Immunotherapy for Ovarian Cancer

Rebecca Porter, MD, PhD, and Ursula A. Matulonis, MD
Division of Gynecologic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

Corresponding author:
Rebecca Porter, MD, PhD
Division of Gynecologic Oncology
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
Tel: 617-632-2334
Fax: 617-632-3479
Email: Rebecca_Porter@dfci.harvard.edu

Abstract: Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, with poor survival rates among patients who have advanced disease despite recent significant advances in therapy, including therapy targeting the homologous recombination pathway. Evidence that cell-mediated antitumor immunity, as well as documented programmed death ligand 1 expression, is correlated with improved survival in EOC garnered early optimism regarding the utility of immune checkpoint blockade (ICB) in ovarian cancer. However, the results of multiple clinical trials investigating ICB have revealed very low levels of activity of single-agent immune checkpoint inhibitors, and the testing of combination therapies has not yet identified any combinations with robust activity in a significant proportion of patients who have EOC. In this review, we summarize the results of the major studies of ICB monotherapy and combinations; review novel combinations under investigation, including ICB with cellular therapies; and discuss potential candidate biomarkers for improving the selection of patients who may respond to ICB.

Keywords
Checkpoint inhibitors, immunotherapy, newly diagnosed, ovarian cancer, recurrent

Epithelial Ovarian Cancer

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy. Although surgery and platinum-based chemotherapy effectively induce remission,[1] most women ultimately succumb to recurrent and therapy-resistant disease. Women with platinum-resistant ovarian cancer (PROC) have a median overall survival (OS) of less than 16 months, even with chemotherapy and bevacizumab,[2] so that novel therapeutic strategies are needed. A great deal of interest has been shown in utilizing immunotherapy approaches in EOC, given the discovery nearly 2 decades ago that tumor-infiltrating lymphocytes (TILs) are detected in approximately 50% of these tumors, and their presence is associated with longer survival.[3,4] Tumors with TILs have higher levels of intratumoral lymphocyte-activating cytokines and interferon gamma (IFN-γ), further supporting the importance of antitumor immunity in this disease.[3,5] EOC TILs exhibit cytotoxic activity against autologous tumor-associated antigens in vitro[6]; however, it is well appreciated that a plethora of other cellular and noncellular factors in the tumor microenvironment (TME) interact to determine the overall tumor immune response.

In recent years, immune checkpoint blockade (ICB) has shifted the treatment paradigm in certain solid tumors and hematologic

Table 1. Selected Key Clinical Trials With Single-Agent and Combination ICB in EOC

Approach	Trial	Study Drug(s)	Population	ORR, %	mPFS, mo
Single-agent ICB	JAVELIN (phase 1b ovarian expansion)[12]	Avelumab	Recurrent PROC	9.6	1-y PFS rate: 10%
	KEYNOTE-100[10,11]	Pembrolizumab	Pembrolizumab Recurrent EOC (PSOC + PROC)	8.0	2.1
	NINJA[14]	Nivolumab	Recurrent PROC	7.6	2.0
ICB + chemotherapy	JAVELIN-100[38]	C/P	Newly diagnosed EOC		NR
		C/P → avelumab			16.8 (HR, 1.43)
		C/P + avelumab → avelumab			18.1 (HR, 1.14)
	JAVELIN-200[42]	PLD	Recurrent PROC		3.5
		Avelumab			1.9 (HR, 1.68)
		PLD + avelumab			3.7 (HR, 0.78; NSS)
ICB + anti-angiogenesis	NIVO-BEV[45]	Nivolumab + bevacizumab	Recurrent EOC (PSOC + PROC)	29.9	8.0
			PSOC	40	
			PROC	17	
	LEAP-005[50]	Pembrolizumab + lenvatinib	Recurrent OC	29	
ICB + PARPi	MEDIOLA[56,57]	Durvalumab + olaparib	Recurrent PSOC: *BRCA*wt *BRCA*m	*BRCA*wt: 31.3	
				*BRCA*m: 72	11.0
	TOPACIO[58]	Pembrolizumab + niraparib	PROC (80% *BRCA*wt)	18	
Dual ICB (PD-1 + CTLA-4)	NRG-GY003[63]	Nivolumab	Recurrent EOC (PSOC + PROC)	12.2	2.0
		Nivolumab + ipilimumab		31.4	3.9
Triplet combinations	MEDIOLA[56]	Durvalumab + bev + olaparib	Recurrent PSOC, *BRCA*wt	77.4	
	Magyn050[39]	C/P/bev	Newly diagnosed EOC		ITT: 18.4; PD-L1+: 18.5
		C/P/bev + atezolizumab			ITT: 19.5; PD-L1+: 20.8

bev, bevacizumab; *BRCA*m, B*RCA* mutated; *BRCA*wt, *BRCA* wild-type; C/P, carboplatin and paclitaxel; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; EOC, epithelial ovarian cancer; HR, hazard ratio; ICB, immune checkpoint blockade; ITT, intent to treat; mPFS, median progression-free survival; NR, not reported; NSS, not statistically significant; ORR, overall response rate; PARPi, poly(ADP-ribose) polymerase inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant ovarian cancer; PSOC, platinum-sensitive ovarian cancer; y, year.

malignancies.[7,8] Pembrolizumab (Keytruda, Merck) is now approved for patients with metastatic or unresectable cancers that have progressed following other treatment, who have no satisfactory alternative treatment options, and who have tumors that exhibit (1) mismatch repair deficiency (MMRd) or high microsatellite instability (MSI-H) or (2) a high tumor mutational burden (TMB). However, outside these disease-agnostic indications, which are unfortunately rare in EOC and even rarer in certain histologic subtypes, such as low-grade endometrioid, mucinous, and clear cell carcinomas, ovarian cancer remains a disease with no ICB-specific approvals. To date, the results of multiple studies of ICB therapy in newly diagnosed and recurrent EOC have been disappointing. Here, we review the results from ICB clinical trials in EOC to date, barriers limiting the success of single-agent

ICB, the strategies currently under investigation to overcome these challenges, and potential biomarkers to guide the clinical development of ICB in ovarian cancer.

Single-Agent Immune Checkpoint Blockade Experience in EOC

Several trials testing the efficacy of single-agent ICB have been reported in EOC, initially in recurrent cancers. All of these trials demonstrated very modest activity (Table 1). Several of these ICB monotherapy and combination trials have included evaluations of programmed death ligand 1 (PD-L1) expression—measured in either tumor and immune cells with the combined positive score (CPS)[9] or in tumor cells alone with the tumor proportion score (TPS)—or alternative assessments of the immune phenotype of tumors, such as the inflamed gene expression profile (GEP)[10]; these are discussed in more detail within the section on biomarkers below. In the ovarian cancer cohort of the phase 1b KEYNOTE-028 study, which included 26 patients with PD-L1–expressing recurrent ovarian cancer, the objective response rate (ORR) with pembrolizumab was 11.5% even though this was a biomarker-selected population.[11] The phase 2 KEYNOTE-100[12] trial examined the efficacy of pembrolizumab in women with recurrent EOC, who were evaluated in 2 separate cohorts according to number of prior lines of therapy. The ORR with pembrolizumab across the 2 cohorts was 8.0%, with a median progression-free survival (PFS) of 2.1 months.[12,13] Similarly, in the phase 1b ovarian expansion cohort of the JAVELIN[14] trial, which tested the efficacy of avelumab (Bavencio, EMD Serono/Pfizer) in recurrent PROC, the ORR was 9.6%, with a 1-year PFS rate of 10%.[14] Single-agent nivolumab (Opdivo, Bristol Myers Squibb) has also been studied; initially promising activity was observed in a small phase 2 study of women with PROC, who had an ORR of 15%, including 2 durable complete responses.[15] More recently, the phase 3 NINJA trial compared the efficacy and safety of nivolumab monotherapy vs chemotherapy in women with PROC.[16] The trial attempted to answer definitively whether single-agent ICB should be used for women with PROC, especially given that these patients typically have high-grade serous tumors that are microsatellite stable (MSS) with a low TMB. Nivolumab ICB was inferior to nonplatinum chemotherapy, with significantly worse PFS and a nonsignificantly lower ORR (7.6% vs 13.2%; P=.191). Notably, in the patients who did respond to treatment, the median duration of response was 18.7 months (95% CI, 2.5-not evaluable) in those who received chemotherapy vs 7.4 months (95% CI, 3.0-10.3) in those who received nivolumab. Importantly, ICB trials in other tumor types have reported unbalanced effects on PFS and OS, with modest improvements in PFS but more significant extensions of OS,[17] suggesting a potential effect on the immune microenvironment that translates to delayed but longer-term responses. These observations underscore the importance of both long-term follow-up in studies and continued efforts to identify populations of patients with EOC who may be likely to benefit from ICB (further discussed below). In addition to programmed death 1 (PD-1)/PD-L1–directed therapies, targeting of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) has also been investigated in EOC; a phase 2 trial testing ipilimumab (Yervoy, Bristol Myers Squibb) monotherapy in women with recurrent platinum-sensitive ovarian cancer (PSOC) reported an ORR of 10.3%, but with poor tolerability (NCT01611558). As discussed below, anti–CTLA-4 therapy has more recently been investigated in combination with anti–PD-1 therapy in EOC. Taken together, these studies demonstrate that ICB has the potential to induce durable responses in only a very limited subset of patients with EOC, and that ICB should not be used as monotherapy in EOC without a further definition of reliable biomarkers to delineate the appropriate subpopulations, clinical settings, and/or combinations that allow improved activity.

