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REVIEW

Immunotherapy in the Treatment of Platinum-Resistant Ovarian Cancer: Current Perspectives

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Abstract: Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer. The gold standard therapeutic approach is a combination of surgery plus chemotherapy. Unfortunately, 80% of patients with EOC suffer recurrence within 2-years and the overall response rate for platinum-resistant epithelial ovarian cancer to cytotoxic chemotherapy or poly-(adenosine diphosphate)-ribose polymerase (PARP) inhibitor is modest. New therapies are needed to improve overall survival. The role of immunotherapy has been established in endometrial and cervical cancers, however its effective use in EOC has been limited due to the intrinsic genomics and micro-immune environment associated with EOC. Studies evaluating immunotherapy, largely immune checkpoint inhibitors (ICI), have shown limited activity, yet some patients benefit greatly. Thus, significant efforts must be devoted to finding new strategies for the use of immunotherapy/immunomodulatory drugs (IMiDs). Immunotherapy has a well-tolerated safety profile; however, cost-effectiveness can be an obstacle. The aim of this article is to review the most recent research into the use of IMiDs in patients with platinum-resistant epithelial ovarian cancer.

Keywords: ovarian cancer, platinum-resistant, recurrent, immunotherapy, immune checkpoint inhibitors, adverse events

Introduction/Background

Ovarian cancer is the second most common gynecologic malignancy with a lifetime risk of 1.3% and remains the leading cause of death secondary to gynecologic cancer in the United States. In total, there were approximately 21,400 new cases and 13,770 cancer-related deaths in 2021 from ovarian cancer.[1] Epithelial ovarian cancer (EOC) accounts for 90% of ovarian cancer. Histologically, high-grade serous ovarian carcinoma (HGSOC) accounts for 80% of the EOC, whereas other types include endometrioid, clear cell, low-grade serous, and mucinous carcinoma. Due to non-specific symptoms and the lack of accurate screening tools, 75% of patients with HGSOC present as advanced stage (III–IV) disease. Frontline therapy consists of surgical cytoreduction, adjuvant platinum-based chemotherapy, and in certain cases neoadjuvant chemotherapy.[2]

Cancer stage is the main prognostic factor associated with improved outcomes. Stage III/IV disease has a 5-year relative survival rate of approximately 29%, contrasted with 92% for early-stage disease.[3] Genomic pre-disposition to EOC is now well recognized in up to 20% of affected women. Breast cancer susceptibility genes *BRCA1* and *BRCA2* account for 65–75% of hereditary EOC.[4] *BRCA1* and *BRCA2* are the tumor suppressor genes involved in DNA repair processes, their functional mutation impairs DNA repair and cause irregularities in the DNA synthesis.[5] *BRCA1* or *BRCA2* germline mutations increase the likelihood of platinum sensitivity, response to poly-(adenosine diphosphate)-ribose polymerase (PARP) inhibitors and improved survival compared with those with non-*BRCA*-related ovarian cancer.[6]

The HGSOC predominantly harbors defects in DNA repair pathways. HGSOC is characterized by low tumor mutation burden (TMB) and microsatellite stable (MSS).[7] Eighty percent of HGSOC respond to chemotherapy, but

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unfortunately 80% recur within the first 2-years following therapy completion, with response rate to subsequent line of therapy being low (15–20%), a median progression-free survival (PFS) of 3–4 months and overall survival (OS) of 12-months.[5]

The platinum-free interval (PFI) is the time from the last platinum-based therapy and disease recurrence. PFI is the most important parameter in predicting the response to subsequent lines of cytotoxic agents. Platinum-resistant disease is defined as PFI < 6 months. Platinum resistance is multifactorial involving tumor genomics, intracellular mechanisms, and tumor microenvironment (TME) changes that continue to evolve over time, making clinical detection of such changes clinically challenging.[2]

Indeed, given the guarded prognosis for platinum-resistant ovarian cancer (PROC) with standard single-agent therapies and combination chemotherapy regimen, novel therapeutic strategies are warranted. For example, PARP inhibitor and anti-angiogenic agent (eg, bevacizumab) are now established as maintenance therapy after the first-line chemotherapy.[8,9] Immunotherapy has had limited success in ovarian cancer owing to predominantly "cold" or immuno-suppressive nature of most epithelial ovarian cancer. The presence of tumor infiltrating lymphocytes (TIL) and programmed death-ligand 1 (PD-L1) expression are favorable prognostic factors, making immunotherapy an attractive therapeutic option.[10]

Cancer immunotherapy is a revolutionary and attractive strategy for which in the year 2018, Dr. James P. Allison and Dr. Tasuku Honjo won a Nobel Prize in Physiology or Medicine for the discovery of cancer therapy by inhibiting the negative immune regulation.[11] Immunotherapy has been found to be not only highly specific, which makes it more tolerable than chemotherapy but also has a durable effect secondary to immunological memory. Immunotherapy can be broadly classified as active, passive, or immunomodulatory (Figure 1). Active immunotherapy works by recognizing antigens on the tumor cell surface, inducing a cascade of effects to destroy malignant cells. Examples of active immunotherapy include cancer vaccines, chimeric antigen receptor-T cell therapy (CAR-T cell), or targeted antibodies therapy such as trastuzumab (target HER-2) or cetuximab [target epidermal growth factor receptor (EGFR)]. "Passive immunotherapy" initiates anti-tumor activity by enhancing immune activity and indirectly targeting tumor cells. Immune check-point inhibitors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)/PD-L1 monoclonal antibodies are examples of passive immunotherapy.[12] In general, immunomodulators are

