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REVIEW

Immunotherapy For Ovarian Cancer: Recent Advances And Combination Therapeutic Approaches

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Abstract: Epithelial ovarian cancer (EOC) is the most lethal gynaecological cancer. Although many advances have been made in therapeutic strategies, the global standard of care still remains radical surgery plus chemotherapy, but new scenarios need to be explored to improve survival. The role of immunotherapy in EOC treatment is controversial. Results obtained from studies evaluating immunotherapy are contradictory: in particular data on survival are not as good as expected when immunotherapy was administered alone, and other data are still immature. Thus, significant efforts must be devoted to finding new strategies for the use of immunotherapy. The aim of this paper is to review the most recent findings of the use of immunotherapy in ovarian cancer, with a particular focus on combination approaches.

Keywords: immunotherapy, ovarian cancer, adoptive cell therapy, combination strategies, therapeutic vaccination, immune-checkpoint inhibitors

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer in developed countries with 22,530 estimated new cases and 13,980 deaths in 2019 in the USA.[1] Although many advances have been made in therapeutic strategies, the global standard of care for the past 20 years has been radical surgery and platinum/taxane-based chemotherapy eventually associated with bevacizumab.[2,3] Currently, the initial response rate (RR) is 60–80%; nonetheless, 70% of advanced-stage patients will relapse within 5 years, and many of them develop drug-resistant disease.[4] For platinum-resistant (Platinum Free Interval (PFI) >1 and <6 months) or refractory (disease progression during the last line of platinum therapy or within 4 weeks from the last platinum dose) patients the life expectancy does not exceed 1 year; indeed, most patients sensitive to first-line therapy also experience a relapse within 2 years from diagnosis, so it is essential to find new attack strategies to improve survival. The advent of poly (ADP-ribose) polymerase (PARP) inhibitors (PARPis) has certainly significantly improved the outcomes of EOC patients, both for Breast Related Cancer Antigens (BRCA)-mutant and for BRCA-wild type tumors, but new therapy scenarios need to be explored.[5]

Immunotherapy, which recognizes different approaches, had a strong growth in recent years and experienced encouraging results in melanoma, non-small cell lung cancer, kidney and urothelial cancers.[6,7] EOC has long been considered a poorly immunogenic neoplasm, but evidence of mechanisms of immune evasion,

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spontaneous tumor regressions[8,9] and responses to immune-checkpoint inhibitors (ICIs) have proven otherwise.[10] Many studies have been conducted, and some evidences show that EOC could benefit from immunotherapy.

Immunotherapy in Ovarian Cancer: Background

Immunotherapy knows three different strategies (Table 1): active immunotherapy, passive immunotherapy and immunomodulation. The first has the aim of stimulating an anti-tumor response from the patient's own immune system itself inducing also an immunological memory. Passive immunotherapy uses the administration of immune components that directly act and promote an anti-tumor response. Finally, "immunomodulation" includes all those approaches, hardly classifiable, that enhance general immune responsiveness.[11]

The potential role of the immune response has been investigated in EOC and in some studies a correlation was found between the presence of tumor-infiltrating lymphocytes (TILs), the expression of PD-1 and the overall survival (OS).[12,13]

According to the status of TILs, tumors can be classified into two categories. "Inflamed tumors" are characterized by the presence of a high density of $CD8^+$ T cells, so could benefit from therapies acting on T cell checkpoint implicated in immune-tolerance. In the "non-inflamed tumors" T cells are absent in tumor beds and tumor edges. So, this type of tumors is generally affected by a failure in T cell priming and needs strategies that could deliver autologous/allogenic effector cells into the cancer.[14,15]

Other types of tumors, defined as "immune-excluded", are characterized by the modification of tumor microenvironment (TME) and the presence of inhibitory cells that prevent $CD8^+$ T cells from entering the tumor islets, even if they are present in the stroma. Such patients could benefit from strategies aiming to increase the infiltrations of tumors by immune effector cells such as T cell tracking modulators, epigenetic modulators, TME remodeling molecules, radiation therapy.[16]

BRCA 1/2 mutated high grade serous ovarian cancer (HGSOC) shows a higher mutational load and increased expression of TILs, programmed cell death (PD-1) and its ligand (PD-L1). Furthermore, patients with T-cell-rich tumors experience longer progression-free and OS,[12] while immune evasion mechanisms are associated with poor survival.[17,18]

The aim of this paper is to review the most recent data and the ongoing studies on immunotherapy in ovarian cancer.

A search in Pubmed was performed combining the following keywords: "immunotherapy", "immune environment", "ovarian cancer", "PD1/PD-L1 expression", to retrieve preclinical data. A search in PubMed with keywords "ovarian cancer", "immune-checkpoint inhibitors",

Table 1 Types of Cancer Immunotherapies

Mechanism of Action	Classes			
Active	Cancer vaccines (preventive/treatment)	Dendritic cells Peptide Allogenic		
	Immune-checkpoint inhibitors	Anti-CTLA-4 Anti-PD-1/PD-L1		
Passive	Monoclonal antibodies (MABs)			
	Cytokines			
	Adoptive cell transfer	MHC-independent	Genetically modified	NK cells LAK cells CIK cells CAR cells
		MHC-dependent	Genetically modified	TIL cells TCR cells
Immunomodulation	Drugs hardly classifiable	IDO inhibitors COX-2 inhibitors		

Abbreviations: CAR, chimeric antigen receptor; CIK, cytokine-induced killer cells; COX-2, cyclooxygenase 2; CTLA-4, cytotoxic T lymphocyte-associated protein 4; IDO, indoleamine 2,3-dioxygenase; LAK, lymphokine activated killer; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TCR, T cell receptor; TIL, gtumor-infiltrating lymphocytes.

"adoptive cell therapy" and "vaccination" was performed to retrieve published clinical trials. ClinicalTrial.gov was searched for ongoing trials with the same keywords.