Combination Immune Checkpoint Blockade

Anti–PD-1/PD-L1 agents exert their effects by targeting the final step of the well-described cancer immunity cycle.[18] Although these agents have shown great potential to revolutionize therapy in some cancer types, their success is still limited by both primary and acquired resistance,[19] and it is now clear that this approach is insufficient to induce effective antitumor immunity in EOC. A detailed understanding of the mechanisms driving the low response rates to ICB in EOC is rapidly being unveiled, including both tumor cell–intrinsic and –extrinsic characteristics that can promote cancer progression and limit the efficacy of anti–PD-1/PD-L1 therapy. Cell autonomous mechanisms limiting responses in EOC include a relatively low TMB, lack of an inflamed GEP,[10] suppressed major histocompatibility complex (MHC) protein expression, and/or antigenic loss.[20] Specific somatic alterations such as activating mutations in the phosphatidylinositol 3-kinase (PI3K)/AKT pathway and phosphatase and tensin homolog (PTEN) loss, as well as those increasing Wnt signaling, have also been associated with immune cell exclusion, suppression of T-cell cytotoxic function, lack of antitumor immunity, and poor prognosis in EOC.[21-25] In addition, the unique TME within the peritoneal cavity permits interactions between tumor and immune cells, as well as fibroblasts[26] and adipocytes,[27] and dampens the response to ICB

in EOC via many mechanisms.[28] Innate and adaptive immune cells, including regulatory T cells (Tregs),[29] M2-polarized tumor-associated macrophages (TAMs),[30] tumor-associated neutrophils (TANs), and myeloid-derived suppressive cells (MDSCs),[31] all contribute by elaborating cytokines and inflammatory factors that limit T-cell homing and suppress T-cell effector function, upregulate inhibitory receptors on tumor and immune cells, and alter dendritic cell function and maturation,[32,33] overall shifting the balance to a tumor-permissive environment.[34] Given the multiple co-occurring mechanisms of immune suppression in EOC tumors, combinatorial strategies to target various stages of the cancer immunity cycle are likely necessary for robust and durable antitumor immune responses. Approaches to enhance T-cell trafficking to the TME, increase T-cell priming and activation, and stimulate neoantigen generation/presentation are being tested by combining immune checkpoint inhibitors with various agents and are discussed below.

Immune Checkpoint Blockade Combined With Chemotherapy

Preclinical work has demonstrated the ability of chemotherapy to potentiate the effect of immunotherapy in EOC by inducing local immune activation in the TME.[35-39] These data, combined with the modest activity of single-agent ICB in ovarian cancer, have prompted investigation of combinations of anti–PD-1/PD-L1 therapy with chemotherapy (Table 1). The phase 3 JAVELIN-100 trial evaluated avelumab with and/or following carboplatin and paclitaxel in the upfront treatment of EOC. This study was negative and terminated early when the planned interim analysis demonstrated futility regarding the primary endpoint of PFS with the addition of avelumab. The median PFS (mPFS) was not reached in the chemotherapy-alone arm and was 16.8 months (hazard ratio [HR], 1.43; 95% CI, 1.05-1.95) and 18.1 months (HR, 1.14; 95% CI, 0.83-1.56) in the maintenance avelumab and concurrent avelumab plus maintenance avelumab arms, respectively.[40] More recently, the IMagyn050 trial tested the safety and efficacy of first-line bevacizumab, carboplatin, and paclitaxel with or without the anti–PD-L1 agent atezolizumab (Tecentriq, Genentech).[41] This trial was also designed to also test whether the addition of ICB to chemotherapy and antiangiogenic agents[42,43] improved outcomes. IMagyn050 did not meet its co-primary endpoint of significantly improving PFS with the addition of atezolizumab, either in the intent-to-treat (mPFS, 19.5 vs 18.4 months; HR, 0.92; 95% CI, 0.79-1.07) or the PD-L1–positive population (mPFS, 20.8 vs 18.5 months; HR, 0.80; 95% CI, 0.65-0.99).[41] It also did not meet its co-primary endpoint of OS at the first interim analysis, although these data remain immature. This trial is another example of a study in which longer-term follow-up may be necessary to unveil potential benefit in a subset of patients.[44] In addition to being tested as first-line therapy, the combination of ICB and chemotherapy has also been tested in recurrent PROC in JAVELIN-200, a phase 3 trial randomly assigning women to avelumab combined with pegylated liposomal doxorubicin (PLD), avelumab alone, or PLD alone. This trial also did not demonstrate significant improvement in PFS or OS across arms with avelumab alone or in addition to PLD chemotherapy in women with PROC.[45] The mPFS was 3.7 months, 3.5 months, and 1.9 months in the combination therapy, PLD-alone, and avelumab-alone groups, respectively, whereas the HR was 1.68 (93% CI, 0.59-1.24) for avelumab vs PLD and 0.78 (93% CI, 1.32-2.60) for the combination vs PLD. Although this was a negative study, a nonsignificant trend toward improved PFS was noted at the 12-month mark in the combination arm, again suggesting the need for the better identification of specific populations of patients who may benefit and experience a long duration of response.

Immune Checkpoint Blockade Combined With Antiangiogenic Therapies

The interplay between angiogenic signaling and immune suppression in the TME has been demonstrated preclinically, with vascular endothelial growth factor (VEGF) and other angiogenic factors contributing to immunosuppression by inducing vascular abnormalities, inhibiting antigen presentation, suppressing immune effector cells, and augmenting the activity of immunosuppressive Tregs, MDSCs, and TAMs.[42,46] The resulting balance of immunosuppressive to effector cells in the TME further stimulates angiogenesis and perpetuates this cycle; thus, combinations targeting both angiogenesis and the PD-1/PD-L1 pathway are being investigated as a strategy to overcome resistance to ICB.[47] A combination of nivolumab and bevacizumab was evaluated in a single-arm phase 2 study of 38 patients with recurrent EOC, demonstrating an ORR of 28.9.[48] Notably, the response rate was 40% in PSOC vs 17% in PROC, suggesting some promising clinical activity in the platinum-sensitive setting. In recurrent PSOC, the ongoing ATALANTE/ENGOT-ov29 study is testing the combination of carboplatin-based chemotherapy, bevacizumab, and atezolizumab (Table 2; NCT02891824). In PROC, the NRG-GY009 phase 2/3 trial is testing PLD and atezolizumab with and without bevacizumab in recurrent PROC (NCT02839707), and the AGO-OVAR-2.29 study is evaluating the addition of atezolizumab to platinum-based chemotherapy plus bevacizumab (NCT03353831). Beyond bevacizumab, the combination of pembrolizumab with the multiple kinase inhibitor lenvatinib (Lenvima, Eisai)—which has shown