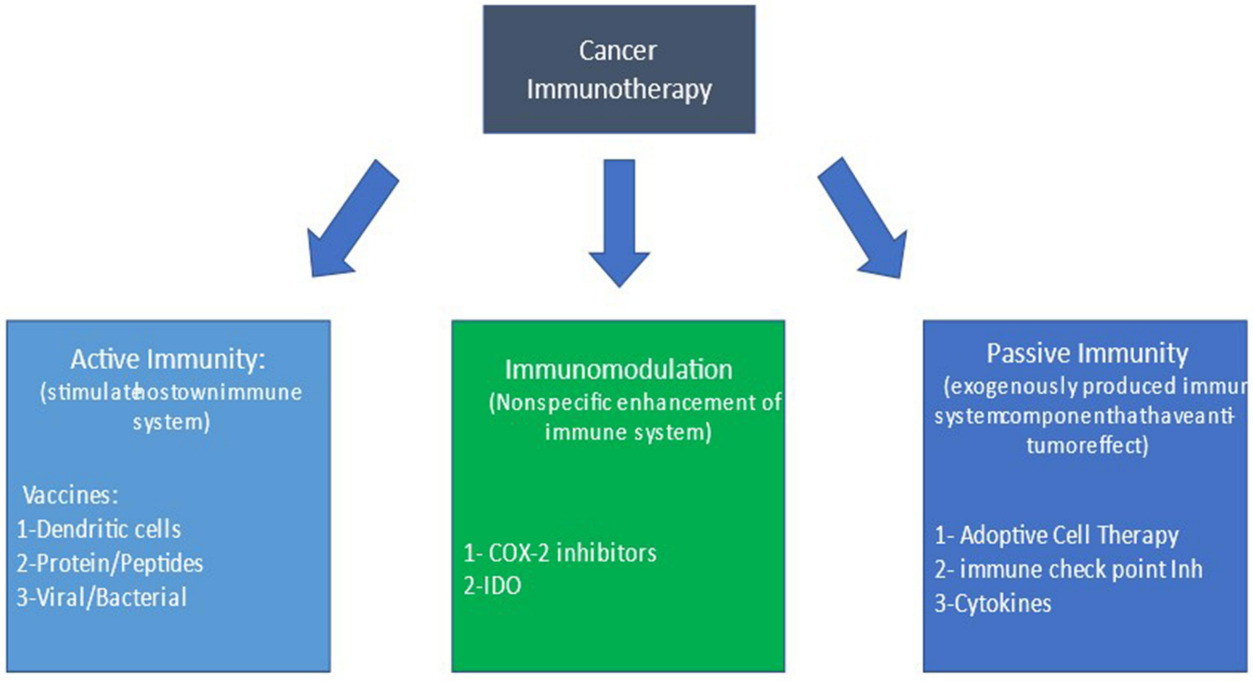

Figure 1 Immunotherapeutic modalities and their application in cancer therapy.

molecules that act on the pathways that regulate the immune system's activity and include the above-mentioned immune check point inhibitors, but also cytokines (messenger molecules that regulated immune cell maturation, growth, and responsiveness), agonists (which activate pathways that promote adaptive immune responses by activating killer T cells or innate immune cells), and adjuvants (which activate pathways involved in the innate immune system).[13] In this mini-review, we provide current perspectives on immunotherapy and IMiD strategies targeting platinum-resistant ovarian cancer by highlighting the opportunities and challenges in this emerging clinical research field.

Rationale for Immunotherapy in Epithelial Ovarian Cancer

The immune system was proven to play an essential role in controlling the progression of solid tumors. As such, tumors were classified based on their interaction with the host immune system. Hot tumors are characterized by the presence of tumor-infiltrating lymphocytes (TILs), PD-L1 positivity and having genomic instability. On the other hand, "cold tumors" are described as immunologically ignorant with negative or low PD-L1 status, low mutational burden and low neoantigen expression. As opposed to "cold tumors", "hot tumors" hold favorable prognostic outcomes.[14] Ovarian cancer is an immunogenic cancer with about half of patients demonstrating T-cell infiltration and 28–40% expressing PD-L1.[15] Among the different types of EOC, the HGSOC with a known *BRCA*1/2 gene mutation carries a higher tumor mutational load in addition to an augmented expression of PD-L1 and TILs.[16] Immunotherapies that increase the antitumor immune response, such as interleukin-2 (IL-2), or blockage of cytotoxic T lymphocyte antigen 4 (CTL4), PE1 or PDL1, have the potential to benefit a significant percentage of patients.[13]

The TME consists of an extracellular matrix (ECM) made of matrix metalloproteinases (MMPs) and stromal cells, including cancer cells (CCs), cancer stem cells (CSCs), cancer-associated fibroblasts (CAFs), endothelial cells (ECs), and other immune cells (Figure 2). Lymphocyte plays an important role in the TME interplay. B-lymphocytes secrete pro-tumorigenic cytokine and regulate T helper type 1 (Th1): Th2 ratio, promoting tumor progression. As for helper T cell (Th cell), Th1 cells are anti-tumorigenic, and Th2 cells accelerate tumor growth by secreting anti-inflammatory cytokines. In addition, cytotoxic T lymphocytes (CTL) are pro-inflammatory and thus assist in tumor rejection. On the other hand, T regulatory lymphocytes (Treg cells) act as immunosuppressors by secreting transforming growth factor-β (TGF-β) and interleukin (IL)-10. The T-cell function in TME is modulated by a series of immune checkpoints including CTLA-4 and PD1/PD-L1. The CTLA-4 and PD-1 are transmembrane glycoproteins expressed on Treg cells, and when bound by their respective ligands (the immunoinhibitory B7 and PD-L1) (Figure 3), they reduce activation of immune response. So, the CTLA-4 and PD-1/PD-L1 monoclonal antibodies inhibit the suppression of activated T killer-cells and promote the destruction of cancer cells.[17]

In addition to T reg cells, other immune players contribute to the immunosuppressive TME. Tumor-associated macrophages (TAM), natural killer (NK), and the myeloid-derived suppressor cells (MDSCs) assist the tumor cells in evading the host immune system, thus favoring cancer growth, angiogenesis, leading to tumor metastasis.[18]

Experience with Immunotherapy in Platinum-Resistant Ovarian Cancer

Immune Check-Point Inhibitor Mono- or Dual-Therapy

In 2012, Brahmer et al[19] studied the safety and activity of anti-PD-L1 antibodies in patients with advanced disease in the ovarian cancer cohort of the 17 patients, 6% (1/17) had a partial response and 18% (3/17) cases had stable disease lasting 24 weeks. Subsequently, a non-randomized Phase IB trial, KEYNOTE-028, studied pembrolizumab (10 mg/kg every 2weeks) in 26 patients with PD-L1 expressing metastatic or recurrent ovarian cancer, treatment continued for 24-months or until the disease progression. The overall response rate (ORR) was 11.5% (one case with complete response, two with partial responses); and seven patients (26.9%) achieved stable disease. The median PFS and OS were 1.9 and 13.8 months, respectively. Grade 3 treatment-related adverse events occurred only in one (4%) patient.[19]

Given the positive results and manageable safety and toxicity profiles, KEYNOTE-100 (a Phase II study) enrolled patients with advanced recurrent ovarian cancer, cohort A (285 patients) with 1–3 prior line of therapy and PFI between 3 and 12 months, and cohort B (91 patients) with 4–6 prior line of treatment and PFI >3 months. Pembrolizumab (200 mg) was given intravenously every 3 weeks for 24 months or until disease progression. The results showed modest activity