Mono-Immunotherapy in Ovarian Cancer

In the last few years, some studies have been published on immunotherapy in EOC mainly involving ICIs, that block immune-checkpoint such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or the programmed death 1 (PD-1) receptor, alone or in combination with other drugs. Hodi et al first showed antitumor effects of ipilimumab (anti-CTLA-44) in nine patients with stage IV ovarian cancer (OC) patients, after vaccination with irradiated, autologous tumor cells engineered to produce Granulocyte-Macrophage Colony-Stimulating Factor (GVAX). In one patient, an objective radiographic response was noted and multiple infusions of anti-CTLA -4 antibody every 3 to 5 months have maintained disease control over 4 years; also, three patients showed disease stability lasting 6, 4 and 2 months, respectively,y as confirmed by Ca 125 (Cancer Antigen 125) levels and radiological evaluation, without important toxicities.[19,20] In 2015, our group reviewed data on ICIs as monotherapy in recurrent platinum-sensitive (PFI> 12 months) or platinum-resistant EOC in second-line, third-line, or fourth-line, concluding that the results can surely be promising in the next future.[21] However, even if the biology of the tumor suggested that EOC patients could potentially benefit from immunotherapy, up to now the results obtained from mono-immunotherapy are not proved to be as satisfactory as in other neoplasms. For example, the use of single-agent antibodies targeting the CTLA-4 or PD-1 or PD-L1 showed modest results in EOC with median RRs of 10–15%. Moreover, a control of disease was showed only in less than half of enrolled women.[22–25] In 2013, Sabbatini et al published data from Phase III clinical trial to evaluate whether abagovomab (Anti-Human CA-125 antibody) maintenance therapy prolongs recurrence-free survival (RFS) and OS in patients with ovarian cancer in first clinical remission. Authors found that abagovomab administered as maintenance therapy for advanced ovarian cancer patients in the first remission after debulking surgery and platinum-based chemotherapy does not prolong RFS or OS.[26] In addition, a subanalysis of the MIMOSA trial was conducted to evaluate whether abagovomab induces protective immune responses in ovarian cancer patients in first clinical remission. Authors measured circulating CA125-specific cytotoxic T lymphocytes (CTL) and human antimouse antibody and anti-anti-idiotypic (Ab3) before starting the treatment and at different time points during induction and maintenance phases showing that abagovomab does not induce CA125-specific CTL. However, patients with CA125-specific CTL perform better than patients without, irrespective of abagovomab treatment. Abagovomab-induced Ab3 is associate with prolonged RFS in patients without CA125-specific CTL.[27] In light of these observations, Battaglia et al evaluated whether the assessment of the immune system status before of abagovomab administration might predict sensitivity to it. Authors found that patients on abagovomab with IFN-γ producing $CD8^+$T cell percentage and absolute count above the cutoff had a better RFS (P= 0.042 and P=0.019, respectively), compared to patients with IFN-γ producing $CD8^+$T cell percentage and absolute count below the cutoff.[28]

Considering these controversial data, in the last few years more attention has been paid to new strategies with a special focus on the combination therapy and unconventional immunotherapeutic agents (Table 2), which could potentiate the positive effects of immunotherapy.

Combination Strategies

Immunotherapy in Combination with Anti Angiogenic Agents

Anti-VEGF (Vascular Endothelial Growth Factor) therapy may enhance response to immunotherapy. In a murine syngenetic model of EOC overexpressing VEGF, VEGF

Table 2 Strategies to Enhance the Efficacy of Immunotherapy

Combinations Strategies	
IMMUNE-CHECKPOINT INHIBITORS plus	ANTI ANGIOGENIC AGENTS PARPis CHEMOTHERAPY OTHER IMMUNE-CHECKPOINT INHIBITORS OTHER AGENTS
Other Strategies	
ACT	MONOTHERAPY COMBINATION
VACCINE	MONOTHERAPY COMBINATION

Abbreviations: ACT, adoptive cell therapy; PARPis, PARP inhibitors.

plus PGE_2 blockade increased T-cell homing to tumors,[29] whereas, in a murine melanoma model, disruption of the VEGF/VEGF receptor 2 axis was shown to increase extravasation of adoptively transferred T cells into the tumor and to improve adoptive cell transfer immunotherapy.[30] In addition, anti-VEGF strategies in combination with a granulocyte-macrophage colony-stimulating factor–secreting tumor vaccine have been shown to reduce the number of $CD4^+CD25^+$ Tregs, which leads to increased CTL induction and improved vaccine efficacy.[31] In a Phase I study, the combination of durvalumab (anti-PD-L1) and cediranib (an oral VEGF receptor inhibitor) was tested in 14 recurrent or metastatic ovarian cancers even with more than 5 previous chemotherapy lines. The disease control rate was 75% with 50% RRs (6 Partial Response PR and 3 stable disease SD) assessed by imaging using response evaluation criteria in solid tumors (RECIST) v1.1 criteria. Recurrent grade 2 and non–dose-limiting toxicity grade 3 and 4 adverse events (AEs) have occurred on the daily schedule (hypertension 2/8 patients, diarrhea 2/8 pulmonary embolism 2/8, pulmonary hypertension 1/8 and lymphopenia 1/8) while in durvalumab plus intermittent cediranib schedule grade 3 and 4 AEs were hypertension 1/6 and fatigue 1/6. Authors concluded that durvalumab plus intermittent cediranib is a tolerable and clinically active combination in this setting of patients.[32] Most recently, a Phase II trial using combined nivolumab (anti-PD-1) and bevacizumab (anti-VEGF monoclonal antibody) showed clinical activity in 38 women affected by recurrent ovarian cancer after 1 to 3 lines of prior chemotherapy. The Objective Response Rate (ORR) was 28.9% (95% exact binomial CI, 15.4–45.9%) with better results in platinum-sensitive setting (ORR 40%, [CI 19.1–64.0%] vs 16.7%, [CI 3.6–41.4%] in platinum-resistant disease). Median Progression Free Survival (PFS) by RECIST was 9.4 months (95% CI, 6.7 months to not available (NA)): 12.1 months (95% CI, 8.4 months to NA) in platinum-sensitive patients vs 7.7 months (95% CI, 4.7 months to NA) in platinum-resistant ones. Thirty-four participants (89.5%) experienced at least 1 treatment-related adverse event and 23.7% a grade 3 or higher treatment-related adverse event.[33]

Immunotherapy in Combination with PARPis

PARPis can activate interferon signaling and activate stimulator of interferon genes in BRCA-deficient tumors and synergize with PD-1 or CTLA-4 blockade in mouse models.[34–36]

Of note, PARPis also can trigger activation of the stimulator of interferon genes pathway to enhance the effects of ICIs independently of BRCA status.[37]

In the phase II MEDIOLA study, durvalumab (anti-PD-L1) with olaparib (PARPi) combination was well tolerated in 32 patients with BRCA-mutated platinum-sensitive e relapsed ovarian cancer. The most common grade ≥3 adverse events were anemia (9%) increased lipase (9%), hyperamylasemia (6%) and neutropenia (3%). The interim analysis showed a Disease Control Rate (DCR) based on RECIST at 12 weeks of 81% in case of co-administration of olaparib and durvalumab. The Complete Response (CR) and Partial Response (PR) rates were, respectively, 19% and 44%, resulting in an ORR of 63% while enhanced responses were seen in patients with only 1–2 prior chemotherapies (ORR 69%).[38]

Furthermore, in a phase I trial, the same combination resulted in an ORR of 17% and a DCR of 83% at 6 months according to RECIST in 12 patients with BRCA wild-type recurrent tumors and up to >5 lines of previous therapy, without dose-limiting toxicity (DLT). The authors concluded that immunotherapy plus PARPis can be considered a tolerable and clinically active treatment.[32]

The results of the phase I/II TOPACIO-KEYNOTE 162 trial have shown that the PARPi niraparib in combination with pembrolizumab (anti-PD-1) is tolerable. A promising antitumor activity was showed in particular for patients with platinum-resistant and platinum-refractory recurrent ovarian carcinoma, especially BRCA-wild Type or non-Homologous Recombination Deficiency (HRD) disease, patients with limited treatment options (1–5 prior lines of therapy), regardless of platinum status, biomarker status, or prior treatment with bevacizumab. In the integrated efficacy phases 1 and 2 ovarian carcinoma population (60 of 62 evaluable patients), ORR was 18% (90% CI, 11–29%), with a disease control rate of 65% (90% CI, 54–75%), including 3 (5%) with confirmed CR, 8 (13%) with confirmed PR, 28 (47%) with stable disease (SD), and 20 (33%) with progressive disease (PD) based on RECIST. The most common adverse events of any grade (n = 53) in Phase 2 were fatigue (53%), nausea (42%), anemia (36%), and constipation (36%). Adverse events of at least grade 3 were anemia (21%) and thrombocytopenia (9%). No treatment-related patient deaths or cases of myelodysplastic syndrome or acute myeloid

leukemia occurred.[39] Currently the study is active but no longer in the enrollment phase.[40]

