Review Article

Immunotherapy With Checkpoint Inhibitors in Patients With Ovarian Cancer: Still Promising?

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Despite advances in surgery and chemotherapy and the integration of antivascular endothelial growth factor therapy as well as poly(adenosine diphosphate-ribose) polymerase inhibitors into daily clinical practice, epithelial ovarian cancer remains the leading cause of death from gynecological cancer. The incorporation of new therapies with the potential to achieve long-term disease remission is a clear need for patients with ovarian cancer. Immunotherapy with checkpoint inhibitors (CPIs) (antiprogrammed cell death protein 1 [anti-PD-1] or antiprogrammed death-ligand 1 [anti-PD-L1]) has been adopted in several malignancies based on improvements shown with regard to progression-free survival and in particular overall survival. Although there is a solid rationale for the use of CPIs in patients with ovarian cancer, to our knowledge the clinical data presented to date are not very convincing. This article reviews the current data regarding CPIs in patients with ovarian cancer along with the future directions and designs of clinical trials aiming to overcome the low efficacy of CPIs in these individuals. ***Cancer* 2019;125:4616-4622**. © *2019 American Cancer Society*.

KEYWORDS: antiprogrammed cell death protein 1 (anti-PD-1), antiprogrammed death-ligand 1 (anti-PD-L1), checkpoint inhibitor, immunotherapy, immunotherapy combinations, ovarian cancer.

INTRODUCTION

Ovarian cancer is the leading cause of death related to gynecological cancer in industrialized countries. Worldwide, 200,000 new cases are diagnosed and >150,000 women die of the disease every year.[1] A late stage of disease at the time of diagnosis is the major factor accounting for the high mortality associated with epithelial ovarian cancer (EOC). For those patients with an advanced stage of disease, surgery remains a cornerstone of treatment because complete cytoreduction achieved during the primary surgery is the main prognostic factor. However, for those patients for whom an experienced surgical team determines that it is not possible to achieve complete cytoreduction, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery should be indicated.

All patients with advanced disease will require chemotherapy as a complement to surgery. Tri-weekly intravenous paclitaxel and carboplatin with or without the addition of bevacizumab followed by a maintenance period of bevacizumab is the most accepted standard of care. Response to platinum-based chemotherapy usually is high, especially in patients with the high-grade serous subtype that accounts for approximately 85% of all advanced cases due to a deficiency in the homologous recombination DNA repair system detected in approximately 50% of patients (including 20%-22% of patients with BRCA-mutant tumors, either germline or somatic).[2] Unfortunately, up to 70% of patients will develop disease recurrence during the first 3 years depending on their initial International Federation of Gynecology and Obstetrics (FIGO) stage of disease, the presence of residual tumor after upfront surgery, and the use of NACT. For the aforementioned reason, new therapies are needed to improve patient outcomes against this devastating disease.

Immunotherapy with checkpoint inhibitors (CPIs) has revolutionized the treatment of different types of tumors (with melanoma, non-small cell lung cancer, bladder cancer, renal cancer, and head and neck cancer as paradigm shifts), and has provided unprecedented long-term survivorship in diseases for which the median overall survival (OS) was reported to be <12 months only a few years ago.[3] Many immunotherapy modalities also have been studied in patients with ovarian cancer. Although some signals of activity have been demonstrated, progress in immunotherapy for ovarian cancer is lagging behind that for the earlier mentioned diseases. Herein, we review some of the landmark phase 2 and phase 3 trials with antiprogrammed cell death protein 1 (anti-PD-1) and/or antiprogrammed death-ligand 1 (anti-PD-L1) treatment as monotherapy, together with combinations currently being developed in clinical trials.