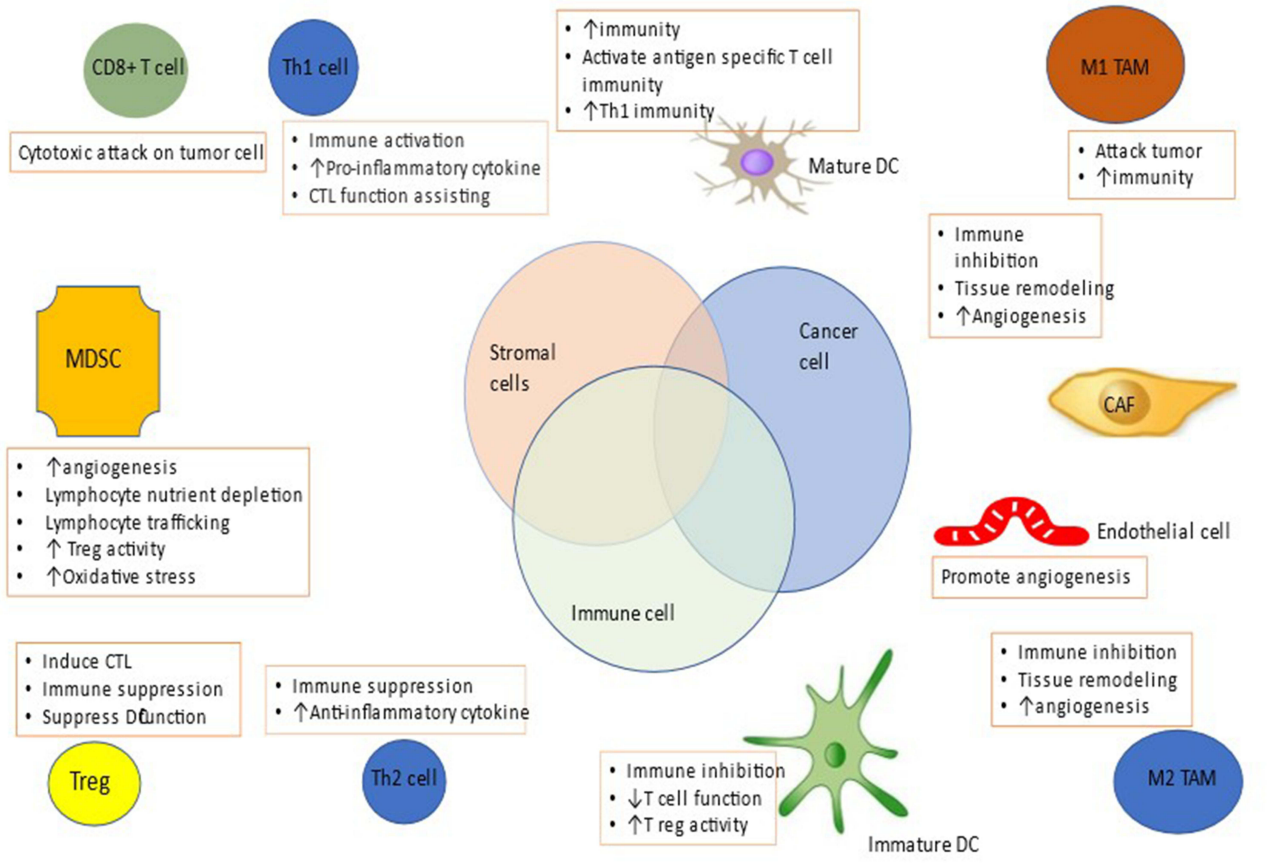

Figure 2 A schematic representation of the tumor microenvironment interplay. Angiogenesis and immune evasion create a microenvironment that supports tumor growth and progression. The MDSCs exert immunosuppressive functions, such as the inhibition of T-effector and natural killer (NK)-cells. M2 macrophages promote immunosuppression by producing cytokines that inhibit T-effectors proliferation and enhance T-regs function. While M1 macrophages and mature dendritic cells activate host immunity and increase Th1 cell recruitment and cytotoxic attack on tumor cells.

Abbreviations: TAM, tumor-associated macrophages; CAF, cancer-associated fibroblast; T-reg, regulatory T cell; Th1, T helper 1; Th2, T helper 2; MDSC, myeloid-derived suppressive cell; DC, dendritic cell; CD, cluster differentiation; CTL, cytotoxic T-cell.

with ORR 7.4% (cohort A) and 9% (cohort B). While median OS was not reached for cohort A, it was 17.6 months in cohort B. The higher PD-L1 expression correlated with the higher response.[20]

Despite initial promising results, single-agent PD-L1 monoclonal antibodies have modest responses in ROC. Zamarin et al[21] enrolled 100 patients with recurrent measurable disease and 1–3 prior line of treatment to nivolumab (PD1/PD-L1 antagonist) vs nivolumab + ipilimumab (CTLA-4 antagonist). The combination showed higher response rate at 6-months (31.4 vs 12.2%), and median PFS (3.9 vs 2.0 months). The hazard ratio of death (0.79) favored the combination, but it was not statistically significant. Even though grade 3 or greater treatment-related adverse events (TRAE) were higher in the combination group, it did not reach statistical significance (66.7 vs 55.1%).[21]

Immune Check-Point Inhibitor Compared to or Added to Cytotoxic Chemotherapy

Despite early thoughts that chemotherapy is an immunosuppressive modality in cancer management, recent evidence showed that it regulates the composition and function of tumor infiltrating lymphoid (TIL) and myeloid cells which influence positively patient's prognosis.[22] For example, the platinum drugs alter the immune system by the modulation of PD-L1 and mannose-6-phosphate receptor expression, thus enhancing the host immune response against the cancer cells.[23] In addition, pegylated liposomal doxorubicin (PLD), an anthracycline, can play the role of an immunosensitizer for dendritic cells and CD8+ T-cell. Also, PLD was thought to relieve tumor-induced immunosuppression as it was shown to trigger direct tumor cell death, enhance immune effector cell activation and eliminate immunosuppressive myeloid-derived suppressor cells (MDSCs).[24]