Finally, a phase I study has been testing the combination of cediranib (VEGF receptor inhibitor), durvalumab (anti-PD-L1) and olaparib (PARPi) with an escalation in order to determine the recommended phase 2 dose (RP2D) while RRs, pharmacokinetic and correlative analyses were secondary endpoints. Nine patients (7 affected by recurrent platinum-resistant or sensitive OC or primary peritoneal cancer, median 3 prior therapies [2–6]) were treated. Adverse events (Grade 3/4) were not common and included hypertension (1/9), anemia (1/9) and lymphopenia (3/9) and none of these was a dose-limiting toxicity. The identified RP2D was cediranib 20 mg (5 days on/2 days off) with full doses of durvalumab (1500 mg IV every 4 weeks) and olaparib (300 mg BID). The ORR was 44% (4/9) with all PR (RECIST criteria), lasting a median of 8.5months [7–26 months]. Three patients had SD lasting ≥6 months, yielding a 67% clinical benefit rate. No significant effects of the combination on pharmacokinetic were identified.[41] A phase 2 expansion study is now enrolling for recurrent ovarian cancer patients.[42]

Immunotherapy in Combination with Chemotherapy

The standard chemotherapeutic approach for newly diagnosed ovarian cancer contemplates the combination of carboplatin and paclitaxel.[43] This doublet has been associated successfully with PD-1 blockade in non–small-cell lung cancer (NSCLC), where the immunochemotherapy combination outperformed chemotherapy.[44] Several authors studied carboplatin-paclitaxel and immunotherapy in newly diagnosed ovarian cancer with contradictory data. A randomized, open-label, multicenter, phase 3 study evaluated the efficacy (per RECIST v1.1) and safety of avelumab (anti-PD-L1) in combination and/or following chemotherapy in patients with previously untreated epithelial ovarian cancer (JAVELIN OVARIAN 100). The study was prematurely closed based on the results of a planned interim analysis that showed the futility of efficacy. The last results of December 2019 showed a PFS of 16.8 months in the group of chemotherapy followed by avelumab vs 18.1 months in arm treated with chemotherapy plus avelumab followed by avelumab vs NA (Not Available) (due to a limited number of events) in the group of chemotherapy alone plus observation. HR estimated were 1.43 (chemotherapy followed by avelumab vs chemotherapy alone plus observation) and 1.14 (chemotherapy+ avelumab followed by avelumab vs chemotherapy alone plus observation) with P value >0.05 (NCT02718417).[45]

ICIs are not the unique immunotherapeutic tools that were tested in combination with upfront chemotherapy. A recent Phase II, randomized, the study evaluated carboplatin-paclitaxel chemotherapy in association with oregovomab, a high affinity murine monoclonal antibody specific for Ca 125, in 97 cases of optimally resected, Stage III/IV disease. At a median follow up of 42 months, the study revealed an increase in PFS and OS of statistically and clinically significant magnitude: the median PFS was 41.8 months (95% C.I.: 21.8 – NE Not Estimable) for the combination and 12.2 months (10.4–18.6) for the chemotherapy alone (P= 0.0027, HR 0.46, CI 0.28–0.7). For OS, the median has not yet been reached (NE) in the oregovomab group (45.2-NE) while, in the other arm, it was of 43.2 months (31.8-NE) (P= 0.043, HR 0.35, CI 0.16–0.74). In addition, the administration of antibodies did not change the toxicity profile of standard chemotherapy.[46]

Simultaneously, efforts have been made in the evaluation of predictive factors for the response to treatment with oregovomab itself. Thus, Battaglia et al have recently assessed that efficacy of oregovomab is associated with a less suppressive immune environment at baseline: a low number of circulating myeloid-derived suppressor cells, subset type 4 (MDSC4), and a low neutrophil-and-monocyte to lymphocyte ratio (NMLR) were found in patients with a better response to treatment with oregovomab in addition to chemotherapy. Both parameters resulted significantly predictive for relapse-free survival (MDSC 4: P= 0.012, NMLR P=0.0014), while NMLR was related also with OS (P= 0.048).[47]

In case of recurrent ovarian cancer, several chemotherapeutic approaches are available, according to platinum sensitivity. In particular platinum-resistant or refractory disease represents the principal challenge for the oncologist. Among drugs available for these patients, guidelines cite weekly paclitaxel, pegylated liposomal doxorubicin (PLD), docetaxel, cyclophosphamide, gemcitabine and topotecan.[43] Concerning the combination with immunotherapy, data showed that PLD could synergize with it:[48] PLD would enhance tumor immunosurveillance and inhibit tumor immunosuppression but it would also synergize with immunotherapy improving indeed the sensitivity of tumor cells to

the cytotoxic activity of natural killer (NK) cells, γδT or $CD8^+$ T lymphocytes.[49]

Several authors have addressed the issue of the administration of immunotherapy and chemotherapy in platinum-resistant relapses, with various results.

First of all, about the schedule with PLD in a phase II trial, the combination of durvalumab (anti-PD-L1) in 53 patients with recurrence after first or second-line platinum-based chemotherapy, resulted in a best ORR of 15%, with a CR of 5%, and PFS rate at 6 months of 47.7% with RECIST v1.1, leaning towards the hypothesis of a promising efficacy (NCT02431559).[48,50]

The preliminary results of another phase II study of PLD with pembrolizumab (anti-PD-1) in 26 women with platinum-resistant ovarian cancer (who received ≤2 cytotoxic regimes for recurrent or persistent disease) were on the same line: the ORR and DCR were 19 and 42% respectively, with 5 PR and 6 SD, defined as RECIST v1.1. The combination also resulted well tolerated with grade 3–4 adverse events of anemia (12%), rash (12%), and increased liver enzymes (12%).[51]

On the opposite, in a phase II randomized study of 297 patients with recurrent EOC (Up to 2 prior cytotoxic regimens), the addition of a TLR8 agonist (motolimod) to PLD did not improve OS (log-rank one-sided P 0.923, HR 1.22) and PFS (log-rank one-sided P 0.943, HR 1.21) assessed by the Immune-Related RECIST (irRECIST) criteria.[52] Similarly, the phase III JAVELIN Ovarian 200 study compared PLD with the combination of PLD and the anti-PD-L1 antibody avelumab in platinum-resistant /refractory ovarian cancer received up to 3 lines of systemic anticancer therapy for platinum-sensitive disease and no prior systematic therapy for platinum-resistant disease. Authors concluded that the combination of PLD+ avelumab did not show a statistically significant improvement when compared with PLD alone in PFS (RECIST) (HR 0.78; CI 0.587−1.244; P= 0.0301) or OS (HR 0.89; CI 0.744–1.241; P= 0.2082) (NCT02580058).[53] The study closed the accrual, and definitive results are awaited.