Table 2. Ongoing Clinical Trials of ICB Combinations in EOC

Strategy	Trial	Study Drugs	Population	Phase	Identifier
ICB, PARPi, anti-angiogenic and chemotherapy combinations	ATALANTE/ ENGOT-ov29	C/chemo + bev + atezolizumab	Recurrent PSOC	3	NCT02891824
	NRG-GY009	PLD + atezolizumab +/- bev	Recurrent PROC	2/3	NCT02839707
	AGO-OVAR 2.29	C/chemo + bev + atezolizumab → bev	Recurrent PROC	3	NCT03353831
	ANITA	C/chemo +/- atezolizumab → niraparib +/- atezolizumab	Recurrent PSOC	3	NCT03598270
	MITO 33	Niraparib + dostarlimab vs PCC	Recurrent PROC	3	NCT04679064
	ATHENA	C/T → rucaparib + nivolumab	Newly diagnosed EOC	3	NCT03522246
	TRU-D	C/T + durvalumab +/- tremelimumab	Newly diagnosed EOC	2	NCT03899610
	NCT03245892	C/T + nivolumab +/- ipilimumab	Newly diagnosed EOC	1	NCT03245892
	MEDI4736	Tremelimumab → durvalumab	Newly diagnosed EOC	2	NCT03026062
		Tremelimumab + durvalumab			
	AGO/DUO/ ENGOT	C/T + bev +/- durvalumab → bev +/- durvalumab +/- olaparib	Newly diagnosed EOC	3	NCT03737643
	ENGOT-ov43	C/T (+/- bev) +/- pembrolizumab → (bev) +/- pembrolizumab +/- olaparib	Newly diagnosed EOC	3	NCT03740165
	FIRST	C/T +/- bev +/- dostarlimab → bev +/- dostarlimab +/- niraparib	Newly diagnosed EOC	3	NCT03602859
ICB + novel targeted therapies	MEDIPAC	Capivasertib + durvalumab + olaparib	Advanced solid tumors	1	NCT03772561
	NCT02521844	ETC-1922159 (PORCNi) +/- pembrolizumab	Advanced solid tumors	1	NCT02521844
	NCT02431559	Doxorubicin + motolimod (TLR8 agonist) + durvalumab	PROC	1/2	NCT02431559
	NCT02335918	Varlilumab (anti-CD27) + nivolumab	Advanced solid tumors	1/2	NCT02335918
	NCT05043402	Navicixizumab +/- paclitaxel	Advanced PROC	3	NCT05043402
	ARTISTRY-7	Nemvaleukin +/- pembrolizumab	Advanced PROC	3	NCT05092360

bev, bevacizumab; C/chemo, carboplatin-based chemotherapy; C/T, carboplatin plus paclitaxel; EOC, endothelial ovarian cancer; ICB, immune checkpoint blockade; PARPi, poly(ADP-ribose) polymerase inhibitor; PCC, physician's choice of chemotherapy; PLD, pegylated liposomal doxorubicin; PORCNi, porcupine acetyltransferase inhibitor; PSOC, platinum-sensitive ovarian cancer; PROC, platinum-resistant ovarian cancer; T, paclitaxel; TLR, toll-like receptor.

impressive activity in MSS/MMR-proficient endometrial cancer[49] (for which it now has an FDA approval)—resulted in an ORR of 29% in 31 patients with recurrent ovarian cancer at interim analysis of the LEAP-005 phase 2 basket study.[50]

Immune Checkpoint Blockade Combined With PARP Inhibitors

Poly(ADP-ribose) polymerase (PARP) inhibitors have become a major component of therapy for many women with EOC because approximately half of high-grade EOCs exhibit defects in the homologous recombination DNA damage repair pathway. Deleterious somatic and germline alterations in *BRCA1* or *BRCA2* account for up to 22% of high-grade serous carcinomas; thus, other mechanisms are leading to homologous recombination deficiency (HRD) in this disease.[51,52] It has been demonstrated that *BRCA*-mutant (*BRCA*m) tumors possess more mutations,[53] indels,[54] and $CD8^+$ TILs than do *BRCA* wild-type (*BRCA*wt) tumors. They also have a higher level of PD-L1 expression and a larger predicted neoantigen load[55] and exhibit IFN-γ immune signatures,[56] raising

the theoretical yet still unproven possibility of increased sensitivity to ICB in EOC tumors with HRD. In addition, work in preclinical models has demonstrated that DNA damage induced by PARP inhibitors in *BRCA*m tumors induces an innate immune response via activation of the stimulator of interferon genes (STING) pathway, resulting in an improved response to anti–PD-L1 therapy.[57,58] Thus, clinical trials have been developed to test the combination of PARP inhibition and ICB (Table 1). In the phase 2 MEDIOLA trial, which evaluated the combination of durvalumab (Imfinzi, AstraZeneca) and the PARP inhibitor olaparib (Lynparza, AstraZeneca) in *BRCA*m[59] vs *BRCA*wt[60] PSOC, the ORR for the combination was 72% in the *BRCA*m patients (notably, a population of patients expected to have a high response rate to PARP inhibition alone) vs 31.3% in the *BRCA*wt cohort.[59] The ongoing ANITA trial is testing the addition of atezolizumab to the combination of carboplatin-based chemotherapy and niraparib (Zejula, GSK) maintenance in recurrent PSOC (NCT03598270). Also in PROC, the combination of pembrolizumab and niraparib was tested in the TOPACIO trial and demonstrated an ORR of 18%, with similar rates across *BRCA* and HRD subgroups.[61] Even in patients without a RECIST (Response Evaluation Criteria in Solid Tumors) response, prolonged stable disease was often observed, the combination demonstrating promising clinical activity especially in the *BRCA*wt and homologous recombination–proficient populations with limited treatment options. In addition, immunogenomic profiling and single-cell imaging of tumor samples from TOPACIO participants identified mutational signature 3 (reflecting HRD) and a positive immune score (indicating exhausted CD8+ T cells) as 2 biomarkers of improved response to the combination.[62] The phase 2 MOONSTONE trial (NCT03955471) testing the efficacy of niraparib in combination with dostarlimab (Jemperli, GSK) in women with *BRCA*wt PROC was closed to enrollment early on the basis of interim futility analysis. The combination of a PARP inhibitor with ICB is currently being compared with chemotherapy in PROC in the ongoing MITO 33 trial, which is comparing dostarlimab plus niraparib vs chemotherapy (NCT04679064).

In addition, several ongoing trials are comparing the combination of an anti–PD-1/PD-L1 agent and a PARP inhibitor added to and/or following first-line chemotherapy with or without bevacizumab in newly diagnosed EOC (Table 2). For example, the ATHENA trial is evaluating the combination of nivolumab plus rucaparib (Rubraca, Clovis Oncology) as maintenance therapy following response to first-line platinum-based chemotherapy in advanced EOC (NCT03522246). Several additional trials with similar strategies are also underway in the setting of first-line treatment of advanced disease. The phase 3 AGO/DUO/ENGOT trial is evaluating platinum-based chemotherapy and bevacizumab with or without concurrent durvalumab and maintenance durvalumab with or without maintenance olaparib in the first-line treatment of advanced EOC (NCT03737643). ENGOT-ov43 is testing pembrolizumab added to chemotherapy with or without bevacizumab and to maintenance with and without olaparib (NCT03740165). The FIRST trial is testing the benefit of adding dostarlimab to chemotherapy with or without bevacizumab and to niraparib maintenance (NCT03602859), and ENGOT-ov39 is evaluating the addition of atezolizumab to both front-line chemotherapy plus bevacizumab and maintenance with bevacizumab (NCT03038100).

Immune Checkpoint Blockade Combined With Anti–CTLA-4 Blockade

It is known that CTLA-4 is an inhibitory immune checkpoint molecule that promotes additional effector T-cell dysfunction beyond that of PD-1.[63] Up to 50% of EOC TILs were found to express both PD-1 and CTLA-4, and combined blockade of both resulted in rescue of TIL function and led to tumor regression in murine models.[64] It was recently demonstrated that CTLA-4 attenuates CD28 costimulatory signals by antigen-presenting cells in EOC, and that augmentation of CD28 costimulation by anti–CTLA-4 therapy enhances TIL activation in response to anti–PD-1.[65] Clinically, the combination of anti–PD-1 and anti–CTLA-4 therapy was tested in NRG-GY003, a phase 2 study comparing nivolumab plus ipilimumab vs nivolumab alone in recurrent EOC. This study reported a superior ORR with the combination, 31.4% vs 12.2% (odds ratio, 3.28; P=.034), as well as longer mPFS (3.9 vs 2.0 months).[66] However, related grade 3 or higher adverse effects were reported in 49% of patients receiving the combination vs 33% of those receiving nivolumab alone, findings consistent with those of prior studies of this combination. The Fc-enhanced anti–CTLA-4 antibody AGEN1181 is being tested in combination with the anti–PD-1 agent balstilimab in a phase 1 study of advanced solid tumors (NCT03860272). There were 2 confirmed PRs and 2 cases of stable disease in the 9 evaluable patients with ovarian cancer included in this study,[67] and randomized phase 2/3 trials are being initiated in PROC, endometrial cancer, and MSS colorectal cancers.