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Rationale for Immunotherapy With CPIs in Patients With Ovarian Cancer

Role of tumor-infiltrating lymphocytes

In 2003, Zhang et al first reported that CD3-positive (CD3+) tumor-infiltrating lymphocytes (TILs) are associated with an approximately 8-fold improvement in the 5-year survival rate (38% vs 4.5%) in patients with ovarian cancer.[4] Years later, a meta-analysis demonstrated that CD8+ TILs were associated with a 2.2-fold survival advantage.[5]

Prognosis is most strongly linked to intraepithelial TILs (ie, T cells found within malignant tumor epithelium) as opposed to stromal T cells, suggesting that CD8+ TILs mediate their antitumor effects through direct contact with tumor cells. This effect is enhanced by CD4+ and CD20+ TILs but diminished by regulatory T cells (Tregs), as demonstrated by some authors.[6,7]

Role of PD-L1 expression in patients with ovarian cancer

The ligands for PD-1, an immunoinhibitory receptor belonging to the CD28 family of receptors, are PD-L1 and PD-L2. It has been proposed that aberrant expression of PD-1 ligands on tumor cells impairs antitumor immunity, resulting in immune evasion of tumor cells.

In 2007, Hamanishi et al reported a 68% rate of PD-L1 expression in 70 patients with ovarian cancer.[8] Patients with a higher expression of PD-L1 were found to have a significantly poorer prognosis compared with patients with lower expression. The 5-year survival rate for patients with high-expressing versus low-expressing PD-L1 tumors was 52.6% ± 7.7% versus 80.2% ± 8.9% ($P = .016$).

A significant inverse correlation was observed between PD-L1 expression and the intraepithelial CD8+ T-lymphocyte count, suggesting that PD-L1 on tumor cells directly suppresses antitumor CD8+ T cells. A multivariate analysis demonstrated that the expression of PD-L1 on tumor cells and intraepithelial CD8+ T-lymphocyte counts are independent prognostic factors.

However, to the best of our knowledge, the most current data regarding the role of PD-L1 as a prognostic factor in patients with ovarian cancer have been contradictory. Although some authors[9] have confirmed the observation by Hamanishi et al,[8] others have shown exactly the opposite.[10-12] These controversial results have raised several questions regarding the method of determination, which types of cells should be scored for surface PD-L1 expression (tumor cell vs immune infiltrate vs both), and the best cutoff percentage of scored cells with which to determine PD-L1 positivity.

Anti-PD-1 and anti-PD-L1 therapy in patients with ovarian cancer

PD-1 and/or PD-L1 blockade was proposed as a potential strategy for restoring antitumor immunity in patients with ovarian cancer. Several antibodies directed against PD-1 and PD-L1 have been developed and were tested clinically in patients with ovarian cancer. Data regarding the activity in early phase 1/2 trials with nivolumab, pembrolizumab, avelumab, and atezolizumab have been reported and are summarized in Table 1.[13-16] In a phase 2 study with 2 dose levels, nivolumab (anti-PD-1) demonstrated 3 responses (2 complete responses [CRs] and 1 partial response [PR]) among 20 patients with platinum-resistant EOC. It is interesting to note that 2 of the responses were long lasting and there was no relationship noted between response and PD-L1 expression.[13] Treatment with pembrolizumab (anti-PD-1) achieved 3 responses (1 CR and 2 PRs) among 26 patients included in the KEYNOTE-028 trial who were not candidates for standard therapy, and whose tumors expressed PD-L1 in 1%. The response duration was >24 weeks.[14] Treatment with avelumab (anti-PD-L1) was found to be associated with an overall response rate (ORR) of 9.6% among 125 patients with refractory or recurrent EOC who developed disease progression within 6 months or after second-line or third-line therapy. Responses were observed in patients with PD-L1-positive (12.3%) and PD-L1-negative (5.9%) tumors based on a threshold of ≥1%.[15] Finally, atezolizumab (anti-PD-L1) demonstrated a response in 2 of 8 heavily pretreated patients.[16]

All these trials shared the following common issues: 1) they were developed in a heavily pretreated population; 2) the ORR was low (10%-15%), but long-term responders were observed[13-15]; and 3) PD-L1 expression was not a clear predictive factor.