Finally, some authors proved that also low-dose intravenous or oral metronomic chemotherapy can have important immunomodulatory effects. Between these, low-dose cyclophosphamide has been shown to attenuate Tregs and improve vaccination as well as adoptive cell therapy (ACT) efficacy,[54] whereas, in combination with ICIs, it stimulates the generation of $CD8^+$ TILs.[55] Thus, cyclophosphamide was evaluated in recurrent ovarian cancer itself. In particular, an open-label phase II study has been testing the combination of cyclophosphamide with bevacizumab (anti-VEGF) and pembrolizumab (anti-PD-1) in 40 patients with recurrent OC, platinum-resistant or platinum-sensitive refusing platinum-based therapy regardless of the number of previous chemotherapies. This has been evaluating the clinical RRs using both RECIST1.1 and irRECIST.[56] To a preliminary analysis, the combinations were well tolerated and it was found that the tumor responses were higher and longer than those obtained with monotherapy: the ORR was 37.5% (all PR), and the overall PFS rate was 70% at 6 months (59% in the platinum-resistant population, 100% in platinum-sensitive ones; P= 0.024).[57]

To sum up, some authors proofed that the combination of chemo-immunotherapy could improve the efficacy of the treatment, even in OC with the worst prognosis, but data are not universally consistent. Thus, further studies are needed to establish it with certainty.

Other Combinations

Pembrolizumab (anti-PD-1) combined with mirvetuximab soravtansine (a folate receptor-a [FRa] antibody-drug conjugate that comprises an FRa-binding antibody linked to the tubulin-disrupting maytansinoid DM4) also has shown preliminary signs of efficacy in a heavily pre-treated population (no upper limit on the number of prior treatments) of 14 FRa-positive patients with platinum-resistant ovarian cancer in the phase Ib/II FORWARD II trial: In the subset of 8 patients with medium to high FRa expression levels by immunohistochemistry, confirmed PR were observed in 3 individuals according to RECISTv1.1 and CA125 evaluations; 2 were ongoing with at least 5 months on treatment; and the third had a duration of therapy of 7 months.[58] These findings supported the ongoing enrollment of patients in an expansion cohort.[59]

Combinations of Immune-Checkpoint Inhibitors

Combining the activation of different mechanisms of the immune system can achieve more pronounced antitumor activity than blockade of a single pathway alone.

As good evidence of this, Co-targeting of CTLA-4 (ie ipilimumab) plus PD-1 (ie nivolumab) resulted in significantly stronger activity in non-gynecological tumors[60] due to the synergism of amplification of T-cells in lymphoid organs and tumor tissue by anti-CTLA-4, and PD-1 inhibition that overcomes immune suppression in tumor tissues.

An NRG Oncology phase II study has been testing these agents together in a population of 100 patients with recurrent ovarian cancer with up to 3 prior lines of therapy and a platinum-free interval of up to 12 months. It reported ORR by RECIST v1.1 of 33.3% and PFS 3.9 months for the combination vs ORR 12.2% and PFS 2.0 months with nivolumab alone. Adverse events occurred more frequently in the combination arm (Grade 3 or greater AEs in 67%) versus the single-agent arm (Grade 3 or greater AEs in 55%).[61] The trial is no more recruiting but still ongoing, analysing new biomarkers for response.[62]

A phase I/ll dose escalation and cohort expansion trial is testing the safety, tolerability and efficacy of varlilumab (an anti-CD27 antibody) and nivolumab (anti-PD-1) in advanced refractory solid tumors among which eight cases of ovarian cancer. Overall, upon an initial analysis, the combination was well tolerated, associated with strong biological signals, and had evidence of clinical activity (based on RECIST) in subsets of patients with tumor types resistant to PD-1 inhibitor monotherapy.[63] Up to now results from phase 2 cohort in ovarian cancer are awaited.[64]

All in all, these data, although preliminary and coming from phase I–II studies, are promising.

Other Strategies

Adoptive Cell Therapy

Adoptive Cell Therapy (ACT) is an immunotherapeutic technique that uses autologous or allogeneic antitumor lymphocytes to induce regression in cancers that are less responsive or refractory to ICIs.

The approach of autologous ACT is illustrated in Figure 1 and involved cell types are summarized in Table 1.[65]

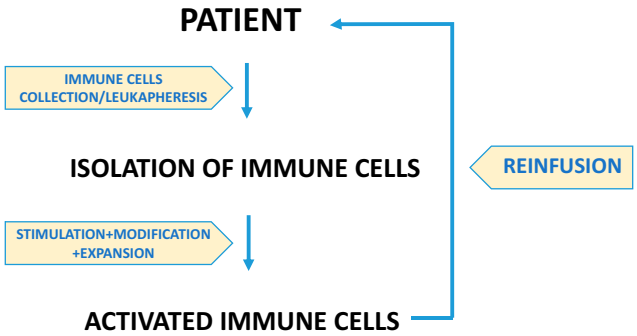

Figure 1 Autologous ACT is based on reinfusion of immune cells after stimulation, modification and expansion in vitro in order to amplify autologous response against tumors. These tumor-specific cytotoxic T cells, either isolated from the tumor or in the peripheral blood by leukapheresis, are then infused after lymphodepleting chemotherapy.

The potential role of Natural Killer (NK) cell adoptive immunotherapy for OC was recognized in 2007 when it was shown that resting NK cells can recognize and kill OC cells in vitro[66] and subsequently, in 2016, a new mouse model was established for intraperitoneal administration of NK cell immunotherapy for OC allowing further research.[67]

A phase II study analyzed the role of another class involved in ACT, the Cytokine-Induced Killer (CIK) cells, in the approach to OC: Liu et al tested this therapy versus observation in 92 patients with completed remission after first-line treatment for advanced OC. The median PFS was 37.7 months in the treatment group and 22.2 months in the control group (P= 0.004) with slight side effects, although with a no significant difference in OS (61.5 months vs 55.9 months, P= 0.289).[68]

In 2018, a retrospective analysis by Zhou et al further sustained the effectiveness of maintenance CIK cell therapy as a therapeutic approach to prolonging the survival in 646 OC patients after first-line treatment. Specifically, patients who received CIK exhibited a significantly more favourable OS than control group patients (median OS, 63.6 vs 39.6 months, P= 0.001), while Kaplan–Meier curves showed a favourable PFS (median PFS, 41.6 vs 26.1 months), but with the not-significant p-value (P= 0.117).[69]

Referring to TILs, the first data date back to before the end of the 90s.

Some of the most relevant results obtained with autologous TILs are summarized in Table 3.[70–73]

The therapeutic effect of TILs in OC is still under evaluation.