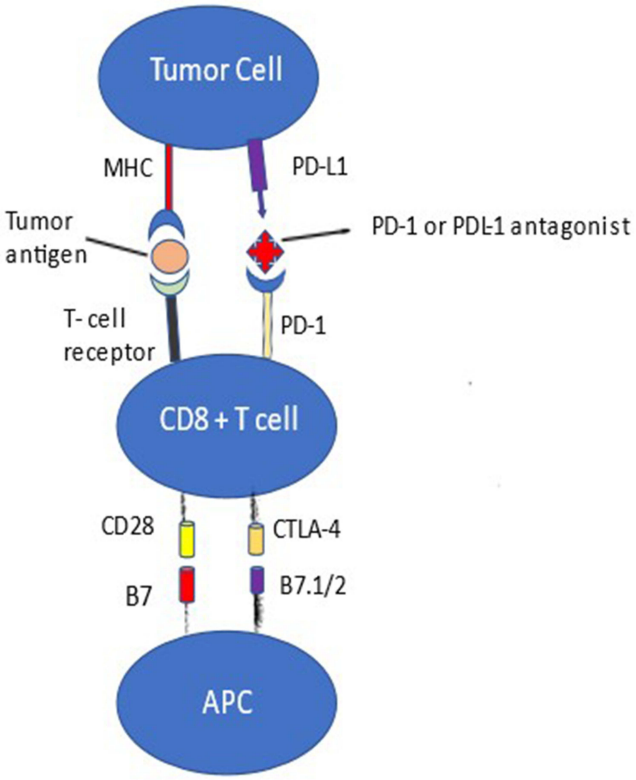

Figure 3 A schematic representation of the immune check-point inhibitor mechanisms of action. When PD-L1, a protein on certain cancer cells binds PD-1 a checkpoint transmembrane protein on T-cells, it causes T-cell dysfunction, exhaustion, neutralization thus helping the cancer cell evade the immune system. CTLA-4 is a transmembrane protein expressed on activated T-cell and transmit inhibitory signals to the T-cells. CTLA-4 is thought to regulate T-cell proliferation early in an immune response, primarily in lymph nodes, whereas PD-1 suppresses T-cells later in an immune response, primarily in peripheral tissues.
Abbreviations: MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1, CTLA-4, cytotoxic T-lymphocyte-associated protein 4, APC, antigen presenting cell.

Recently, Pujade-Lauraine et al[25] in JAVELIN Ovarian 200 trial studied 566 patients with PROC in an open label, three-arm, randomized Phase III study where patients were assigned to three arms: i) PD-L1 monoclonal antibody avelumab (10 mg/kg IV every 2 weeks), ii) pegylated liposomal doxorubicin (PLD 40 mg/m^2 IV every 4 weeks), or iii) combination of avelumab+PLD. Despite a rational pre-clinical hypothesis for this trial, JAVELIN 200 found that neither avelumab nor the combination therapy significantly improved PFS or OS as compared to PLD alone.[25]

In the NINJA trial, 316 patients with PROC (≤1 regimen after resistance diagnosis) were randomly assigned to PD-1 monoclonal antibody nivolumab (200 mg IV every 2 weeks) or chemotherapy in the form of gemcitabine 1000 mg/m^2 on days 1, 8, and 15 in a 4-week cycle or PLD 50 mg/m^2 very 4-weeks. This study showed no statistical differences in the OS (10.1 months in nivolumab vs 12.1 months in chemotherapy group), with the ORR and PFS worse in nivolumab group (7.6% vs 13.2% and 2-months vs 3.8 months, respectively). Notably, progressive disease was observed in 63.9% (nivolumab group) vs 39.5% (chemotherapy group) cases; while the duration of response was higher in nivolumab compared to chemotherapy group (18.7 vs 7.4 months). On the other hand, nivolumab was well tolerated with lower incidence of TRAE (any grade 61.5% vs 98.1%; grade 3–4 TRAE 10.9% vs 65.2%)[26] (Table 1).

Lee et al[27] performed a phase II trial that included 23 patients with PROC and ≤2 prior line of chemotherapy who were given pembrolizumab 200 mg IV q 3-weeks and PLD 40 mg/m^2 IV q 4-weeks. The clinical benefit rate (complete + partial response + stable disease) was 52.2%, with well-tolerated safety and toxicity profiles. Of note, 73% of patients had PD-L1 positive tumors and the PD-L1 MPS (melanocytic plasticity signature) score did not significantly correlate with response rate.[27] However, Walsh et al[28] failed to show any benefit of adding pembrolizumab to gemcitabine and cisplatin in PROC cohort with ORR 60% and a 4.9-month duration of response.

Table 1 A Summary of Key Trials Related to Immune Checkpoint Inhibitors in Platinum-Resistant Epithelial Ovarian Cancer

Study Name/ NCT Number	Phase	Cohort	Intervention	End-Points	Results
Keynote-028 (NCT02054806)[19]	Ib	PD-L1+ ROC (n = 26)	Pembrolizumab	ORR	• ORR 11.5% • mPFS 1.9 mo • mOS 13.8 mo
Keynote-100 (NCT02674061)[20]	II	Cohort A ROC after 1–3 therapies, TFI 3–12 mo (n=285). Cohort B ROC after 6 lines, TFI >3 mo (n=91)	Pembrolizumab	ORR	• ORR 8.0% (ITT) • DCR 37% (ITT) • ≥G3 AEs: 19.7%; 2 treatment-related deaths
NCT02865811[27]	II	PR-ROC, fallopian tube or peritoneal cancer (n=26)	Pembrolizumab + PLD	Clinical Benefit Rate (CR, PR, SD)	• ORR 19% • ≥G3 AEs: rash (19%), ↑ALT (8%)
NCT02853318[15]	II	PS- and PR-ROC (n=40)	Pembrolizumab + Bevacizumab + Cyclophosphamide	ORR, mPFS	• ORR 47.5%, • mPFS 10 mo • 6 mos PFS: 100% (PS-ROC), 59% (PR-ROC) (p=0.024)
TOPACIO/ Keynote-162 (NCT02657889)[34]	I–II	PR-ROC (n=62)	Pembrolizumab + Niraparib	ORR	• ORR 25% • DCR 68% • BRCAm: ORR 45%, DCR 73% • ≥G3 AEs: anemia (21%), thrombocytopenia (9%)
UMIN000005714[26]	II	PR-ROC (n=20)	Nivolumab (1 and 3 mg/kg)	BOR	• 2 CR • DCR 45% • mPFS 3.5 mo • mOS 20 mo • ≥G3 AEs 40%, 2 SAEs, 11% discontinuation
NRG-GY003 (NCT02498600)[21]	II	PS- and PR-ROC (n=100)	Nivolumab vs Nivolumab + Ipilimumab → Nivolumab Maintenance	ORR	• ORR 31.4% (N + I) vs 12.2% (N) (p=0.034) • PFS 3.9 (N + I) vs 2 (N) mo (HR=0.53) • OS 28.1 (N + I) vs 21.8 (N) mo (HR=0.79) • responses not associated with PD-L1 • ≥G3 AEs: 33% (N), 49% (N + I).
NCT02873962[35]	II	PS- and PR-EOC (n=38)	Nivolumab + Bevacizumab	ORR	• ORR: 28.9% (40% PS-ROC, PR-ROC 16.7%) • mPFS 9.4 mo (12.1 mo PS-ROC) • PD-L1- better than PD-L1+ pts • AEs 89.5% • ≥G3 AEs 23.7%.