To the best of our knowledge, the largest trial published to date using CPIs as monotherapy for ovarian cancer is the KEYNOTE-100 trial. This study included 376 patients with recurrent, nonmucinous ovarian cancer who were treated with pembrolizumab at a dose of 200 mg intravenously every 3 weeks in 2 different cohorts. In cohort A (285 patients), patients who received 1 to 3 prior lines and had a treatment-free interval of 3 to 12 months were included. Conversely, patients in cohort B (91 patients) were allowed 4 to 6 prior lines of treatment and a treatment-free interval >3 months. The primary endpoint was the ORR, which was found to be 7.4% in cohort A and 9.9% in cohort B. The median duration of response was 8.2 months in cohort A and was not reached in cohort B. The median progression-free survival (PFS) was 2.1 months in both cohorts.[17]

TABLE 1. Early Phase 1/2 Trials With Anti-PD-1 and/or Anti-PD-L1 in Patients With EOC

	Nivolumab[13]	Pembrolizumab (KEYNOTE-028)[14]	Avelumab (Phase 1b)[15]	Atezolizumab[16]
Population	20 PTR EOC 55% received ≥4 lines	26 Phase 1b 73% received ≥3 lines	125 PTR-EOC 65% received ≥3 lines	12 Phase 1b 58% received >6 lines
Global ORR	15% (10% CR rate)	11.5% (4% CR rate)	9.6% (0.8% CR rate)	25% (2/8)
Cutoff PD-L1 value	IHC 2/3+ (80%)	≥1% (100%)	≥1% (77%)	IHC 2/3+ (83%)
PD-L1- ORR	1/4 (25%)	–	7.9% (3/38)	–
PD-L1+ ORR	2/16 (12.5%)	3/26 (11.5%)	11.8% (9/76)	–

Abbreviations: +, positive; -, negative; CR, complete response; EOC, epithelial ovarian cancer; IHC, imunohistochemistry; ORR, overall response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTR, platinum-resistant.

The second coprimary endpoint was ORR according to PD-L1 expression measured as the combined positive score (CPS). The CPS is the rate of the total number of PD-L1-positive cells (tumor, lymphocytes, or macrophages) per the total number of cells. In the confirmation set, the ORR for both cohorts together was 5% for a CPS <1, 10.2% for a CPS ≥1, and 17.1% for a CPS ≥10. These values demonstrate how PD-L1 expression can distinguish a group of patients with a higher response to pembrolizumab. However, PD-L1 could not be considered as a predictive biomarker based exclusively on these findings due to the nonrelevant differences in the ORR and the fact that PD-L1 was determined in archival tissue. Currently, to the best of our knowledge it is not known whether there is a good correlation between PD-L1 expression at the time of diagnosis and at disease recurrence, and the use of PD-L1 in archival tissue may have some limitations.

Why do patients with ovarian cancer not respond well to treatment with CPIs alone? And why does PD-L1 expression not distinguish responding patients adequately? Both questions appear to point to an important issue for immunotherapy for patients with ovarian cancer, namely, the frequency of well-known predictive biomarkers for response to CPIs. Basically, 2 types of biomarkers for response to CPIs have been identified: 1) those related to the tumor neoantigen burden, essentially the tumor mutational burden (TMB) and microsatellite instability; and 2) those indicative of a T-cell-inflamed tumor microenvironment, including PD-L1 expression on the tumor and immune cells and gene signatures of activated T cells (ie, T-cell–inflamed gene expression profile [GEP]).

In a recent article, the probability of response to pembrolizumab in the KEYNOTE series was analyzed, and the authors concluded that the combination of high TMB and high GEP was associated with a higher ORR and longer PFS. In a subsequent estimation presented by the authors in the same article, it was shown that serous ovarian cancers were composed mainly of tumors that had low TMB and low GEP (70%-75%) or low TMB and high GEP (20%-25%), and <5% were found to have high TMB. This observation could be one of the explanations for the low response rate to CPIs noted among patients with ovarian cancer.[18]

Future Directions With Anti-PD-1 and/or Anti-PD-L1 Inhibitors in Patients With Ovarian Cancer

A better knowledge of the tumor microenvironment and its relationship with ovarian cancer cells is key to developing effective immunotherapy strategies. Chen and Mellman described 3 main cancer immune phenotypes, immune desert, immune inflamed, and immune excluded, that could explain why some tumors do not respond to CPIs and, more important, could provide ideas concerning how to combine CPIs to be more effective.[19] Essentially, immune-desert and immune-excluded tumors are cold tumors, in contrast to immune-inflamed tumors, which are characterized by the presence of CD4 and CD8 T cells in the tumor parenchyma very close to the tumor cells. Immune-inflamed tumors do respond more often to anti-PD-L1 and/or anti-PD-1 inhibitors.