In 2018, results from a pilot study in platinum-resistant recurrent OC with lympho-depleting chemotherapy followed by the infusion of unselected TILs and IL2 were published. Clinical response was assessed using the RECIST 1.1 criteria but the Positron Emission Tomography (PET) Response Criteria in Solid Tumors (PERCIST 1.0) was studied in order to identify the difference between the two models. The therapy was feasible and with no unexpected toxicities related and early indications of activity were found: all patients had SD after 6 weeks and five of them had a reduction of target lesions. Two patients maintained this response for 5 months. Subsequently, five patients developed PD due to the occurrence of new lesions. In this way, the road toward the possibility of enhancing ACT combining it to ICIs was opened.[74] Subsequently, the same group managed to expand TILs from 34 tumors specimen of OC and found the recognition of autologous tumor cell in >50% of the

Table 3 Some Relevant Results of ACT Obtained Up to 2000 with Autologous TILs

Author/Year	Results of Study
Aoki et al[70]	• 17 patients • Advanced or Recurrent OC • Treatment: TILs ±cisplatin • Combination (10 pts)→CR 70%, PR 20% • Monotherapy (7pts)→CR 14.3%, PR 57.1%
Ikarashi et al[71]	• 22 patients • Advanced EOC (FIGO II-III-IV) • Treatment: TILs • TILs group (12 pts)→Immunoactivation of cellular immunity, 2-year survival rate: 100% • No-TILs group (10 pts)→No changes in immunological markers, 2-year survival rate: 100%
Freedman et al[72]	• 11 patients • Advanced EOC refractory to platinum-based chemotherapy • Treatment: IL2 ip ±TILs • IL2+TILs group (8 pts)→No measurable clinical response. 4/8 secondary response • IL2 group (3 pts) → No measurable clinical response
Fujita et al[73]	• 24 patients • EOC with CR after first-line chemotherapy • Treatment: TILs • TILs group (13 pts)→3-year survival rate 100%, • No-TILs group (11pts)→ 3-year survival rate 67.5%

Abbreviations: CR, complete response; EOC, epithelial ovarian cancer; IP, intraperitoneal; OC, ovarian cancer; PR, partial response; PTS, patients; TILs, gtumor-infiltrating lymphocytes.

patients. Furthermore, they isolated and subsequently expanded antigen-specific TILs. These findings support the hypothesis that women with OC can benefit from ACT with TILs and encourage further studies.[75] Anyway, these studies revealed some of the potential limitations of TILs-ACT in recurrent EOC that have to be overcome: the exhausted phenotype of TILs[74] and/or the low frequency of tumor-reactive TILs in the infusion product.[75]

With the aim of improving the therapeutic efficacy, genetically modified peripheral blood lymphocytes have been being studied with more interest (Figure 2). They can express a chimeric antigen receptor (CAR) or a tumor-antigen specific T-cell receptor (TCR).

The main targets for CAR-T cells in OC include MUC16 (Mucin 16)/Ca 125, mesothelin and folate receptor-α[76–78] while for TCR, they are MAGE-A4 (Melanoma-associated antigen 4), WT1 (Wilms' tumor protein 1), and NY-ESO-1 (New York oesophageal-1). Among them the last one is the most widely studied and proved to be overexpressed not only in OC but also in all gynecological cancers.[79–82]

The main evidences from experimental animal models and clinical data on CAR-T and TCR-T role in OC are illustrated in Table 4.[83–87]

Although their administration has shown a potential in the treatment of OC, it still has to face many challenges. Currently, several phase I/II clinical trials are ongoing.

Therapeutic Vaccine

Cancer vaccines are immunotherapeutic agent, usually a tumoral antigen, that stimulate an immune response (T cells) directed against specific malignant cells.[88]

A number of tumor-associated antigens for vaccine have been identified in EOC. The ideal ones should not be present in normal tissue, while expressed at high concentration in tumor ones, having a role in its progression. Moreover, it should be able to be recognized by immune cells and activate the immune system response event at low doses, characteristics known as "strong immunogenicity". None of the currently known antigens, however, completely meet these criteria.

Anyway, among antigens possibly involved for immunotherapy in OC, the cancer-testis (CT) family is quite wide and includes the NY-ESO-1. Several trials evaluating NY-ESO -1–based vaccine have been conducted in the treatment of EOC, in different schedules. Data from these trials showed a favourable efficacy, with an improved OS of at least 2 years in case of vaccination in both newly diagnosed or recurrent OC.[48,89-93] Currently other several single antigens, eg MUC-1 (Mucin 1), mesothelin, HER2 (human epidermal growth factor receptor), MUC-16/Ca125, p53, Testis Expressed 19 (TEX 19)[94] can be seen as a possible target of vaccines for OC.

Moreover, since cancer vaccination has the purpose to educate the immune system to generate specific effector T-cells able to detect and kill tumor cells, dendritic cell-based vaccines are a particularly attractive option for immunotherapy, due to the capability of these cells to process and present cancer antigens, and to initiate and regulate both innate and adaptive immunity.[95,96] A phase II trial tested a MUC-1 targeted Dendritic Cell treatment (CVac) as a maintenance therapy versus observation to 56 patients in complete response after a first or second-line chemotherapy. Although a response was induced in all CVac-treated based on RECIST v1.1, the effect on PFS was not significant in

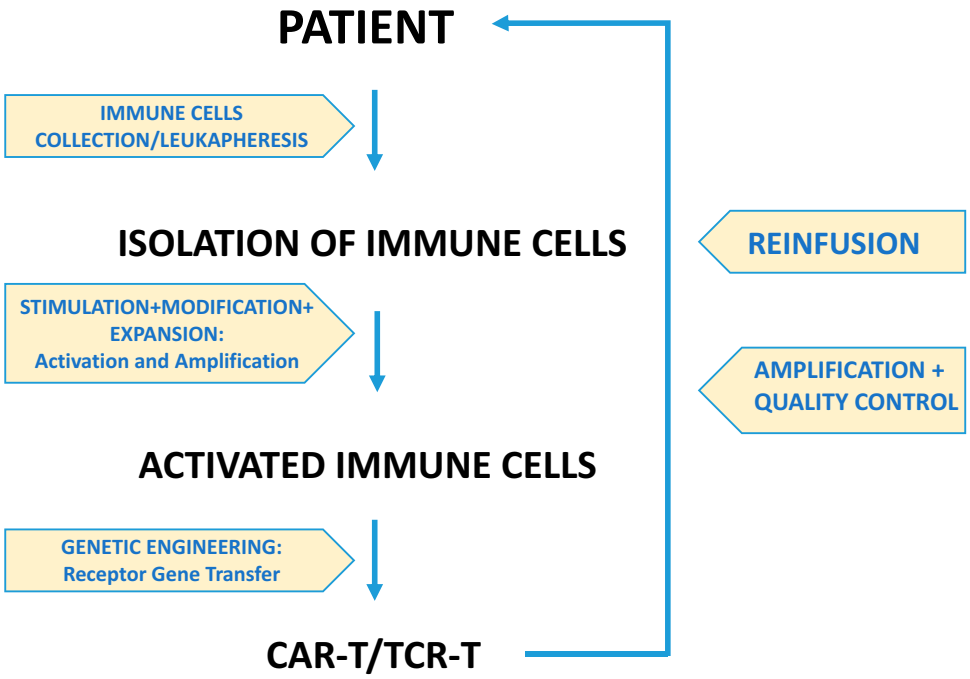

Figure 2 Immune cells (T cells) are isolated from patients. They are activated and amplified in vitro and then modified by genetic engineering (receptor gene transfer through viral vector transfection). After amplification and quality control, CAR-T cells and TCR-T cells are reinfused to the patient.

