? *J. Cancer* **2017**, *8*, 2369–2383, doi:10.7150/jca.19473.
75. Dafni, U.; Martín-Lluesma, S.; Balint, K.; Tsourti, Z.; Vervita, K.; Chenal, J.; Coukos, G.; Zaman, K.; Sarivalasis, A.; Kandalaf, L.E. Efficacy of Cancer Vaccines in Selected Gynaecological Breast and Ovarian Cancers: A 20-Year Systematic Review and Meta-Analysis. *Eur. J. Cancer Oxf. Engl. 1990* **2021**, *142*, 63–82, doi:10.1016/j.ejca.2020.10.014.
76. Tanyi, J.L.; George, E. Personalized Vaccination against Ovarian Cancer: What Are the Possibilities? *Expert Rev. Vaccines* **2018**, *17*, 955–958, doi:10.1080/14760584.2018.1541743.
77. Mittica, G.; Genta, S.; Aglietta, M.; Valabrega, G. Immune Checkpoint Inhibitors: A

- New Opportunity in the Treatment of Ovarian Cancer? *Int. J. Mol. Sci.* **2016**, *17*, doi:10.3390/ijms17071169.
78. Topalian, S.L.; Drake, C.G.; Pardoll, D.M. Immune Checkpoint Blockade: A Common Denominator Approach to Cancer Therapy. *Cancer Cell* **2015**, *27*, 450–461, doi:10.1016/j.ccell.2015.03.001.
79. Teng, M.W.L.; Ngiew, S.F.; Ribas, A.; Smyth, M.J. Classifying Cancers Based on T-Cell Infiltration and PD-L1. *Cancer Res.* **2015**, *75*, 2139–2145, doi:10.1158/0008-5472.CAN-15-0255.
80. Rizvi, N.A.; Hellmann, M.D.; Snyder, A.; Kvistborg, P.; Makarov, V.; Havel, J.J.; Lee, W.; Yuan, J.; Wong, P.; Ho, T.S.; et al. Mutational Landscape Determines Sensitivity to PD-1 Blockade in Non-Small Cell Lung Cancer. *Science* **2015**, *348*, 124–128, doi:10.1126/science.aaa1348.
81. Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma | NEJM Available online: <https://www.nejm.org/doi/full/10.1056/nejmoa1406498> (accessed on 26 October 2020).
82. Tumeh, P.C.; Harview, C.L.; Yearley, J.H.; Shintaku, I.P.; Taylor, E.J.M.; Robert, L.; Chmielowski, B.; Spasic, M.; Henry, G.; Ciobanu, V.; et al. PD-1 Blockade Induces Responses by Inhibiting Adaptive Immune Resistance. *Nature* **2014**, *515*, 568–571, doi:10.1038/nature13954.
83. Gaillard, S.L.; Secord, A.A.; Monk, B. The Role of Immune Checkpoint Inhibition in the Treatment of Ovarian Cancer. *Gynecol. Oncol. Res. Pract.* **2016**, *3*, 11, doi:10.1186/s40661-016-0033-6.
84. Lheureux, S.; Braunstein, M.; Oza, A.M. Epithelial Ovarian Cancer: Evolution of Management in the Era of Precision Medicine. *CA. Cancer J. Clin.* **2019**, *69*, 280–304, doi:10.3322/caac.21559.
85. Levinson, K.; Dorigo, O.; Rubin, K.; Moore, K. Immunotherapy in Gynecologic Cancers: What We Know Now and Where We Are Headed. *Am. Soc. Clin. Oncol. Educ. Book Am. Soc. Clin. Oncol. Annu. Meet.* **2019**, *39*, e126–e140, doi:10.1200/EDBK_237967.
86. Marth, C.; Wieser, V.; Tsibulak, I.; Zeimet, A.G. Immunotherapy in Ovarian Cancer: Fake News or the Real Deal? *Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc.* **2019**, *29*, 201–211, doi:10.1136/ijgc-2018-000011.
87. Demircan, N.C.; Boussios, S.; Tasci, T.; Öztürk, M.A. Current and Future Immunotherapy Approaches in Ovarian Cancer. *Ann. Transl. Med.* **2020**, *8*, doi:10.21037/atm-20-4499.