(*Continued*)

Table 1 (Continued).

Study Name/ NCT Number	Phase	Cohort	Intervention	End-Points	Results
JAVELIN 200 (NCT02580058)[25]	III	PR-ROC (n=566)	Avelumab vs avelumab + PLD vs PLD	PFS, OS	• Ave + PLD: PFS 3.7 mos (HR vs PLD = 0.78, p=0.03), OS 15.7 mos (HR vs PLD = 0.89, p=0.2) • avelumab vs PLD HR for OS = 1.14, HR for PFS = 1.68 • PD-L1+: trend for longer PFS and OS Ave+PLD vs PLD • ≥G3 AEs: 49.7%(Ave), 68.7% (Ave + PLD), 59.3% (PLD)
NINJA[26]	III	PR-ROC (n = 316)	Nivolumab vs Gemcitabine or PLD	OS	• No OS differences (HR = 1.03) • PFS 2 (N) vs 3.8 mo (gem/PLD) (HR=1.46; p=0.002) • ≥G3 AEs: 22.4% (N), 68.4% (gem/PLD)
ENCORE-603 (NCT02915523)	II	PR-ROC (n=126)	Avelumab + Entinostat vs Avelumab + PBO	PFS	• No differences in ORR (6% vs 5%), or OS (NE vs 11.3 mo) • mPFS = 1.64 (A + E) vs 1.51 mo (A + P) (p=0.031) • AEs: 93% (A + E), 78% (A + P); ≥G3 AEs: 41% (A + E), 10% (A + P)
NCT02431559	I–II	PR-ROC (n=40)	Durvalumab + PLD	PFS @6 m	• PFS: 47.7% • ORR 15%
NCT02484404	II	PR-ROC (n=35)	Durvalumab + Olaparib	ORR	• ORR 14% • ≥G3 AE: anemia (31%)
NCT02485990[35]	I–II	PR-ROC (n=24)	Tremelimumab vs Tremelimumab + Olaparib	ORR	• 1 PR, 9 SD • ≥G3 AEs: rash (13%), hepatitis (8%), colitis (8%) • no ≥G4 AEs

Abbreviations: AE, adverse event; mo, months; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOR, best overall response; BRCAwt, BRCA wild type; CR, complete response; DCR, disease control rate; gBRCAm, germline BRCA-mutated; ICI, immune-checkpoint inhibitor; ITT, intention-to-treat; mOS, median overall survival; mPFS, median progression-free survival; OC, ovarian cancer; ORR, overall response rate; PBO, placebo; PD-L1, programmed death ligand 1; PLD, pegylated liposomal doxorubicin; PR, partial response; PR-ROC, platinum-resistant recurrent ovarian cancer; PS-ROC, platinum-sensitive recurrent ovarian cancer; SD, stable disease; gem, Gemcitabine.

Immune Check-Point Inhibitor with PARP Inhibitors or Anti-Angiogenics

Given the modest efficacy of immune checkpoint inhibitors (ICI), other trials assessed their efficacy in combination with other established active agents such as PARP inhibitors or anti- vascular endothelial growth factor (VEGF). VEGF plays a key role in tumor angiogenesis by binding to VEGF receptor tyrosine kinases: VEGF-A to VEGFR-1/2, VEGF-B to VEGFR-1, and VEGF-C/D to VEGFR-2/3. VEGF blockade leads to inhibition of endothelial proliferation and deprivation of tumor vascular supply.[29] In 2014, bevacizumab, anti-VEGF-A, was FDA approved for use in platinum-resistant ovarian cancer as AURELIA trial showed significant improvement of PFS [6.7 months vs 3.4 months, hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.38–0.60, $p < 0.001$] and overall response rate (ORR) [27.3% vs 11.8%, p=0.001] over chemotherapy alone.[30]

Cellular DNA damage repair response initiates when DNA damage is detected, activating cellular pathways to repair and preserve genetic integrity. The primary repair mechanism is homologous recombination (HR) mediated by *BRCA1/2* genes that repair double stranded breaks.[31] The PARPs, a family of nuclear enzymes, contribute to the repair of single-stranded DNA

breaks via a base-excision repair pathway. When cells with a *BRCA* mutation are exposed to PARP inhibitors, single-stranded DNA breaks accumulate, leading to fatal double-stranded breaks. Consequently, the PARP-inhibitor (PARP-i) exploits the concept of synthetic lethality in HR-deficient tumors in order to affect the cancer cell death.[32]

In a Phase I study, Lee et al[33] tested durvalumab (10 mg/kg every 2 weeks or 1500 mg every 4 weeks) with either Olaparib (PARP inh) 300 mg twice a day, or cediranib (VEGF receptor inh) 20 mg, 5 days on/2 days off in parallel 3 + 3 dose escalations. The primary endpoint was the recommended phase II dose (RP2D). In the durvalumab plus olaparib cohort, disease control rate (DCR) was 83% which include two partial responses (≥15 months and ≥11 months) and eight stable diseases ≥4 months. Among the durvalumab plus cediranib cohort, DCR was 75% including six partial responses (≥5 months to ≥8 months) and three stable diseases ≥4 months. Response to therapy was independent of PD-L1 expression.[33]

The TOPACIO/KEYNOTE-162 trial enrolled 62 patients in its phase I and phase II population with previously treated advanced or metastatic ovarian cancer considered platinum-sensitive to the first-line therapy with subsequently acquired platinum-resistance. Patients were treated with 200 mg of oral niraparib once daily for days 1 to 21 and 200 mg of intravenous pembrolizumab on day 1 of each 21-day cycle. After pooling phase I and phase II cohorts, the ORR was 18%, with a disease control rate of 65%, including three (5%) cases with confirmed complete responses, eight (13%) cases with confirmed partial responses, 28 (47%) cases with stable disease, and 20 (33%) cases with progressive disease. Grade 3 TRAE occurred in 16 patients (30%), anemia being the most common (in 21% cases)[34] (Table 1).