the treated arm compared with the control one (13 months vs 9 months, P= 0.36, HR 0. 73).[97]

Alternatively, the so-called neoantigens (NeoAgs) could ensure high specificity, reducing the potential for immunological tolerance, and inducing robust immunogenicity. They arise from somatic DNA alterations as a result of genetic instability that generate peptides entirely absent from the normal human genome. For these reasons, they are cancer-specific and strongly immunogenic.[98]

Table 4 Evidence from Experimental Animal Models and Clinical Data on TCR-T and CAR-T Role in OC

Author/Year	Type of Act	Mice/Women	Conclusion
Chekmasova et al[83] 2010	CAR-T MUC 16 IP	OC Mice	• 100% of mice: eradication of most evident disease • 75% of mice: relapse at a later time • 25% of mice: NED after 120 days.
Carpenito et al[84]	CAR-T mesothelin IV IP IT	OC Mice	• Therapy reduced the tumor burden ((even complete eradication) • IT injection is marginally faster than IV but significantly better than IP.
Tanyi et al[85]	CAR-T mesothelin IV	6 Women Recurrent OC	• Clearing of malignant cells in the pleural fluid (1 patient) • 100% SD at 1 monthh after treatment (RECIST and mRECIST criteria)
Song et al[86]	CAR-T FRα IV IP IT	OC Mice	• CAR-T cells eradicate large pre-established tumors in vivo • IV and IP: activity delayed in regression by ~7 days relative to IT
Anderson et al[87]	TCR-T_{1045} IV	OC Mice	• Vaccine+TCR_{1045} T cells Group: TTP 112 days • TCR_{1045} T cells Group: TTP 91 days • No-Treatment Group: TTP 77 days

Abbreviations: ACT, adoptive cell therapy; CAR, chimeric antigen receptor; FRα, folate receptor α; IP, intraperitoneal; IT, intratumoral; IV, intravenous; mRECIST, modified response evaluation criteria in solid tumors; NED, no evidence of disease; OC, ovarian cancer; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TCR, T cell receptor; TTP, time to progression.

Table 5 Ongoing Studies Evaluating the Combination of Immune-Checkpoint Inhibitors with Other Agents in Ovarian Cancer Treatment

Study	Phase/ Randomization	Immunotherapy	Disease	Combination with	Primary End Point	Treatment/ Maintenance
NCT03038100 (IMAGYN050/GOG3015/ ENGOT-ov39)[105]	III RANDOM.	ATEZOLIZUMAB	NEWLY DIAGNOSED STAGE III–IV OC/TC/ PPC	BEVACIZUMAB CARBOPLATIN PACLITAXEL	PFS OS	TREATMENT+ MAINTENANCE
NCT02891824 (ATALANTE)[106]	III RANDOM	ATEZOLIZUMAB	PLATINUM-SENSITIVE RECURRENT OC	BEVACIZUMAB CARBOPLATIN PACLITAXEL GEMCITABINE PLD	PFS	TREATMENT+ MAINTENANCE
NCT02659384[107]	II RANDOM.	ATEZOLIZUMAB	RECURRENT PLATINUM-RESISTANT OC/ TC/PPC	BEVACIZUMAB ACETYLSALICYLIC ACID	PFS	TREATMENT
NCT02839707 (NRG-GY009)[108]	II–III RANDOM.	ATEZOLIZUMAB	PLATINUM-RESISTANT RECURRENT OC/ TC/PPC	BEVACIZUMAB PLD	DLT PFS OS	TREATMENT
NCT03598270 (ANITA)[109]	III RANDOM.	ATEZOLIZUMAB	RECURRENT PLATINUM-SENSITIVE OC/ TC/PPC (UP TO 2 PRIOR LINES)	CARBOPLATIN PACLITAXEL GEMCITABINE PLD NIRAPARIB	PFS	TREATMENT+ MAINTENANCE
NCT03353831 (AGO-OVAR 2.29)[110]	III RANDOM.	ATEZOLIZUMAB	RECURRENT PLATINUM-RESISTANT OC/ TC/PPC (UP TO 3 PRIOR LINES)	PACLITAXEL PLD BEVACIZUMAB	OS PFS	TREATMENT
NCT02484404[42]	I–II NON RANDOM.	DURVALUMAB	PERSISTENT ADVANCED OR PLATINUM-RESISTANT RECURRENT OC/TC/PPC (2 PRIOR PLATINUM-CONTAINING REGIMENS)	CEDIRANIB OLAPARIB	PHASE I: RP2D PHASE II: ORR	TREATMENT
NCT03737643 (DUO-O)[111]	III RANDOM.	DURVALUMAB	NEWLY DIAGNOSED STAGE III–IV OC/TC/ PPC	OLAPARIB BEVACIZUMAB CARBOPLATIN PACLITAXEL	PFS	TREATMENT+ MAINTENANCE

NCT02431559[112]	I–II NON RANDOM.	DURVALUMAB	RECURRENT PLATINUM-RESISTANT OC/TC/PPC	PLD MOTOLIMOD	PHASE I: MTD PHASE II: TEAES PHASE II: PFS	TREATMENT+ MAINTENANCE
NCT02726997[113]	I–II SINGLE ARM	DURVALUMAB	NEWLY DIAGNOSED STAGE III–IV OC/TC/PPC	CARBOPLATIN PACLITAXEL	PHARMACODYNAMIC	TREATMENT+ MAINTENANCE
NCT02873962[114]	II NON RANDOM.	NIVOLUMAB	RECURRENT OC/TC/PPC (UP TO 3 PRIOR LINES)	BEVACIZUMAB RUCAPARIB	ORR	TREATMENT
NCT03522246 (ATHENA)[115]	III RANDOM.	NIVOLUMAB	NEWLY DIAGNOSED STAGE III–IV OC/TC/PPC	RUCAPARIB	PFS	MAINTENANCE
NCT02571725[116]	I–II SINGLE ARM	TREMELIMUMAB	BRCA1 AND BRCA2 MUTATION CARRIERS WITH RECURRENT OC	OLAPARIB	PHASE I: RP2D PHASE II: ORR	TREATMENT
NCT02485990[117]	I–II RANDOM.	TREMELIMUMAB	RECURRENT OR PERSISTENT EO/TC/PPC (PFI<12 MONTHS)	OLAPARIB	AES	TREATMENT
NCT03642132 [118] **(JAVELIN OVARIAN PARP100**	III RANDOM.	AVELUMAB	NEWLY DIAGNOSED STAGE III–IV OC/TC/PPC	TALAZOPARIB CARBOPLATIN PACLITAXEL BEVACIZUMAB	PFS	TREATMENT+ MAINTENANCE
NCT02580058 [119] **(JAVELIN OVARIAN 200)**	III RANDOM.	AVELUMAB	PLATINUM-RESISTANT/REFRACTORY OC/TC/PPC	PLD	OS PFS	TREATMENT
NCT02657889[40] **(TOPACIO- KEYNOTE 162)**	I–II SINGLE ARM	PEMBROLIZUMAB	RECURRENT PLATINUM-RESISTANT OC/TC/PPC	NIRAPARIB	PHASE I: DLT PHASE II: ORR	TREATMENT
NCT03740165 [120] **(KEYLYNK-001/ENGOT-ov43)**	III RANDOM.	PEMBROLIZUMAB	BRCA NON-MUTATED NEWLY DIAGNOSED ADVANCED OC/TC/PPC	OLAPARIB CARBOPLATIN PACLITAXEL BEVACIZUMAB	PFS OS	TREATMENT+ MAINTENANCE
NCT02606305[59] **(FORWARD II)**	I–II NON RANDOM.	PEMBROLIZUMAB	FOLATE RECEPTOR ALPHA POSITIVE ADVANCED EPITHELIAL OC/TC/PPC	MIRVETUXIMAB SORAVTANSINE BEVACIZUMAB CARBOPLATIN PLD	TEAES DLT ORR	TREATMENT

(*Continued*)

Table 5 (Continued).