Combination of CPIs and chemotherapy

Immune-desert ovarian cancer is characterized by the absence of immune cells both in the tumor and stroma. This phenotype most likely reflects the absence of a prior immune response. Therefore, actions that could increase tumor antigen release potentially may stimulate an immune response and transform this noninflamed phenotype into an inflamed one.

Chemotherapy may be synergistic in combination with immunotherapy, through its ability to increase tumor immunogenicity. Emerging evidence has indicated that chemotherapy promotes antigen release and may enhance tumor-specific T-cell activation when combined with immune checkpoint blockade.

In addition, a new apoptotic cell death modality that elicits antigen-specific immune responses against dead cell antigens has been identified. This type of cell death has been termed "immunogenic cell death" and initially was characterized within the context of anticancer chemotherapy. Chemotherapy-induced cell death generates specific changes in cell surface structures and the release of soluble mediators that allow dendritic cells (DCs) to detect the dying cell and initiate an antitumor immune response. During this process, DCs engulf parts of the stressed or dying cell and incorporate antigenic peptides into major histocompatibility complexes for presentation to T cells.[20,21] Moreover, some chemotherapies have been shown to reduce the number of circulating Tregs, which are a key component in immunosuppression.

Based on this background, 2 phase 3 trials have explored the addition of avelumab to standard chemotherapy in frontline treatment (Avelumab in Previously Untreated Patients With Epithelial Ovarian Cancer [JAVELIN 100]) and in cases of platinum-resistant disease recurrence (JAVELIN 200).

The JAVELIN 200 trial included 566 patients with recurrent platinum-resistant or platinum-refractory ovarian, fallopian tube, or peritoneal cancer who were treated with up to 3 prior lines of chemotherapy and had received no prior therapy for platinum-resistant disease who were randomized to either avelumab at a dose of 10 mg/kg every 2 weeks (188 patients), avelumab at a dose of 10 mg/kg every 2 weeks plus pegylated liposomal doxorubicin (PLD) at a dose of 40 mg/m^2 every 4 weeks (188 patients), or PLD at a dose of 40 mg/m^2 every 4 weeks (190 patients).[22] Unfortunately, the addition of avelumab to PLD did not significantly prolong either the median PFS (3.5 months vs 3.7 months) or the median OS (13.1 months vs 15.7 months) (hazard ratio, 0.89; 95% CI, 0.74-1.24). One of the prespecified areas for analysis was the correlation of PD-L1 in archival tumors as determined by the SP263 antibody with the outcome. Globally, approximately 57% of the 507 patients with available tissue were found to be positive for PD-L1. A trend toward a benefit in PFS and OS with the combination of avelumab and PLD was observed in patients with PD-L1-positive disease, thereby generating the hypothesis that PD-L1 could be a potential biomarker for anti-PD-L1 inhibitors. This hypothesis should be validated prospectively in other randomized clinical trials.

The Avelumab in Previously Untreated Patients With Epithelial Ovarian Cancer (JAVELIN OVARIAN 100) study was stopped in December 2018 after a planned interim analysis demonstrated futility of efficacy. The Avelumab and Talazoparib in Untreated Advanced Ovarian Cancer (JAVELIN OVARIAN PARP 100) study, a phase 3 trial assessing the potential of avelumab in combination with chemotherapy followed by maintenance therapy with avelumab and talazoparib in treatment-naive patients with advanced ovarian cancer, continued until March 2019. The study was discontinued after enrolling 79 patients due to the lack of benefit with avelumab for the frontline treatment of ovarian cancer in an unselected patient population.