Gaillard et al[35] treated 24 total patients with recurrent/persistent EOC who had progression <12 months from last platinum exposure with Tremelimumab, a CTLA-4 inhibitor, 10 mg/kg every 4 weeks × 7 then every 12 weeks (Arm A) or same Tremelimumab regimen as above with Olaparib 150 or 300 mg twice daily at three planned dose levels (Arm B) (12 on Arm A, and 12 on Arm B). The cohort median number of prior regimens was 3.5 (range 1–9). Twenty patients were evaluated for response, one had PR (Arm B), and nine patients had SD (six on Arm A, and three on Arm B). Two patients in Arm B had PFS at >6 months. The most adverse events (AEs) were attributable to Tremelimumab, and the most common grade 3 toxicities were rash (13%), immune-mediated hepatitis (8%), and colitis (8%). No grade ≥4 toxicities were identified[35] (Table 1).

Lampert et.al[36] enrolled 35 patients with recurrent ovarian cancer, immune checkpoint inhibitor-naïve with measurable disease per RECIST criteria. Patients received Olaparib 300 mg twice daily and durvalumab 1500 mg intravenously every (4 weeks) until disease progression, unacceptable toxicity, or withdrawal of consent. In this phase II trial, patient characteristics were as such: median four prior therapies (range 2–5.5), platinum-resistant (86%), *BRCA* wild-type (77%) and received at least one full cycle of treatment. The ORR was 14%, DCR (PR+SD) was 71%. Treatment enhanced interferon-γ and tumor-infiltrating lymphocytes (TIL) indicating an immunostimulatory environment, which was associated with improved PFS [HR 0.37 (95% CI, 0.16–0.87), p= 0.023], while increased VEGFR3 levels were associated with worse PFS so one can conclude that VEGF/VEGFR pathway blockade would enhance the efficacy of the combination.[36]

Liu et al[37] conducted a phase II trial to evaluate the activity of combined nivolumab and bevacizumab in women with relapsed ovarian cancer. Participants received intravenous nivolumab and intravenous bevacizumab once every 2 weeks. The primary endpoint was the objective response rate (ORR) as measured by Response Evaluation Criteria In Solid Tumors [RECIST] 1.1. Of the 38 women enrolled, 18 had platinum-resistant with an ORR of 16.7% (95% CI 3.6–41.4%) compared to an ORR of 40% in platinum-sensitive cohort. Median PFSPFS by RECIST was 7.7 months in PROC vs 12.1 months in platinum-sensitive patients. Nine participants (23.7%) experienced a grade 3 or higher TRAEs.[37]

Zsiros et al[15] performed an open-label phase II cohort study for recurrent ovarian cancer with measurable disease per the immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) (Table 1). Out of 40 patients, 30 were platinum-resistant and received [pembrolizumab 200 mg, bevacizumab 15 mg/kg IV every 3 weeks and oral cyclophosphamide 50 mg PO daily until disease progression or unacceptable toxic effects]. In the platinum-resistant cohort, the ORR was 43.3%, 93.3% cases had clinical benefit and the duration of response was 5.5 months. Ten cases (25%) of the study cohort had durable response (≥12 months) with a median PFS of 10-months. Notably, any grade TRAE was seen in 32.5% cases, most commonly fatigue (45%), diarrhea (32.5%), and hypertension (27.5%). The most common grade 3 TRAEs were lymphopenia and hypertension (7.5% and 15%, respectively).[15]

Toxicity Related to Immune Checkpoint Inhibitors

While disinhibiting T-cell function, ICI can cause immune-related adverse events (irAE). The pathophysiology may involve autoreactive T-cells, autoantibodies, and cytokines, that in turn, lead to loss of tolerance to the host tissues. The irAE usually occur 1–12 weeks after the initiation of therapy, even though late onset has also been reported as late as 1-year after the therapy discontinuation (Figure 4). Most commonly, it can affect skin, colon, endocrine organ, liver, lung, while less common (the most serious, even fatal) irAEs are myocarditis and neurological disorders (Table 2).

The irAEs are graded as 0–5, based on the symptoms' severity. While the majority being reversible with appropriate treatment, consultation with a medical specialist is encouraged to help with the diagnosis and optimal management plan. Mild toxicity (grade 1) is managed symptomatically, unless it involves neurological, cardiac, or hematological toxicity, ICI can be continued. Meanwhile, with moderate toxicity (grade 2), the treatment is withheld and may start 0.5–1.0 mg/kg/day prednisone with the plan to taper for 4-weeks once irAE improves to mild level. Once the irAEs are severe (grade 3), the ICI must be withheld and intravenous prednisone 1–2 mg/kg/day should be administered, if symptoms improve taper corticosteroid over 4–6 weeks, but if symptoms do not improve within 48 hours, use other immunosuppressive agents [eg, mycophenolate, tacrolimus, tumor necrosis factor (TNF)-α antagonist], after irAEs are reverted to grade 1, the ICI can be resumed with caution in cases of early onset irAE. As for the life-threatening toxicity (grade 4), the ICIs are permanently discontinued unless they have endocrinopathy that is controlled with replacement therapy.[38]

Other Categories of Emerging Immunotherapy

Mutations at the level of tumor cell genome create non-self-proteins called tumor-associated antigens (TAA) that trigger the host immune response, and use of vaccines generated against tumor-specific neo-antigens is one way to help activate the immune system and allow it to recognize tumor cells (Figure 5), which in turn, improves prognosis.[39] Criteria that make a specific tumor antigen an attractive target for vaccine development are aberrant expression in tumor cells, with limited or no expression in normal cells, high immunogenicity and involved in tumor progression.[40]

Biomarkers such as cancer antigen-125 (CA-125), mucin 1 (MUC1), carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2)/neu, tumor protein p53, folate receptor-α, and New York-esophageal squamous cell carcinoma-1 (NY-ESO-1) due to their reported immunogenicity have been proposed as vaccine