88. Bezu, L.; Gomes-de-Silva, L.C.; Dewitte, H.; Breckpot, K.; Fucikova, J.; Spisek, R.; Galluzzi, L.; Kepp, O.; Kroemer, G. Combinatorial Strategies for the Induction of Immunogenic Cell Death. *Front. Immunol.* **2015**, *6*, 187, doi:10.3389/fimmu.2015.00187.
89. Bracci, L.; Schiavoni, G.; Sistigu, A.; Belardelli, F. Immune-Based Mechanisms of Cytotoxic Chemotherapy: Implications for the Design of Novel and Rationale-Based Combined Treatments against Cancer. *Cell Death Differ.* **2014**, *21*, 15–25, doi:10.1038/cdd.2013.67.
90. Galluzzi, L.; Zitvogel, L.; Kroemer, G. Immunological Mechanisms Underneath the Efficacy of Cancer Therapy. *Cancer Immunol. Res.* **2016**, *4*, 895–902, doi:10.1158/2326-6066.CIR-16-0197.
91. Mathios, D.; Kim, J.E.; Mangraviti, A.; Phallen, J.; Park, C.-K.; Jackson, C.M.; Garzon-Muvdi, T.; Kim, E.; Theodoros, D.; Polanczyk, M.; et al. Anti-PD-1 Antitumor Immunity Is Enhanced by Local and Abrogated by Systemic Chemotherapy in GBM. *Sci. Transl. Med.* **2016**, *8*, 370ra180, doi:10.1126/scitranslmed.aag2942.
92. Langer, C.J.; Gadgeel, S.M.; Borghaei, H.; Papadimitrakopoulou, V.A.; Patnaik, A.; Powell, S.F.; Gentzler, R.D.; Martins, R.G.; Stevenson, J.P.; Jalal, S.I.; et al. Carboplatin and Pemetrexed with or without Pembrolizumab for Advanced, Non-Squamous Non-Small-Cell

- Lung Cancer: A Randomised, Phase 2 Cohort of the Open-Label KEYNOTE-021 Study. *Lancet Oncol.* **2016**, *17*, 1497–1508, doi:10.1016/S1470-2045(16)30498-3.
93. Emens, L.A.; Middleton, G. The Interplay of Immunotherapy and Chemotherapy: Harnessing Potential Synergies. *Cancer Immunol. Res.* **2015**, *3*, 436–443, doi:10.1158/2326-6066.CIR-15-0064.
94. Galluzzi, L.; Buqué, A.; Kepp, O.; Zitvogel, L.; Kroemer, G. Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents. *Cancer Cell* **2015**, *28*, 690–714, doi:10.1016/j.ccell.2015.10.012.
95. Pujade-Lauraine, E.; Fujiwara, K.; Ledermann, J.A.; Oza, A.M.; Kristeleit, R.; Ray-Coquard, I.-L.; Richardson, G.E.; Sessa, C.; Yonemori, K.; Banerjee, S.; et al. 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. *Lancet Oncol.* **2021**, *22*, 1034–1046, doi:10.1016/S1470-2045(21)00216-3.
96. Kandalaft, L.E.; Odunsi, K.; Coukos, G. Immunotherapy in Ovarian Cancer: Are We There Yet? *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2019**, *37*, 2460–2471, doi:10.1200/JCO.19.00508.
97. Herrera, F.G.; Irving, M.; Kandalaft, L.E.; Coukos, G. Rational Combinations of Immunotherapy with Radiotherapy in Ovarian Cancer. *Lancet Oncol.* **2019**, *20*, e417–e433, doi:10.1016/S1470-2045(19)30401-2.
98. Ott, P.A.; Hodi, F.S.; Buchbinder, E.I. Inhibition of Immune Checkpoints and Vascular Endothelial Growth Factor as Combination Therapy for Metastatic Melanoma: An Overview of Rationale, Preclinical Evidence, and Initial Clinical Data. *Front. Oncol.* **2015**, *5*, 202, doi:10.3389/fonc.2015.00202.
99. Voron, T.; Colussi, O.; Marcheteau, E.; Pernot, S.; Nizard, M.; Pointet, A.-L.; Latreche, S.; Bergaya, S.; Benhamouda, N.; Tanchot, C.; et al. VEGF-A Modulates Expression of Inhibitory Checkpoints on CD8+ T Cells in Tumors. *J. Exp. Med.* **2015**, *212*, 139–148, doi:10.1084/jem.20140559.