Combination of CPIs with antiangiogenic therapy

The immune-excluded phenotype is characterized by the presence of abundant immune cells. However, the immune cells do not penetrate into the parenchyma but instead are retained within the stroma. Accordingly, one of the options to make these tumors inflamed (hot) is to facilitate the ability of T cells to enter the tumor parenchyma.

Vascular endothelial growth factor has been shown to have immunosuppressive properties, including the inhibition of DC differentiation, induction of PD-L1 expression, activation of Tregs, and reduction of T-cell endothelial adhesion in addition to intratumoral migration. Based on this background, the blockade of vascular endothelial growth factor has been proposed as a way to promote the activity of CPIs.

At the European Society for Medical Oncology 2018 Congress, held October 19 to 23, 2018, in Munich, Germany, Liu et al presented a phase 2 trial of the combination of nivolumab at a flat dose of 240 mg and bevacizumab at a dose of 10 mg/kg every 2 weeks until disease progression that included 38 patients with recurrent ovarian cancer.[23] In 20 patients with platinum-sensitive disease, the ORR was 40%, and was 16.7% among 18 patients with platinum-resistant disease. Durable responses or prolonged stable disease were observed, even among patients with platinum-resistant disease. The median PFS was 8.1 months in the entire study population (9.4 months in patients with platinum-sensitive disease and 5.3 months in patients with platinum-resistant disease).

A phase 1 study in a 3+3 dose escalation format by Lee et al in which 26 patients were enrolled compared the combination of CPIs and durvalumab with a PARPi (olaparib) or antiangiogenic therapy (cediranib). A total of 19 patients with ovarian cancer were included, 12 of whom had received previous bevacizumab and 6 of whom had received a previous PARPi. The study was able to establish the recommended phase 2 dose of both

combinations as well as provide evidence of the durable activity of both combinations in heavily pretreated patients.[24]

Two ongoing, randomized, phase 3 clinical trials are assessing the role of atezolizumab plus bevacizumab in patients with ovarian cancer in 2 different settings: the frontline setting (Gynecologic Oncology Group [GOG] 3015/European Network for Gynaecological Oncological Trial [ENGOT] OV-39/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]) and within the setting of first platinum-sensitive disease recurrence (ENGOT OV-29/Atezolizumab vs Placebo Phase III Study in Late Relapse Ovarian Cancer Treated With Chemotherapy+Bevacizumab [ATALANTE] trial).

In the GOG 3015/ENGOT OV-39/ IMagyn050 trial, patients with FIGO stage III and macroscopic residual disease after undergoing primary debulking surgery or stage IV disease received standard treatment with paclitaxel, carboplatin, and bevacizumab followed by maintenance bevacizumab and were randomized to atezolizumab at a dose of 800 mg every 3 weeks or placebo given during chemotherapy and in the maintenance phase. NACT was allowed but was limited to a specific percentage of patients. Patients included in this trial were stratified according to PD-L1 status, stage of disease, use of NACT, and ECOG performance status. The study closed in March 2019, and data currently are maturing.

The ENGOT OV-29/ATALANTE trial is a randomized trial of patients with recurrent ovarian cancer who are limited to having received ≤2 prior lines of treatment and having a platinum-free interval of >6 months. Patients included in the ENGOT OV-29/ATALANTE trial receive a standard carboplatin combination, which, according to the choice of the physician, can be paclitaxel, PLD, or gemcitabine; this combination is associated with bevacizumab followed by maintenance bevacizumab until disease progression, with placebo or atezolizumab also administered until disease progression. In this study, a recent biopsy is needed for stratification according to PD-L1 expression.