Study	Phase/ Randomization	Immunotherapy	Disease	Combination with	Primary End Point	Treatment/ Maintenance
NCT02853318[56]	II SINGLE ARM	PEMBROLIZUMAB	RECURRENT OC/TC/PPC	BEVACIZUMAB ORAL METRONOMIC CYCLOPHOSPHAMIDE	AES PFS	TREATMENT
NCT02440425[121]	II SINGLE ARM	PEMBROLIZUMAB	PLATINUM-RESISTANT RECURRENT OVARIAN CANCER	PACLITAXEL	PFS AES	TREATMENT
NCT02520154[122]	II SINGLE ARM	PEMBROLIZUMAB	NEWLY DIAGNOSED STAGE III–IV OC/TC/PPC	CARBOPLATIN PACLITAXEL	RR PFS	TREATMENT+ MAINTENANCE
NCT02766582[123]	II SINGLE ARM	PEMBROLIZUMAB	NEWLY DIAGNOSED SUBOPTIMALLY CYTOREDUCED STAGE III–IV OC/TC/PPC	CARBOPLATIN PACLITAXEL	PFS	TREATMENT+ MAINTENANCE
NCT03602859[124]**(FIRST/ ENGOT-ov44)**	III RANDOM.	DOSTARLIMAB	NEWLY DIAGNOSED STAGE III–IV OC/TC/PPC	NIRAPARIB CARBOPLATIN PACLITAXEL BEVACIZUMAB	PFS	TREATMENT+ MAINTENANCE
NCT03806049[125] **(ENGOT-ov42-NGSO /AVANOVA-triplet)**	III RANDOM.	DOSTARLIMAB	PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER WITH KNOWN BRCA MUTATION	NIRAPARIB BEVACIZUMAB CARBOPLATIN PACLITAXEL	PFS	TREATMENT
NCT02498600[62]	II RANDOM.	IPILIMUMAB	RECURRENT OR PERSISTENT EPITHELIAL OC/TC/PPC	NIVOLUMAB	OBJECTIVE TUMOR RESPONSE	TREATMENT+ MAINTENANCE

Abbreviations: AES, adverse events; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; OC, ovarian cancer; ORR, overall response rate; OS, overall survival; PFI, platinum-free interval; PFS, progression free survival; PLD, pegylated liposomal doxorubicin; PPC, primary peritoneal cancer; RP2D, recommended phase 2 dose; RR, response rate; TC, tubal carcinoma; TEAES, ttreatment-emergent adverse events.

Table 6 Ongoing Studies Evaluating ACT or Vaccine in Monotherapy or in Combination with Other Agents in Ovarian Cancer Treatment

Study	Phase/ Randomization	Immunotherapy	Disease	Combination with	Primary end point	Treatment/ Maintenance
NCT02487693[126]	II NON RANDOM.	CIK CELLS	FIGO STAGE II OC	RADIOFREQUENCY ABLATION	RECURRENCE FS	TREATMENT
NCT03814447[127]	EARLY I SINGLE ARM	ANTI- MESOTHELIN CAR-T CELLS	REFRACTORY RELAPSED OC	FLUDARABINE CYCLOPHOSPHAMIDE	AES	TREATMENT
NCT03692637[128]	EARLY I SINGLE ARM	ANTI MESOTHELIN CAR NK CELLS	MESOTHELIN-POSITIVE STAGE II–IV EPITHELIAL OVARIAN CANCER. (RECURRENCE ARE NOT EXCLUDED)	NONE	AES	TREATMENT
NCT03585764[129]	I NON RANDOM.	MOv19-BBz CAR T CELLS	PERSISTENT OR RECURRENT STAGE II–IV OC/TC/PPC	CYCLOPHOSPHAMIDE FLUDARABINE	AES	TREATMENT
NCT01935843[130]	I–II SINGLE ARM	CART-HER-2	CHEMOTHERAPY RESISTANT OR RELAPSED HER-2-POSITIVE OC	NONE	AES	TREATMENT
NCT02541370[131]	I–II SINGLE ARM	ANTI-CD133-CAR VECTOR-TRANSDUCED T CELLS	CHEMOTHERAPY REFRACTORY OR RELAPSED CD 133-POSITIVE OVARIAN TUMORS	NONE	AES	TREATMENT
NCT01567891[132]	I–II SINGLE ARM	NYESO-1C259 T CELLS	HLA-A201, HLA-A205, AND/OR HLA-A206 ALLELE POSITIVE+ NY-ESO-1 POSITIVE RECURRENT OR TREATMENT REFRACTORY OC	NONE	AES	TREATMENT
NCT03691376[133]	I SINGLE ARM	AUTOLOGOUS NY-ESO-1 ENGINEERED T CELLS AND HSCS	PLATINUM-SENSITIVE OR PLATINUM-RESISTANT RECURRENT OR REFRACTORY OC/TC/PPC	MELPHALAN ALDESLEUKIN	AES MTD	TREATMENT
NCT02457650[134]	I SINGLE ARM	ANTI-NY ESO-1 TCR-TRANSDUCED T CELLS	HLA AND NY-ESAO-1 POSITIVE OVARIAN CANCER	CYCLOPHOSPHAMIDE FLUDARABINE	AES	TREATMENT
NCT02869217[135]	I NON RANDOM.	NY-ESO-1 SPECIFIC TCR GENE TRANSDUCED AUTOLOGOUS T LYMPHOCYTES	METASTATIC OR RECURRENT UNRESECTABLE HLA-A*02:01 OR HLA-A*02:06 POSITIVE OC WITH NY-ESO-1 EXPRESSION	CYCLOPHOSPHAMIDE FLUDARABINE	AES RP2D	TREATMENT

(*Continued*)

Table 6 (Continued).