Other ongoing studies are testing the combination of anti–PD-1 and anti–CTLA-4 therapy in EOC, in both the first-line and the recurrent setting (Table 2). The phase 2 TRU-D trial is testing the addition of durvalumab with or without the anti–CTLA-4 antibody tremelimumab to neoadjuvant carboplatin and paclitaxel in women with

newly diagnosed advanced EOC (NCT03899610). A similar combination of nivolumab with or without ipilimumab added to neoadjuvant or adjuvant chemotherapy in advanced EOC is also being tested (NCT03245892). An ongoing phase 2 trial, MEDI4736, is also testing the combination of durvalumab and tremelimumab in recurrent EOC (NCT03026062).

Triplet and Other Targeted Therapy Combinations

Given the apparent additive activity of ICB combined with chemotherapy, PARP inhibitors, antiangiogenic agents, or anti–CTLA-4 drugs, triplet combinations are now being testing in EOC with the goal of rendering these tumors more vulnerable to ICB treatment and increasing the likelihood of potentially durable responses. In recurrent EOC, the previously mentioned MEDIOLA trial also includes a cohort of patients with non-germline *BRCA*m PSOC undergoing treatment with the combination of durvalumab, bevacizumab, and olaparib. Preliminary results for this combination are promising, with a reported disease control rate and ORR of approximately 77%.[59] The phase 2 OPAL trial (NCT03574779) examined the combination of dostarlimab, niraparib, and bevacizumab in patients with recurrent EOC. In the PROC cohort, which comprised mostly *BRCA*wt patients, the ORR was 17.9%, with 7 partial responses and 23 of 39 evaluable patients with stable disease,[68] suggesting clinical activity in a population predicted to have poor responses to systemic therapies. A single-arm phase 2 cohort study also evaluated the combination of pembrolizumab with oral metronomic cyclophosphamide and bevacizumab in patients with recurrent EOC, 75% of whom had PROC.[69] There were 3 complete and 14 partial responses in the 40 patients treated with this combination, with an ORR of 47.5% and a clinical benefit rate of 95.0%. Moreover, durable responses of longer than 12 months were observed in 25%. A phase 1 study of the combination of durvalumab, olaparib, and the VEGF receptor 1-3 inhibitor cediranib in recurrent gynecologic cancers reported a clinical benefit rate of 67%, with 4 of 9 patients exhibiting a partial response.[70] On the basis of these findings, the ongoing phase 2 NRG-GY023 trial is comparing this triplet combination with durvalumab and cediranib or physician's choice of chemotherapy in women with PROC (NCT04739800).

Novel Investigational Strategies

Targeting PI3K, Wnt, and Notch Pathways. Several oncogenic pathways have been shown to facilitate the ability of tumor cells to evade antitumor immunity[71,72]; the PI3K/AKT and Wnt pathways are particularly relevant in EOC. Genomic alterations activating the PI3K/AKT pathway, loss of PTEN function, or both are frequently observed in EOC and are associated with reduced TIL numbers and cytotoxic function.[22,73] Accordingly, PI3K and AKT inhibitors have been shown to increase immune infiltrating cells,[74] activate CD8+ TILs,[75] and selectively inhibit the proliferation of Tregs,[73] thereby increasing sensitivity to anti–PD-1 therapy in preclinical models.[74] Trials based on this rationale are underway (Table 2), testing the combination of PI3K and AKT inhibitors with ICB, including a phase 1 study of the AKT inhibitor capivasertib combined with durvalumab and olaparib in advanced solid tumors. An expansion cohort in gynecologic malignancies is ongoing (NCT03772561).

Wnt signaling in cancers, including EOC, has effects on immune cells, including effector T cells and dendritic cells, that can promote immune exclusion and resistance to ICB.[36,76,77] Thus, trials are now underway (Table 2) testing the effect of suppressing Wnt signaling with porcupine acetyltransferase (PORCN) inhibitors (NCT01351103, NCT02521844). In addition, the combination of the PORCN inhibitor ETC-1922159 and pembrolizumab is being evaluated in a phase 1 basket study of solid tumors (NCT02521844).

Notch signaling plays critical roles in vascular homeostasis, and crosstalk between this pathway and VEGF regulates cancer angiogenesis. In EOC, Notch signaling is also implicated in stem cell maintenance, epithelial-mesenchymal transition, chemoresistance, and poor outcomes.[78] Thus, novel therapies targeting gamma secretase and delta-like ligand 4 (DLL4) are being tested therapeutically in EOC. Navicixizumab, a novel anti-DLL4/VEGF bispecific antibody designed to target Notch and VEGF signaling simultaneously, has received an FDA fast track designation for the treatment of patients with recurrent EOC. A phase 1b study of navicixizumab combined with paclitaxel in 44 heavily-pretreated patients with PROC reported 1 complete response, 18 partial responses, and 15 patients with stable disease, with a manageable safety profile.[79] A randomized, multicenter phase 3 study comparing navicixizumab with or without paclitaxel vs paclitaxel alone in patients with PROC expressing certain RNA markers is planned (NCT05043402).

Selective Stimulation of Cytotoxic T Cells. Strategies to activate cytotoxic T cells preferentially and avoid the stimulation of immunosuppressive T-cell populations are currently under active investigation. For example, nemvaleukin, an engineered protein comprising a modified interleukin 2 (IL-2) and high-affinity IL-2 alpha receptor chain, is hypothesized to selectively activate the intermediate-affinity IL-2 receptor complex. Nemvaleukin was recently granted FDA fast track designation for use in combination with pembrolizumab in advanced PROC. The phase 1/2 ARTISTRY-1 trial, which is evaluating nemvaleukin alone and in combination with

pembrolizumab in advanced solid tumors, reported 1 complete response and 1 partial response in 13 evaluable patients with heavily pretreated PROC, with 9 experiencing disease control.[80] Building upon this signal of activity, the phase 3 ARTISTRY-7 trial, which is a 4-arm study evaluating nemvaleukin alone or in combination with pembrolizumab vs pembrolizumab alone or physician's choice of chemotherapy, is ongoing (NCT05092360).

Simultaneous Targeting of the Innate Immune System. Although the actions of anti–PD-1/PD-L1 therapy were historically attributed to activation of the adaptive immune system, it is now clear that stimulation of the innate immune system is also required to induce T-cell responses.[81,82] Direct or indirect activation of the innate immune system via targeting of immune cells (eg, natural killer cells and dendritic cells) or activation of pattern recognition receptors, such as toll-like receptors (TLRs) and the cGAS/STING pathway, has demonstrated preclinical activity in various cancers.[83,84] Proof of concept for the combination of innate and adaptive immune targeting has been demonstrated in EOC murine models.[85] Currently, different combinations targeting both innate and adaptive immunity are under clinical investigation (Table 2). For example, ongoing phase 1/2 studies are testing the combination of doxorubicin, durvalumab, and the TLR8 agonist motolimod in PROC (NCT02431559) and the combination of the anti-CD27 antibody varlilumab and nivolumab in solid tumors, including ovarian cancer (NCT02335918).