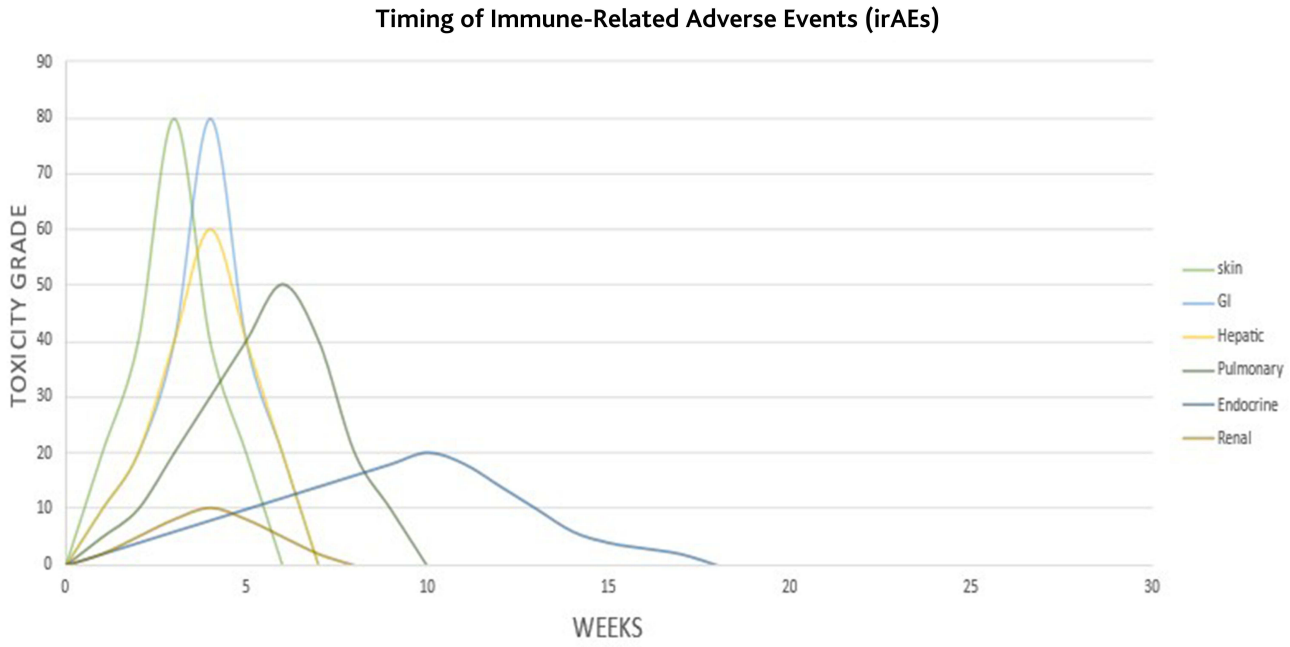

Figure 4 A schematic representation of the timing of immune-related adverse events (irAEs) in various organ systems.
Abbreviation: GI, gastrointestinal.

Table 2 A Summary of the Incidence of irAEs with Immune Checkpoint Inhibitors in Various Organ Systems

	CTLA-4 Inhibitor (%)	PD-1 Inhibitor (%)
Skin		
Pruritis	25–30	11–21
Rash	33–34	10–21
Vitiligo	3–4	9–11
GI		
Diarrhea	36–38	8–20
Colitis	8–10	1–3
Hepatic		
ALT	< 1	1–8
AST	1–2	1–10
Hepatitis	< 1	1–2
Endocrine		
Hypothyroid	1–2	4–10
Hyperthyroid	0–2	0–4
Hypophysitis	2–3	< 1
Diabetes	-	0.6
Renal failure	1	1–3
Pneumonitis	< 1	1–6
Neurological	< 1	< 1

Abbreviations: irAEs, immune-related adverse events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; GI, gastrointestinal; ALT, alanine transaminase; AST, aspartate transaminase.

development targets. There are a variety of platforms developed for oncologic therapeutic vaccine delivery including i) cell-based vaccine where TAA are incorporated into isolated autologous dendritic, ii) peptide-based vaccines are recombinant vaccines based on a defined TAA ± immune modulator, iii) tumor lysate, and iv) genetic or epigenetic vaccines.[39,41]

Most recently, in a Phase 1b study, Manyam et al[42] used intraperitoneal oncolytic viral immunotherapy in heavily pre-treated patients with platinum-resistant ovarian cancer. The authors used Olvi-Vec, a modified oncolytic vaccinia virus whose replication is dependent on high-level thymidine, and that is capable of infecting and killing tumor cells (usually rich in thymidine). In a cohort of 12 patients, the authors found ORR 9%, 46% stable disease at >15 weeks and median PFS of 15.7 months.[42] A multi-center phase II trial of Olvi-Vec followed by platinum-doublet therapy with or without bevacizumab has since been completed and presented at IGCS 2020 and ESMO 2020 conferences.[43,44] Furthermore, a multi-institutional randomized phase III trial in PRROC with Olvi-Vec is currently underway [NCT05281471].

Adoptive T-cell therapy (ACT) uses T-cells derived from peripheral blood lymphocytes (PBLs) or TILs that are modified and expanded ex vivo, then re-infused into the patients (Figure 5). Lymphodepleting chemotherapy can improve response to ACT.[39] However, the process of isolating and expanding TILs is labor intensive, and contemporary efforts are directed toward engineered peripheral T-cells that express anti-tumor receptors such as T-cell receptors (TCR) or chimeric antigen receptors (CAR).[40]

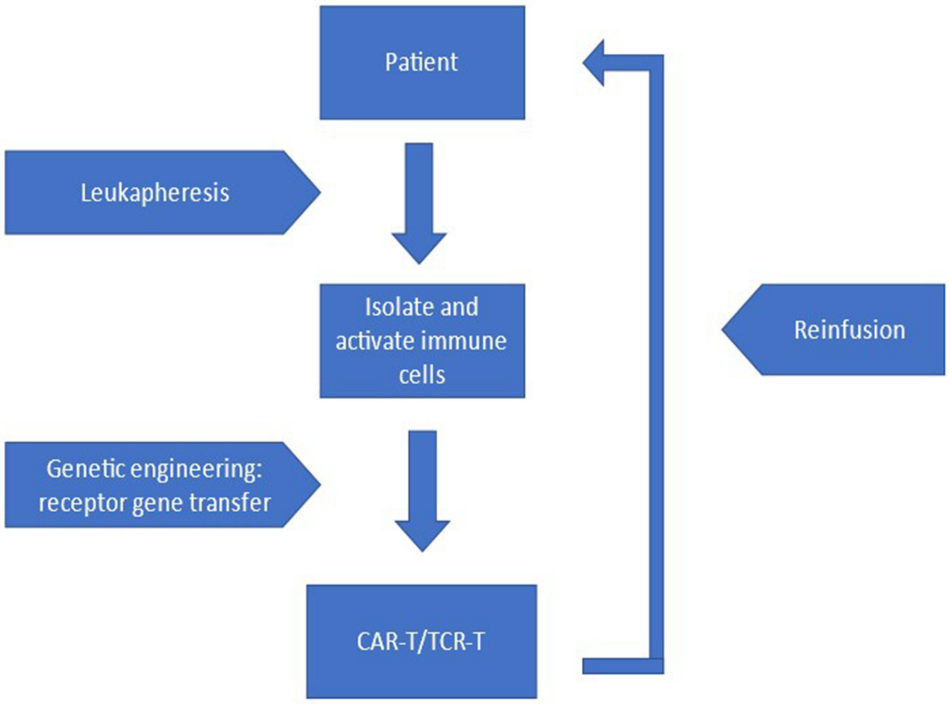

Figure 5 Tumor-specific cytotoxic T-cells, either isolated from the tumor or in the peripheral blood by leukapheresis, are modulated by genetic engineering and activated. Once they undergo lymphodepleting chemotherapy, they are infused back to the patient.