Combination of CPIs and PARPi

The rationale for the combination of PARPi with CPIs is based on multiple observations. Some preclinical models have demonstrated the upregulation of PD-L1 after exposure to PARPi.[25] In addition, treatment with niraparib was found to provide evidence of increasing activity of the stimulator of interferon genes and interferon pathways, thereby enhancing intratumoral immune cell infiltration and upregulating granzyme B–positive T cells.[26,27]

This biological observation has been tested clinically in 3 phase 2 studies. The Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors (MEDIOLA) trial included 32 patients with germ-line BRCA-mutant and platinum-sensitive, recurrent ovarian, fallopian tube, or peritoneal cancer who were treated with durvalumab and olaparib and achieved a significant ORR of 63% (19% CR rate) from a chemotherapy-free regimen.[28] The same combination was studied in a population of 32 patients, with the majority of patients with platinum-resistant disease recurrences (83%) achieving an ORR of 14%.[29] Finally, the Niraparib in Combination With Pembrolizumab in Patients With Triple-negative Breast Cancer or Ovarian Cancer (TOPACIO)/KEYNOTE-162 trial included 60 pretreated patients with recurrent ovarian, fallopian tube, or peritoneal cancer, 48% of whom had platinum-resistant disease, 27% of whom had platinum-refractory disease, and 24% of whom were not eligible for further platinum treatment. The majority of the patients had tumor BRCA wild-type disease (79%). The ORR was 18% (5% CR rate and 13% PR rate) and the median duration of response had not been reached at the time of the data cutoff (range, 4.2 to ≥14.5 months).[30]

The combination of PARPi and CPIs is considered a promising strategy in patients with ovarian cancer and is being explored in patients with recurrent disease for whom platinum is an option (ENGOT-OV41/GEICO 69-O/ Platinum-based Chemotherapy With Atezolizumab and Niraparib in Patients With Recurrent Ovarian Cancer [ANITA]) and in 4 randomized trials (Durvalumab Treatment in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib Treatment in Advanced Ovarian Cancer Patients [DUO-O]/ENGOT OV-46; ENGOT OV-43; A Randomized, Double-Blind, Phase 3 Comparison of Platinum-Based Therapy with Dostarlimab (TSR-042) and Niraparib Versus Standard of Care Platinum-Based Therapy as First-line Treatment of Stage III or IV Nonmucinous Epithelial Ovarian Cancers [FIRST]/ENGOT OV-44; and A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy [ATHENA]/GOG 3020/ENGOT OV-45) in the upfront setting. The trial designs are summarized in Table 2.

TABLE 2. Summary of Phase 3 Clinical Trials in the Frontline Treatment of Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer Incorporating Anti-PD-1 and/or Anti-PD-L1 and PARP Inhibitors

Trial	Setting	Patient Selection	Treatment Arms
ENGOT OV-46/AGO leaded/DUO-O	Frontline	tBRCA nonmutated PDS or IDS Any residual LGSOC excluded	CP-Bev-placebo-placebo CP-Bev-durvalumab-placebo CP-Bev-durvalumab-olaparib
ENGOT OV-43/BCOG leaded/	Frontline	tBRCA nonmutated Any histotype PDS or IDS Any residual Bev optional	CP-placebo-placebo CP-Pembro-placebo CP-Pembro-olaparib
ENGOT OV-44/GINECO leaded/FIRST	Frontline	PDS (high risk) or IDS Bev optional Mucinous excluded	tBRCA mutated –CP-placebo-niraparib –CP-TSR-042-niraparib tBRCA wild-type –CP-placebo-placebo –CP-placebo-niraparib –CP-TSR-042-Niraparib
ATHENA/GOG3020/ENGOT OV-45	Maintenance after frontline	Stage III-IV and high grade PDS or IDS Response to platinum	Rucaparib-nivolumab Rucaparib-placebo Nivolumab-placebo Placebo-placebo