Cancer Vaccines Combined With ICB. Cancer vaccines are now being investigated in combination with ICB in EOC, with several combinations exhibiting promising preliminary activity and acceptable safety profiles. For example, clinical trials testing the combination of WT-1 or NY-ESO-1 vaccine with nivolumab in recurrent EOC (NCT02737787; Table 3) and the combination of a multi-epitope antifolate receptor (anti-FR) vaccine with durvalumab (NCT02764333) in PROC have reported the combinations to be safe and tolerable.[86,87] In addition, personalized neoantigen vaccines are being combined with ICB in EOC (NCT04024878) and other cancers[88] in an attempt to "steer" the immune response while simultaneously "releasing the brakes" on the immune system, thereby inducing a more robust and specific antitumor immune response. Another novel approach being studied is the autologous tumor cell vaccine gemogenovatucel-T, also known as Vigil, which is engineered to express granulocyte-macrophage colony–stimulating factor (GM-CSF) and bi-shRNA-furin to transforming growth factor beta (TGF-β); the vaccine is being administered as maintenance therapy to women with newly diagnosed advanced EOC following response to upfront surgery and chemotherapy in the VITAL trial (NCT02346747).[89] Initial efficacy results demonstrated longer median relapse-free survival (HR, 0.39; 90% CI, 0.20-0.75) and OS (HR, 0.34; 90% CI, 0.14-0.83) in the vaccine arm than in the placebo arm within the homologous recombination–proficient cohort.[90] Additional trials are ongoing testing this agent in combination with atezolizumab (NCT03073525) and durvalumab (NCT02725489) in advanced gynecologic cancers.

Dendritic cell vaccines (DCVACs) have also been investigated in EOC, with the aim of enhancing antigen presentation in the TME. The production of DCVACs typically involves apheresis to obtain autologous immature dendritic cells, in vitro stimulation and maturation, loading of stimulated dendritic cells with tumor-associated antigens, and then administration of the vaccine into the patient, often in combination with chemotherapy or other therapies (reviewed in Zhang and colleagues[91]). For example, a randomized phase 2 trial comparing DCVAC administration following or during first-line adjuvant chemotherapy with chemotherapy alone in patients with newly diagnosed advanced EOC reported significantly longer PFS and a nonsignificant trend toward extended OS in those who received DCVAC following chemotherapy vs those who received chemotherapy alone.[92] Furthermore, in an exploratory biomarker analysis, outcomes were significantly better in the patients with low levels of CD8+ TILs who received vaccine than in those with low levels of TILs in the chemotherapy-alone arm, suggesting a benefit of DCVAC in immunologically "cold" tumors. Ongoing clinical trials are planned or underway further investigating the safety and efficacy of DCVAC alone or in combination in both newly diagnosed and recurrent EOC[91]; a few of these are included in Table 3.

Adoptive Cellular Therapy Combined With ICB. Another active area of research in EOC is the use of adoptive cell therapies (ACTs), in which autologous immune effector cells are isolated from the patient, cultured and often genetically modified ex vivo, and then reinfused to enhance the antitumor response. These approaches are being combined with ICB in EOC, in part on the basis of initial observations of high levels of PD-1 expression on infused TILs in ACT trials.[93] To date, trials testing TIL ACT alone in EOC have demonstrated feasibility, but modest efficacy (reviewed by Sarivalasis and colleagues[94]). Among other strategies, TIL ACT therapy combined with ICB has shown safety and feasibility, along with preliminary evidence of clinical and immunologic activity, in small, early-phase trials, improving TIL expansion and enhancing CD8+ T-cell tumor reactivity in comparison with TIL ACT alone.[95] Current clinical trials (Table 3) are studying the combination of TIL infusion with aldesleukin (Proleukin, Clinigen Group) and either pembrolizumab (NCT01174121, NCT03158935) or ipilimumab

Table 3. Selected Clinical Trials Combining ICB With Cancer Vaccines and ACT Products

Strategy	Phase	Population	Investigational Products/Combinations	Identifier
Cancer vaccines +/- ICB	1	Recurrent EOC	WT1 or NY-ESO-1 vaccine + nivolumab	NCT02737787
	2	Recurrent PROC	Anti-FRα vaccine + durvalumab	NCT02764333
	1	EOC following response to platinum-based chemotherapy	NeoVax (personalized neoantigen vaccine) + nivolumab	NCT04024878
	2	Newly diagnosed EOC following response to surgery and upfront chemotherapy	Vigil (gemogenovatucel-T) autologous tumor cell vaccine	NCT02346747
	2	Advanced gyn cancers	Vigil + atezolizumab	NCT03073525
	2	Advanced gyn cancers	Vigil + durvalumab	NCT02725489
	1	Newly diagnosed EOC	Allogeneic DCVAC	NCT04739527
	1	Newly diagnosed EOC	DCVAC loaded with FRa peptides	NCT02111941
	1/2	Newly diagnosed EOC	DCVAC combined with NK cell-like cytotoxic T cells	NCT03735589
	2	Recurrent EOC	DCVAC loaded with MUC1 and WT1 peptides	NCT00703105
TILs +/- ICB	2	Recurrent/refractory EOC	MDA-TILs	NCT03610490
	2	Metastatic solid tumors including recurrent EOC	TILs + pembrolizumab peri-infusion or at disease progression	NCT01174121
	1	Metastatic melanoma and EOC	TILs + pembrolizumab	NCT03158935
	1/2	Recurrent EOC	TILs + ipilimumab + nivolumab	NCT03287674
	1	PROC	TILs + utomilumab (4-1BB/CD137 agonist)	NCT03318900
TCRs + ICB				
CAR Ts +/- ICB	1	Mesothelin-positive solid tumors including EOC	2nd-generation mesothelin-directed CAR Ts	NCT02159716
	1	Mesothelin-positive solid tumors including EOC	2nd-generation mesothelin-directed CAR Ts +/- lymphodepleting chemotherapy	NCT03054298
	1/2	Mesothelin-positive solid tumors including EOC	2nd-generation mesothelin-directed CAR Ts + cyclophosphamide + IL-2	NCT01583686
	1	Recurrent EOC	2nd-generation FRα-directed CAR Ts +/- lymphodepleting chemotherapy	NCT03585764
	1	Mesothelin-positive solid tumors including EOC	Knocked-out PD-1, mesothelin-directed CAR Ts	NCT03747965
Bispecific Ab + ICB	1/2	Recurrent EOC	MUC16xCD3 bispecific antibody +/- cemiplimab	NCT03564340

Ab, antibody; ACT, adoptive cell therapy; CAR Ts, chimeric antigen receptor T cells; DCVAC, dendritic cell vaccine; EOC, endothelial ovarian cancer; FRα, folate receptor alpha; gyn, gynecologic; ICB, immune checkpoint blockade; IL-2, interleukin 2; MDA-TILs, autologous expanded tumor-infiltrating lymphocytes; MUC1, mucin 1; NK, natural killer; NY-ESO-1, New York esophageal squamous cell carcinoma 1; PD-1, programmed death 1; PROC, platinum-resistant ovarian cancer; TILs, tumor-infiltrating lymphocytes; TCRs, T-cell receptors; WT1, Wilms tumor gene 1.

and nivolumab (NCT03287674).

Beyond TILs, other ACT approaches, including T-cell receptor (TCR)–engineered T cells[96] and chimeric antigen receptor (CAR) T cells, are being investigated in EOC. These strategies differ from TILs in that T cells are genetically altered to be directed to specific peptides, typically tumor-associated antigens (TAAs). To date, the most common CAR T-cell targets tested clinically include folate receptor alpha (FRα), mesothelin, and MUC16; several ongoing clinical trials are also testing third-generation CAR T cells directed against additional known TAAs in EOC (reviewed by Benard and colleagues[97]). TCRs engineered to recognize specific epitopes from TAAs, including WT1, p53, NY-ESO-1, and MAGE-A4,

have been developed, and NY-ESO-1 has been tested in phase 1/2 clinical trials,[98] with additional trials ongoing (Table 3). As of now, several barriers still limit the success of TCR-based and CAR T-cell therapies in EOC and other solid tumors, including the limited number and heterogeneous expression of membrane antigen targets, inadequate tracking of T cells to tumor sites, and limited fitness and survival in the TME. Novel strategies capitalizing on viral vector–based gene editing to overcome immunosuppressive and/or inhibitory signals are showing promising preclinical and early-phase clinical activity.[99,100] For example, mesothelin-directed CAR T cells with CRISPR-Cas9–mediated knockout of PD-1 are being tested in mesothelin-positive solid tumors, including EOC (NCT03747965).

Bispecific antibodies are antibody constructs that recognize both a specific TAA expressed on tumor cells and the CD3 complex expressed on T cells.[101] They therefore redirect endogenous polyclonal T cells to the tumor to induce tumor cell–specific lysis without the need for ex vivo expansion and genetic manipulation.[102,103] An MUC16 bispecific antibody has shown potent preclinical activity and is currently being tested clinically alone and in combination with the anti–PD-1 agent cemiplimab (Libtayo, Sanofi-Aventis/Regeneron; NCT03564340).