Cost Considerations

The cost of cancer care in the United States was estimated to be $158 billion in the year 2020.[45] The efficacy of pembrolizumab is well established in advanced or recurrent endometrial cancer with ORR as high as 57% in microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) patients.[46] Barrington et al[47] studied the cost-effectiveness of pembrolizumab in advanced endometrial cancer and the authors estimated that pembrolizumab cost per cycle was $9026 in the year 2016–17, the cost of its most common grade 3–4 toxicity (anemia) was $1000, in the MSI-H cohort the cost of pembrolizumab was $57.9 million to yield 507 2-year survivors. The incremental cost-effectiveness ratio (ICER) for pembrolizumab was $147,249 in MSI-H. However, in non-MSI-H the cost of pembrolizumab therapy was $318.3 million with 1804 2-year survivors with an ICER of $341,830, which questions the cost-effectiveness in the MSI stable cohort.[45] Thus, given the low response rate of pembrolizumab in PROC, we can extrapolate that cost-effectiveness is an ongoing issue/concern that should always be under consideration while managing PROC patients with novel immunotherapy, especially those who are older and often have limited resources and coverage. With the anticipated increased incidence of ovarian cancer and the advent of immunotherapeutic options, the overall cost of treatment for PROC is expected to rise. It therefore becomes imperative that we continue to investigate mechanisms to modulate the tumor micro-immune environment to optimize all ovarian cancer therapies, including iMiDs.

Future Perspectives

LEAP-005 a phase II trial assessing a combination of immunotherapy (pembrolizumab) and tyrosine kinase inhibitor (lenvatinib) has promising results. The combination has proven active I endometrial cancer that are MMR proficient. In the LEAP-005, the ORR was 32% with manageable safety in patients with recurrent EOC.[48]

Multiple clinical trials have ongoing efforts to test the efficacy of ICIs and PARP inhibitors in patients with recurrent EOC. For example, the MOONSTONE trial [NCT03955471], a phase II open-label, single-arm study to evaluate the efficacy and safety of the combination of niraparib (PARP-i) and dostarlimab (TSR-042, ICI) in patients with platinum-resistant ovarian cancer (study completion 01/12/2022).[49] The BOLD trial [NCT04015739], a phase II trial assessing the

safety and the efficacy of the bevacizumab, Olaparib (PARP-i) and durvalumab (ICI) combination in patients with advanced epithelial ovarian cancer in relapse (study completion 01/29/2024).[50] The OPAL trial [NCT03574779], a phase II multicohort study to evaluate the safety and efficacy of novel treatment combinations in patients with recurrent ovarian cancer, this combination consists of niraparib (PARP inhibitor), TSR-042 (anti-PD-1) and bevacizumab (study completion 06/12/2025), holds promise.[51]

Furthermore, combining ICI with targeted therapy like mitogen-activated protein kinases (MAPK) inhibitors, which is dysregulated in 3–11% of ovarian cancer patients or MEK (mitogen-activated protein kinase kinase) inhibitors, which can increase CD8+ TILs in TME are emerging strategies in clinical trials. Yet another approach is the addition of another immunomodulatory drug. The ARTISTRY-1 phase I/II trial (NCT02799095) explored efficacy and safety of the combination of pembrolizumab and Nemvaleukin alfa (ALKS4230) in heavily pre-treated recurrent platinum resistant ovarian cancer. Nemvaleukin alfa is a novel engineered fusion protein cytokine comprised of modified interleukin-2 (IL2) and the high-affinity IL-2 alpha receptor chain (IL-2R), designed to preferentially activate memory cytotoxic CD8+ T cells and NK cells without expanding CD4+ T cells, by selectively binding to the intermediate-affinity IL-2 receptor complex. The selectivity of Nemvaleukin is designed to leverage the proven anti-tumor effects of existing IL-2 therapy while mitigating toxicities associated with preferential binding of IL-2 to high-affinity IL2R. Intravenous Nzemvaleukin alfa at 3 micrograms/kilogram plus pembrolizumab induced a notable expansion of CD8-positive T cells and natural \killer cells with minimal impact on regulatory cells. The positive results (ORR of 28.6% and disease control rate of 71.4%) led to a fast-track designation by the FDA and a newly launched phase III trial - ARTISTRY-7.[52]

Conclusions

Platinum-resistant ovarian cancer has an overall poor prognosis with a modest response to cytotoxic chemotherapy and as such it represents a daily challenge for patients and the caring team. Understanding the tumor microenvironment and its prognostic value in treating advanced or recurrent ovarian cancer, immunotherapy is promising and exciting oncologic therapy under investigation for ovarian cancer. Unfortunately, early trials using single-agent immune check-point inhibitors showed limited activity. Higher response rates have been reported using combinations of immune checkpoint inhibitors and PARP inhibitors or cytotoxic chemotherapies, yet phase III trials documenting improvements in PFS and OS are lacking. Notably, immunotherapy has a favorable safety profile. Newer immune drug combinations have shown more promising results in the past year, and several confirmatory trials are underway. Keep in mind that clinicians need to get familiarized with the pseudo-progression when evaluating immunotherapy response, where an initial tumor burden increases (ie, growing and/or new lesions) followed by tumor shrinkage is noted and eventually leads to incorporation of the immune-RECIST criteria to assess the response to immunotherapy.[53] Moreover, once the PD1 or CTLA4 checkpoints are blocked, other immunomodulatory agents that suppress T-reg cells or immunosuppressive macrophages could augment their efficacy. Other novel strategies for immunotherapy include tumor vaccines developed against tumor-specific antigens that target tumor cells in combination with immune checkpoint inhibitors. Novel combination immunotherapies may prove most helpful for patients with platinum-resistant ovarian cancer.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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