Abbreviations: AGO, Arbeitsgemeinschaft Gynakologische Onkologie (Association of Gynecological Oncology); ATHENA, A Multicenter, Randomized, Double-Blind, Placebo- Controlled Phase 3 Study in Ovarian Cancer Patients Evaluating Rucaparib and Nivolumab as Maintenance Treatment Following Response to Front-Line Platinum-Based Chemotherapy; BCOG, Belgium and Luxembourg Gynaecological Oncology Group; Bev: bevacizumab; CP, paclitaxel and carboplatin; DUO-O, Durvalumab Treatment in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib Treatment in Advanced Ovarian Cancer Patients; ENGOT, European Network for Gynaecological Oncological Trial groups; FIRST, A Randomized, Double-Blind, Phase 3 Comparison of Platinum-Based Therapy with Dostarlimab (TSR-042) and Niraparib Versus Standard of Care Platinum-Based Therapy as First-line Treatment of Stage III or IV Nonmucinous Epithelial Ovarian Cancers; GINECO, Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens et du sein (Group of National Investigators for Ovarian Cancer and Breast Cancer Study); GOG, Gynecologic Oncology Group; IDS, interval debulking surgery; LGSOC, low-grade serous ovarian cancer; PARP, poly(adenosine diphosphate-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDS, primary debulking surgery; Pembro, pembrolizumab; tBRCA, tumor tissue BRCA.

ENGOT-OV41/GEICO 69-O/ANITA is an ongoing trial that includes patients with recurrent ovarian, fallopian tube, or peritoneal cancer for whom platinum is an option, and requires a platinum-free interval of >6 months and the receipt of ≤2 prior lines of therapy. Patients are randomized to platinum-based combination chemotherapy according to physician choice (selection between paclitaxel, PLD, or gemcitabine) with either atezolizumab or an atezolizumab placebo. Patients who achieve a CR, PR, or stable disease after chemotherapy can initiate maintenance with niraparib with atezolizumab or an atezolizumab placebo similar to what they were receiving during chemotherapy. Patients included in the trial are randomized according to the platinum doublet selected, their platinum-free interval (6-12 months vs >12 months), BRCA status (mutated vs nonmutated), and PD-L1 status (positive or negative).