Biomarkers of Response to ICB in Ovarian Cancer

Regardless of the response rates across populations of different cancer types, a common observation is that responses to ICB are often more durable than responses to other systemic therapies.[104] Thus, the identification of biomarkers to select patients likely to respond to ICB or combinations containing immune checkpoint inhibitors are necessary, and this is an active area of investigation.

Tumor Cell–Intrinsic Biomarkers

PD-L1 expression in the TME is a well-studied potential biomarker of response to ICB, given its correlation with therapeutic responses across diverse cancer types.[105,106] This correlation has been observed in EOC, although not uniformly across all studies. KEYNOTE-100 reported a positive correlation between response to pembrolizumab and CPS, with a CPS of 1 or higher corresponding to an ORR of 5% and a CPS of 10 or higher corresponding to an ORR of 17.1%.[12] The incidence of cancers demonstrating a CPS of 10 or higher was very low, however. Notably, all 7 complete responses seen on study were in the subgroup with a CPS of 10 or higher. In IMagyn050, stratification by PD-L1 staining in immune cells with a cutoff of 1% did not identify a population that derived benefit from the addition of atezolizumab.[41] However, a potential benefit from the addition of atezolizumab was seen in prespecified exploratory analyses of 2 populations, one with immune cell PD-L1 expression of 5% or higher (HR, 0.66; 95% CI, 0.44-0.98) and another with tumor cell PD-L1 expression of 1% or higher (HR, 0.45; 95% CI, 0.19-1.02). No differences were seen in OS according to PD-L1 expression in the NINJA study, although the PD-L1 analysis was restricted to tumor cells only by using a TPS of 1% or higher for stratification. Several challenges limit the clinical utility of PD-L1 as a biomarker,[107-109] so that further optimization of PD-L1 testing is required, and its use in combination with other methods of assessing the immune-inflamed phenotype of a tumor is likely necessary.[110]

TMB is another leading biomarker candidate because of the assumption that a high proportion of mutations enhances immunogenicity.[111,112] Pembrolizumab is now approved for use in all unresectable or metastatic tumors with a high TMB, determined with the FoundationOne CDx assay (Foundation Medicine). In EOC, the TMB is consistently low,[12,113,114] and a prespecified exploratory analysis assessing TMB in KEYNOTE-100 revealed no association with rates of response to pembrolizumab.[113] In IMagyn050, most tumors had a low TMB regardless of *BRCA1/2* mutation/HRD status, and neither was associated with response to atezolizumab,[114] confirming the KEYNOTE 100 data[12,41] and underscoring the likely low utility of TMB assessment in EOC. *BRCA* mutations have also not been shown to be predictive of cancer responsiveness to ICB.[12,14,59]

Additional transcriptomic analyses have been performed to identify tumors with a T cell–inflamed phenotype[115] or an immunoreactive or mesenchymal molecular subtype.[51] In KEYNOTE-100, a prespecified exploratory analysis comparing expanded GEP signatures (eg, angiogenesis, hypoxia, granulocytic MDSCs, epithelial-mesenchymal transition (EMT)/TGF-β signaling, Wnt signaling) did not reveal any significant associations with clinical outcomes with pembrolizumab,[116] and thus further work is needed to translate the findings of these studies into clinically relevant biomarkers.

Tumor Cell–Extrinsic Biomarkers

The importance of identifying biomarkers of response in the context of the TME is increasingly clear. Early work by Zhang and colleagues[3] established the link between the presence of infiltrating T cells and improved outcomes in ovarian cancer; this was further supported by Li and colleagues,[4] providing a rationale for pursuing immunotherapy-based therapeutic strategies in EOC. The ratio of immune-reactive to immune-tolerant cellular subpopulations in a tumor is correlated with clinical outcomes[39] and

may be an important consideration in terms of predicting response to ICB. Further, single-cell tissue-based cyclic immunofluorescence approaches paired with immunogenic profiling of EOC tumors from the TOPACIO trial identified specific tumor cell mutational signatures and CD8+ T-cell molecular states, as well as spatial interactions between them in the TME, that were associated with response to niraparib and pembrolizumab.[62] These works suggest that single-cell spatially resolved data from clinical samples may be key to developing predictive biomarkers for determining response to therapy and aiding patient stratification.

The quest for more precise biomarkers to predict ICB response in EOC has extended beyond the TME to liquid biopsy–based approaches,[117,118] including circulating tumor DNA,[119] noncoding RNA,[120] circulating tumor cells, and immune cells (CD8+ T cells, MDSCs, neutrophils),[121-123] as well as soluble factors such as PD-L1,[124] cytokines, and chemokines.[125] Although associations with clinical benefit and survival are observed, these observations still require validation in prospective studies. In addition, the microbiome has recently been found to contribute to varied responses to ICB and may represent another source of predictive biomarkers.[126-129] A recent review[130] comprehensively summarizes the growing body of translational work that supports a key role of the gut microbiome in modulating the response to ICB, most convincingly to date in patients with melanoma.[128,129,131] Furthermore, specific microbial phyla have been associated with response to ICB across solid tumors,[132] and these have been identified as potential novel and modifiable biomarkers. As with liquid biopsy–based biomarker candidates, an improved understanding of the interactions between the host and the intestinal microbiome is necessary to identify microbiome-based biomarkers of ICB response. Nonetheless, these studies are exciting and raise the possibility of using the vaginal microbiome as an alternative source of candidate biomarkers in gynecologic cancers.

Conclusions

The low rates of response to ICB in EOC demonstrated thus far provide no justification for the use of single-agent ICB in unselected populations with recurrent EOC unless the cancer is found to be TMB-high or MSI-H/MMRd, and thus qualified for pembrolizumab or dostarlimab treatment on the basis of cancer site–agnostic approval. However, the clinical trials performed to date demonstrate the capability of ICB to produce durable responses in a very small subset of patients. These findings provide opportunities and pose challenges to the medical and scientific community to further uncover the specific barriers limiting the activity of ICB, to employ novel technologies to discover predictive biomarkers, and to develop immunotherapies that extend beyond ICB to help these agents work better. The identification of transformative biomarkers for predicting response to immunotherapy—which ultimately requires a method to test if a patient has a tumor-reactive T-cell repertoire that can access the TME and effectively eliminate cancer cells once there—remains challenging and will likely require the incorporation of multiple parameters. Combining patient data from across ICB trials with low numbers of responders may prove useful for the discovery of new candidates, which could then be validated in prospective trials. Building on what has already been learned and applying emerging technologies that can characterize tumors and their microenvironment at the single-cell level will undoubtedly lead to improved biomarkers; these not only will optimize the selection of patients for ICB therapies but also will also improve our ability to test novel ICB combinations and sequences in the most appropriate populations.

Disclosures

Dr Porter has no disclosures. Dr Matulonis has done consulting for AstraZeneca, Merck, Novartis, NextCure, Blueprint Medicines, and Trillium Therapeutics.

References

1. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. *Nat Rev Dis Primers*. 2016;2:16061.
2. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308.
3. 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(3):203-213.
4. Li J, Wang J, Chen R, Bai Y, Lu X. The prognostic value of tumor-infiltrating T lymphocytes in ovarian cancer. *Oncotarget*. 2017;8(9):15621-15631.
5. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. *Proc Natl Acad Sci USA*. 2005;102(51):18538-18543.
6. Dadmarz RD, Ordoubadi A, Mixon A, et al. Tumor-infiltrating lymphocytes from human ovarian cancer patients recognize autologous tumor in an MHC class II-restricted fashion. *Cancer J Sci Am*. 1996;2(5):263-272.
7. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol*. 2015;33(17):1974-1982.
8. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. *Nat Commun*. 2020;11(1):3801.
9. Kulangara K, Zhang N, Corigliano E, et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Pathol Lab Med*. 2019;143(3):330-337.
10. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med*. 2017;377(25):2500-2501.
11. 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(2):243-250.
12. 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 II KEYNOTE-100 study. *Ann Oncol*. 2019;30(7):1080-1087.
13. Matulonis UA, Shapira R, Santin A, et al. Final results from the KEY-