Study	Phase/ Randomization	Immunotherapy	Disease	Combination with	Primary end point	Treatment/ Maintenance
NCT03159585[136]	I SINGLE ARM	NY-ESO-1-SPECIFIC TCR AFFINITY ENHANCING SPECIFIC T CELL	MULTI-LINE TREATMENT FAILED HLA-A*0201+, NYESO-1+ STAGE IV OV	NONE	AES	TREATMENT
NCT03017131[137]	I SINGLE ARM	NY-ESO-1 TCR ENGINEERED AUTOLOGOUS T CELLS	RECURRENT OR TREATMENT REFRACTORY OVARIAN CANCER	DECITABINE CYCLOPHOSPHAMIDE ALDESLEUKIN	AES	TREATMENT
NCT02498912[138]	I SINGLE ARM	AUTOLOGOUS T CELLS GENETICALLY ENGINEERED TO SECRETE IL-12 AND TO TARGET THE MUC16ECTO ANTIGEN	RECURRENT MUC16ECTO+ OC/TC/ PPC	CYCLOPHOSPHAMIDE FLUDARABINE	MTD	TREATMENT
NCT03132922[139]	I SINGLE ARM	AUTOLOGOUS GENETICALLY MODIFIED MAGE-A4^{c1o3}2T CELLS	HLA-A*02 + MAGE-A4 RNA OR PROTEIN-POSITIVE OC	NONE	AES DLT PERSISTENCE OF GENETICALLY MODIFIED T CELLS IN THE PERIPHERY RCL IN GENETICALLY MODIFIED T CELLS	TREATMENT
NCT03412877[140]	II NON RANDOM.	INDIVIDUAL PATIENT TCR-TRANSDUCED PERIPHERAL BLOOD LYMPHOCYTE	REFRACTORY TO FIRST AND SECOND LINE TREATMENTS OC	CYCLOPHOSPHAMIDE FLUDARABINE ALDESLEUKIN PEMBROLIZUMAB	RR	TREATMENT
NCT02737787[141]	I SINGLE ARM	WT1 VACCINE	RECURRENT OC/TC/PPC	NIVOLUMAB	DLT	TREATMENT
NCT02764333[142]	II SINGLE ARM	TPIV200/HUFR-1(A MULTI-EPITOPE ANTI-FOLATE RECEPTOR VACCINE)	PLATINUM-RESISTANT OC	DURVALUMAB	ORR	TREATMENT
NCT03100006[104] **(ORION-01)**	IB-IIA SINGLE ARM	OREGOVOMAB VACCINE	RECURRENT OC/TC/PPC (AT LEAST 2 PRIOR LINES)	NIVOLUMAB	AES ORR PFS	TREATMENT
NCT03054298[143]	I NON RANDOM.	huCART-MESO CELLS	PERSISTENT OR RECURRENT OC/TC/ PPC ± PLEURAL EFFUSION	CYCLOPHOSPHAMIDE	AES	TREATMENT

NCT03018405 (THINK)[144]	I–II SINGLE ARM	NKR-2 CELLS	METASTATIC OC	NONE	AES	TREATMENT
NCT02366546[145]	I NON RANDOM.	TCR-T ant NY-ESO-I (TBI-1301)	UNRESECTABLE, REFRACTORY TO STANDARD CHEMOTHERAPY OC.	CYCLOPHOSPHAMIDE FLUDARABINE	AES PHARMACODYNAMIC	TREATMENT
NCT00562640[146]	I SINGLE ARM	AUTOLOGOUS WT1 SPECIFIC T CELLS	PLATINUM RESISTANT RECURRENT OR PERSISTENT ADVANCED OC/PPC/ TC	FILGRASTIM CYCLOPHOSPHAMIDE	AES MEAN TD	TREATMENT

Abbreviations: AES, adverse events; CIK, cytokine-induced killer; DLT, dose-limiting toxicity; FS, free survival; HSCS, hematopoietic stem cells; MTD, maximum tolerated dose; OC, ovarian cancer; ORR, overall response rate; PFS, progression free survival; PPC, primary peritoneal cancer; RCL, replication-competent lentivirus; RP2D, recommended phase 2 dose; RR, response rate; TC, tubal carcinoma; TD, tolerated dose; WT1, Wilms' tumor gene 1.

Nevertheless, they are hard to identify due to their patient-specificity itself and are mainly rare events in a patient cohort.[99]

Anyway vaccination efficacy could be compromised by tumor through the selection of antigen-loss variants (immunoediting) and the up-regulation of immune-checkpoint ligands as an escape mechanism.[100,101] Thus, multiple vaccine interventions that activate de novo immune response may not appear to induce tumor regression.[101] In order to overcome this limit, preclinical studies have observed an effective synergy between tumor vaccines and the ICIs. Hence, combining these two approaches may improve the efficacy in patients that would not have responded to either therapy alone.[102]

As a starting point, a phase Ib trial determined the Recommended Dose for Expansion (RDE)/RP2D of the association of oregovomab vaccine and nivolumab to treat recurrent EOC.[103] Further evaluation of this novel combination is ongoing in a dose expansion cohort.[104]

Ongoing Studies

Immunotherapy in combination with other agents, ACT and vaccine are currently being examined in several ongoing clinical trials for newly diagnosed or recurrent ovarian cancer. Their characteristics are summarized in Tables 5 and 6.

Conclusion

Immunotherapy has transformed cancer treatment in certain solid malignant tumor, such as melanoma and renal cell carcinoma. EOC is considered an "inflamed tumor" that could benefit from these agents. However, data are not universally consistent since the majority of studied patients with OC did not benefit from immunotherapy and there are some issues to be addressed.

First of all, it should be considered that many of clinical trials about immunotherapy and OC involved a population of women with a poor prognosis (advanced FIGO stage, platinum-resistant or -refractory disease, numerous previous chemotherapy lines) in which tumor growth and progression are associated with a more pronounced immune suppression. Hence, it remains still unclear at what phase of disease it would be more appropriate to administer immunotherapy.

Moreover, not all the patients with OC do respond to immunotherapy similarly, thus efforts have recently been being paid worldwide to identify some predictive biomarkers of efficacy, including the expression of antigens.

Regarding that, it is important to clarify that EOC is a tumor with high genetic instability. So the evaluation of molecular markers on the tissue obtained during a previous surgery could exclude patients from accessing target immunotherapies subsequently. Thus, a promising tool could be represented by the liquid biopsy: with a non-invasive approach, it can identify blood-circulating cancer cells and their antigens that represent potential biomarkers.

Another difficulty in administrating immunotherapy concerns the evaluation of the response of solid tumors to this class of agents. As a matter of fact, this treatment may lead to atypical patterns characterized by delayed tumor size reduction, mixed response, or the so-called pseudoprogression: an initial tumor burden increase (growing of lesion size and/or appearance of new lesions) with subsequent decrease[147] probably due to immune cells infiltration. This led to the development of new special criteria to evaluate the efficacy of immunotherapy, the Immune-RECIST. Unfortunately, not all clinicians have already gotten used to understanding and using these criteria,[148] despite the drafting of guidelines in 2017.[149] At last, the possibility of immune-related adverse events (pneumonitis, colitis, thyroiditis and pancreatitis) must be considered.

To sum up, this review does not want to establish whether immunotherapy is active in the treatment of OC but the available results of evidence about combinations, ACT or vaccination are encouraging.

Currently, the administration of immunotherapy in OC is possible only in the context of clinical trials but we expect that ongoing phase II–III trials will untie all these knots, leading to important progress in OC treatment.

Disclosure

The authors report no conflicts of interest in this work.

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