Conclusions

Despite there being a solid rationale for its use, anti-PD-L1 and/or anti-PD-1 therapy in patients with EOC clinical data with CPIs used in monotherapy have not been very convincing to date. Nevertheless, long-term responders have been observed in all the single trials, leading to the conclusion that better biomarkers for patient selection clearly are needed. Therefore, the highest expectation currently is focused on the combination of CPIs with antiangiogenic agents and/or PARPi. These combinations are expected to convert cold tumors, either immune desert or immune excluded, into inflamed tumors with a better possibility of responding to anti-PD-L1and/or anti-PD-1 therapy. To the best of our knowledge, several randomized clinical trials currently are exploring these combinations in different settings and will provide relevant information regarding how to better use CPIs in patients with ovarian cancer. In addition, these trials offer an extraordinary opportunity for academic translational research projects that could help to better identify long-term responders.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136:E359-E386.
2. Colombo N, Sessa C, du Bois A, et al; ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol*. 2019;30:672-705.
3. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. *JAMA Netw Open*. 2019;2:e192535.
4. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003;348:203-213.
5. Hwang WT, Adams SF, Tahirovic E, Hagemann IS, Coukos G. Prognostic significance of tumor-infiltrating T cells in ovarian cancer: a meta-analysis. *Gynecol Oncol*. 2012;124:192-198.
6. deLeeuw RJ, Kroeger DR, Kost SE, Chang PP, Webb JR, Nelson BH. CD25 identifies a subset of CD4+FoxP3-TIL that are exhausted yet prognostically favorable in human ovarian cancer. *Cancer Immunol Res*. 2015;3:245-253.
7. Nielsen JS, Sahota RA, Milne K, et al. CD20+ tumor-infiltrating lymphocytes have an atypical CD27- memory phenotype and together with CD8+ T cells promote favorable prognosis in ovarian cancer. *Clin Cancer Res*. 2012;18:3281-3292.
8. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A*. 2007;104:3360-3365.
9. Chatterjee J, Dai W, Aziz NHA, et al. Clinical use of programmed cell death-1 and its ligand expression as discriminatory and predictive markers in ovarian cancer. *Clin Cancer Res*. 2017;23:3453-3460.
10. Darb-Esfahani S, Kunze CA, Kulbe H, et al. Prognostic impact of programmed cell death-1 (PD-1) and PD-ligand 1 (PD-L1) expression in cancer cells and tumor-infiltrating lymphocytes in ovarian high grade serous carcinoma. *Oncotarget*. 2016;7:1486-1499.
11. Aust S, Felix S, Auer K, et al. Absence of PD-L1 on tumor cells is associated with reduced MHC I expression and PD-L1 expression increases in recurrent serous ovarian cancer. *Sci Rep*. 2017;7:42929.
12. Webb JR, Milne K, Kroeger DR, Nelson BH. PD-L1 expression is associated with tumor-infiltrating T cells and favorable prognosis in high-grade serous ovarian cancer. *Gynecol Oncol*. 2016;141:293-302.
13. Hamanishi J, Mandai M, Ikeda T, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. *J Clin Oncol*. 2015;33:4015-4022.
14. Varga A, Piha-Paul S, Ott PA, et al. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: analysis of KEYNOTE-028. *Gynecol Oncol*. 2019;152:243-250.
15. Disis ML, Taylor MH, Kelly K, et al. Efficacy and safety of avelumab for patients with recurrent or refractory ovarian cancer: phase 1b results from the JAVELIN solid tumor trial. *JAMA Oncol*. 2019;5:393-401.
16. Infante JR, Braiteh F, Emens LA, et al. Safety, clinical activity and biomarkers of atezolizumab (atezo) in advanced ovarian cancer (OC) [abstract]. *Ann Oncol*. 2016;27(suppl 6):871.
17. Matulonis UA, Shapira-Frommer R, Santin AD, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the Phase 2 KEYNOTE-100 study. *Ann Oncol*. Published online May 2, 2019. doi:10.1093/annonc/mdz135
18. Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. *Science*. 2018;362(6411).
19. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature*. 2017;541:321-330.
20. Gebremeskel S, Johnston B. Concepts and mechanisms underlying chemotherapy induced immunogenic cell death: impact on clinical studies and considerations for combined therapies. *Oncotarget*. 2015;6:41600-41619.
21. Cook AM, Lesterhuis WJ, Nowak AK, Lake RA. Chemotherapy and immunotherapy: mapping the road ahead. *Curr Opin Immunol*. 2016;39:23-29.
22. Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase III JAVELIN Ovarian 200 trial. Abstract presented at: 50th Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 16–19, 2019; Honolulu, HI.
23. Liu J, Herold C, Luo W, et al. A phase 2 trial of combination nivolumab and bevacizumab in recurrent ovarian cancer. *Ann Oncol*. 2018;29(suppl 8):viii332-viii358. doi:10.1093/annonc/mdy285
24. Lee JM, Cimino-Mathews A, Peer CJ, et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women's cancers: a dose-escalation, phase I study. *J Clin Oncol*. 2017;35:2193-2202.
25. Jiao S, Xia W, Yamaguchi H, et al. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. *Clin Cancer Res*. 2017;23:3711-3720.
26. Shen J, Zhao W, Ju Z, et al. PARPi triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness. *Cancer Res*. 2019;79:311-319. doi:10.1158/0008-5472.CAN-18-1003
27. Wang Z, Sun K, Xiao Y, et al. Niraparib activates interferon signaling and potentiates anti-PD-1 antibody efficacy in tumor models. *Sci Rep*. 2019;9:1853. doi:10.1038/s41598-019-38534-6
28. Drew Y, de Jongeb M, Hongc SH, et al. An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): results in germline BRCA-mutated (gBRCAm) platinum-sensitive relapsed (PSR) ovarian cancer (OC). *Gynecol Oncol*. 2018;(suppl 1):246-247.
29. Lee J, Annunziata CM, Houston N, et al. A phase 2 study of durvalumab, a PD-L1 inhibitor and olaparib in recurrent ovarian cancer (OvCa). *Ann Oncol*. 2018;29(suppl 8):viii332-viii358.
30. Konstantinopoulos PA, Waggoner S, Vidal GA, et al. Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma. *JAMA Oncol*. Published online June 13, 2019. doi:10.1001/jamaoncol.2019.1048