NOTE-100 trial of pembrolizumab in patients with advanced recurrent ovarian cancer [ASCO abstract 6005]. *J Clin Oncol*. 2020;38(15)(suppl).
14. 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(3):393-401.
15. 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(34):4015-4022.
16. Hamanishi J, Takeshima N, Katsumata N, et al. Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant ovarian cancer: open-label, randomized trial in Japan (NINJA). *J Clin Oncol*. 2021;39(33):3671-3681.
17. Schmid P, Rugo HS, Adams S, et al; IMpassion130 Investigators. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(1):44-59.
18. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39(1):1-10.
19. Barrueto L, Caminero F, Cash L, Makris C, Lamichhane P, Deshmukh RR. Resistance to checkpoint inhibition in cancer immunotherapy. *Transl Oncol*. 2020;13(3):100738.
20. Le YS, Kim TE, Kim BK, et al. Alterations of HLA class I and class II antigen expressions in borderline, invasive and metastatic ovarian cancers. *Exp Mol Med*. 2002;34(1):18-26.
21. Stark AK, Sriskantharajah S, Hessel EM, Okkenhaug K. PI3K inhibitors in inflammation, autoimmunity and cancer. *Curr Opin Pharmacol*. 2015;23:82-91.
22. Sai J, Owens P, Novitskiy SV, et al. PI3K inhibition reduces mammary tumor growth and facilitates antitumor immunity and Anti-PD1 responses. *Clin Cancer Res*. 2017;23(13):3371-3384.
23. Luke JJ, Bao R, Sweis RF, Spranger S, Gajewski TF. WNT/β-catenin pathway activation correlates with immune exclusion across human cancers. *Clin Cancer Res*. 2019;25(10):3074-3083.
24. Goldsberry WN, Meza-Perez S, Londoño AI, et al. Inhibiting WNT ligand production for improved immune recognition in the ovarian tumor microenvironment. *Cancers (Basel)*. 2020;12(3):E766.
25. Bodnar L, Stanczak A, Cierniak S, et al. Wnt/β-catenin pathway as a potential prognostic and predictive marker in patients with advanced ovarian cancer. *J Ovarian Res*. 2014;7:16.
26. Cai J, Tang H, Xu L, et al. Fibroblasts in omentum activated by tumor cells promote ovarian cancer growth, adhesion and invasiveness. *Carcinogenesis*. 2012;33(1):20-29.
27. Nieman KM, Kenny HA, Penicka CV, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat Med*. 2011;17(11):1498-1503.
28. Kandalaft LE, Odunsi K, Coukos G. Immune therapy opportunities in ovarian cancer. *Am Soc Clin Oncol Educ Book*. 2020;40(40):1-13.
29. Curiel TJ, Coukos G, Zou L, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med*. 2004;10(9):942-949.
30. Yuan X, Zhang J, Li D, et al. Prognostic significance of tumor-associated macrophages in ovarian cancer: A meta-analysis. *Gynecol Oncol*. 2017;147(1):181-187.
31. Condamine T, Ramachandran I, Youn JI, Gabrilovich DI. Regulation of tumor metastasis by myeloid-derived suppressor cells. *Annu Rev Med*. 2015;66:97-110.
32. Rodriguez GM, Galpin KJC, McCloskey CW, Vanderhyden BC. The tumor microenvironment of epithelial ovarian cancer and its influence on response to immunotherapy. *Cancers (Basel)*. 2018;10(8):E242.
33. Luo X, Xu J, Yu J, Yi P. Shaping immune responses in the tumor microenvironment of ovarian cancer. *Front Immunol*. 2021;12:692360.
34. Kandalaft LE, Odunsi K, Coukos G. Immunotherapy in ovarian cancer: are we there yet? *J Clin Oncol*. 2019;37(27):2460-2471.
35. Khairallah AS, Genestie C, Auguste A, Leary A. Impact of neoadjuvant chemotherapy on the immune microenvironment in advanced epithelial ovarian cancer: prognostic and therapeutic implications. *Int J Cancer*. 2018;143(1):8-15.
36. Jiménez-Sánchez A, Cybulska P, Mager KL, et al. Unraveling tumor-immune heterogeneity in advanced ovarian cancer uncovers immunogenic effect of chemotherapy. *Nat Genet*. 2020;52(6):582-593.
37. Böhm S, Montfort A, Pearce OM, et al. Neoadjuvant chemotherapy modulates the immune microenvironment in metastases of tubo-ovarian high-grade serous carcinoma. *Clin Cancer Res*. 2016;22(12):3025-3036.
38. Mesnage SJL, Auguste A, Genestie C, et al. Neoadjuvant chemotherapy (NACT) increases immune infiltration and programmed death-ligand 1 (PD-L1) expression in epithelial ovarian cancer (EOC). *Ann Oncol*. 2017;28(3):651-657.
39. Leary A, Genestie C, Blanc-Durand F, et al. Neoadjuvant chemotherapy alters the balance of effector to suppressor immune cells in advanced ovarian cancer. *Cancer Immunol Immunother*. 2021;70(2):519-531.
40. Monk BJ, Colombo N, Oza AM, et al. Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(9):1275-1289.
41. Moore KN, Bookman M, Sehouli J, et al. Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). *J Clin Oncol*. 2021;39(17):1842-1855.
42. Datta M, Coussens LM, Nishikawa H, Hodi FS, Jain RK. Reprogramming the tumor microenvironment to improve immunotherapy: emerging strategies and combination therapies. *Am Soc Clin Oncol Educ Book*. 2019;39:165-174.
43. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol*. 2018;15(5):325-340.
44. Branchoux S, Bellera C, Italiano A, Rustand D, Gaudin AF, Rondeau V. Immune-checkpoint inhibitors and candidate surrogate endpoints for overall survival across tumour types: a systematic literature review. *Crit Rev Oncol Hematol*. 2019;137:35-42.
45. Pujade-Lauraine E, Fujiwara K, Ledermann JA, et al. Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, phase 3 study. *Lancet Oncol*. 2021;22(7):1034-1046.
46. Rahma OE, Hodi FS. The intersection between tumor angiogenesis and immune suppression. *Clin Cancer Res*. 2019;25(18):5449-5457.
47. Hack SP, Zhu AX, Wang Y. Augmenting anticancer immunity through combined targeting of angiogenic and PD-1/PD-L1 pathways: challenges and opportunities. *Front Immunol*. 2020;11:598877.
48. Liu JF, Herold C, Gray KP, et al. Assessment of combined nivolumab and bevacizumab in relapsed ovarian cancer: a phase 2 clinical trial. *JAMA Oncol*. 2019;5(12):1731-1738.
49. Makker V, Taylor MH, Aghajanian C, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. *J Clin Oncol*. 2020;38(26):2981-2992.
50. Lwin Z, Gomez-Roca C, Saada-Bouzid E, et al. LEAP-005: phase II study of lenvatinib (len) plus pembrolizumab (pembro) in patients (pts) with previously treated advanced solid tumours [ESMO abstract LBA41]. *Ann Oncol*. 2020;31(4)(suppl).
51. Network CGAR; Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011;474(7353):609-615.
52. Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous recombination deficiency: exploiting the fundamental vulnerability of ovarian cancer. *Cancer Discov*. 2015;5(11):1137-1154.
53. Birkbak NJ, Kochupurakkal B, Izarzugaza JM, et al. Tumor mutation burden forecasts outcome in ovarian cancer with BRCA1 or BRCA2 mutations. *PLoS One*. 2013;8(11):e80023.
54. Alexandrov LB, Nik-Zainal S, Wedge DC, et al; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain. Signatures of mutational processes in human cancer. *Nature*. 2013;500(7463):415-421.
55. Strickland KC, Howitt BE, Shukla SA, et al. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. *Oncotarget*. 2016;7(12):13587-13598.
56. Hao D, Liu J, Chen M, et al. Immunogenomic analyses of advanced serous ovarian cancer reveal immune score is a strong prognostic factor and an indicator of chemosensitivity. *Clin Cancer Res*. 2018;24(15):3560-3571.
57. Ding L, Kim HJ, Wang Q, et al. PARP inhibition elicits STING-dependent antitumor immunity in Brca1-deficient ovarian cancer. *Cell Rep*. 2018;25(11):2972-2980.e5.
58. 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(2):311-319.
59. Drew Y, Penson RT, O'Malley DM, et al. Phase II study of olaparib (O) plus durvalumab (D) and bevacizumab (B) (MEDIOLA): initial results in patients (pts) with non-germline BRCA-mutated (non-gBRCAm) platinum sensitive relapsed

(PSR) ovarian cancer (OC) [ESMO abstract 814MO]. *Ann Oncol*. 2020;31(4)(suppl).
60. Drew Y, Kaufman B, Banerjee S, et al. Phase II study of olaparib + durvalumab (MEDIOLA): updated results in germline BRCA-mutated platinum-sensitive relapsed (PSR) ovarian cancer (OC) [ESMO abstract 1190PD]. *Ann Oncol*. 2019;30(5)(suppl).
61. 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*. 2019;5(8):1141-1149.
62. Färkkilä A, Gulhan DC, Casado J, et al. Immunogenomic profiling determines responses to combined PARP and PD-1 inhibition in ovarian cancer. *Nat Commun*. 2020;11(1):1459.
63. Melero I, Hervas-Stubbs S, Glennie M, Pardoll DM, Chen L. Immunostimulatory monoclonal antibodies for cancer therapy. *Nat Rev Cancer*. 2007;7(2):95-106.
64. Duraiswamy J, Kaluza KM, Freeman GJ, Coukos G. Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors. *Cancer Res*. 2013;73(12):3591-3603.
65. Duraiswamy J, Turrini R, Minasyan A, et al. Myeloid antigen-presenting cell niches sustain antitumor T cells and license PD-1 blockade via CD28 costimulation. *Cancer Cell*. 2021;39(12):1623-1642.e20.
66. Zamarin D, Burger RA, Sill MW, et al. Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG Oncology Study. *J Clin Oncol*. 2020;38(16):1814-1823.
67. El-Khoueiry AB, Bullock A, Tsimberidou A, et al. AGEN1181, an Fc-enhanced anti-CTLA-4 antibody, alone and in combination with balstilimab (anti-PD-1) in patients with advanced solid tumors: phase I results [SITC abstract 479]. *J Immunother Cancer*. 2021;9(2)(suppl).
68. Liu J, Gaillard S, Hendrickson AW, et al. An open-label phase II study of dostarlimab (TSR-042), bevacizumab (bev), and niraparib combination in patients (pts) with platinum-resistant ovarian cancer (PROC): cohort A of the OPAL trial. *Gynecol Oncol*. 2021;162:S17-S18.
69. Zsiros E, Lynam S, Attwood KM, et al. Efficacy and safety of pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide in the treatment of recurrent ovarian cancer: a phase 2 nonrandomized clinical trial. *JAMA Oncol*. 2021;7(1):78-85.
70. Zimmer AS, Nichols E, Cimino-Mathews A, et al. A phase I study of the PD-L1 inhibitor, durvalumab, in combination with a PARP inhibitor, olaparib, and a VEGFR1-3 inhibitor, cediranib, in recurrent women's cancers with biomarker analyses. *J Immunother Cancer*. 2019;7(1):197.
71. Spranger S, Gajewski TF. Impact of oncogenic pathways on evasion of antitumour immune responses. *Nat Rev Cancer*. 2018;18(3):139-147.
72. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168(4):707-723.
73. Abu-Eid R, Samara RN, Ozbun L, et al. Selective inhibition of regulatory T cells by targeting the PI3K-Akt pathway. *Cancer Immunol Res*. 2014;2(11):1080-1089.
74. Borcoman E, De La Rochere P, Richer W, et al. Inhibition of PI3K pathway increases immune infiltrate in muscle-invasive bladder cancer. *OncoImmunology*. 2019;8(5):e1581556.
75. Carnevalli LS, Sinclair C, Taylor MA, et al. PI3Kα/δ inhibition promotes anti-tumor immunity through direct enhancement of effector $CD8^+$ T-cell activity. *J Immunother Cancer*. 2018;6(1):158.
76. Zhou Y, Xu J, Luo H, Meng X, Chen M, Zhu D. Wnt signaling pathway in cancer immunotherapy. *Cancer Lett*. 2022;525:84-96.
77. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. *Nature*. 2015;523(7559):231-235.
78. Ceccarelli S, Megiorni F, Bellavia D, Marchese C, Screpanti I, Checquolo S. Notch3 targeting: a novel weapon against ovarian cancer stem cells. *Stem Cells Int*. 2019;2019:6264931.
79. Fu S, Burger R, Hamilton E, et al. A phase Ib study of navicixizumab and weekly paclitaxel in heavily pretreated platinum resistant ovarian, primary peritoneal or fallopian tube cancer. Scheduled for presentation at: SGO Annual Meeting on Women's Cancer; March 28-31, 2020; Toronto, Canada (meeting cancelled). Abstract 24.5.
80. Winer I, Gilbert L, Vaishampayan U, et al. Clinical outcomes of ovarian cancer patients treated with ALKS 4230, a novel engineered cytokine, in combination with pembrolizumab: ARTISTRY-1 trial [SITC abstract 347]. *J Immunother Cancer*. 2020;8(3)(suppl).
81. Liu X, Hogg GD, DeNardo DG. Rethinking immune checkpoint blockade: 'Beyond the T cell'. *J Immunother Cancer*. 2021;9(1):e001460.
82. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. *Nat Immunol*. 2015;16(4):343-353.
83. Rothlin CV, Ghosh S. Lifting the innate immune barriers to antitumor immunity. *J Immunother Cancer*. 2020;8(1):e000695.
84. James NE, Woodman M, DiSilvestro PA, Ribeiro JR. The perfect combination: enhancing patient response to PD-1-based therapies in epithelial ovarian cancer. *Cancers (Basel)*. 2020;12(8):E2150.
85. Hartl CA, Bertschi A, Puerto RB, et al. Combination therapy targeting both innate and adaptive immunity improves survival in a pre-clinical model of ovarian cancer. *J Immunother Cancer*. 2019;7(1):199.
86. Zamarin D, Walderich S, Holland A, et al. Safety, immunogenicity, and clinical efficacy of durvalumab in combination with folate receptor alpha vaccine TPIV200 in patients with advanced ovarian cancer: a phase II trial. *J Immunother Cancer*. 2020;8(1):e000829.
87. O'Cearbhaill RE, Gnjatic S, Aghajanian C, et al. A phase I study of concomitant galinpepimut-s (GPS) in combination with nivolumab (nivo) in patients (pts) with WT1+ ovarian cancer (OC) in second or third remission [ASCO abstract 5553]. *J Clin Oncol*. 2018;36(15)(suppl).
88. Ott PA, Hu-Lieskovan S, Chmielowski B, et al. A phase Ib trial of personalized neoantigen therapy plus anti-PD-1 in patients with advanced melanoma, non-small cell lung cancer, or bladder cancer. *Cell*. 2020;183(2):347-362.e24.
89. Rocconi RP, Grosen EA, Ghamande SA, et al. Gemogenovatucel-T (Vigil) immunotherapy as maintenance in frontline stage III/IV ovarian cancer (VITAL): a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Oncol*. 2020;21(12):1661-1672.
90. Rocconi RP, Ghamande SA, Barve MA, et al. Maintenance vigil immunotherapy in newly diagnosed advanced ovarian cancer: efficacy assessment of homologous recombination proficient (HRP) patients in the phase IIb VITAL trial [ASCO abstract 5502]. *J Clin Oncol*. 2021;39(15)(suppl).
91. Zhang X, He T, Li Y, et al. Dendritic cell vaccines in ovarian cancer. *Front Immunol*. 2021;11:613773.
92. Rob L, Cibula D, Knapp P, et al. Dendritic cell vaccine (DCVAC) combined with chemotherapy (CMT) in patients with newly diagnosed epithelial ovarian carcinoma (EOC) after primary debulking surgery (PDS): biomarker exploratory analysis of a phase 2, open-label, randomized, multicenter trial [ASCO abstract 5521]. *J Clin Oncol*. 2021;39(15)(suppl).
93. Pedersen M, Westergaard MCW, Milne K, et al. Adoptive cell therapy with tumor-infiltrating lymphocytes in patients with metastatic ovarian cancer: a pilot study. *OncoImmunology*. 2018;7(12):e1502905.
94. Sarivalasis A, Morotti M, Mulvey A, Imbimbo M, Coukos G. Cell therapies in ovarian cancer [published online April 22, 2021]. *Ther Adv Med Oncol*. doi:10.1177/17588359211008399.
95. Kverneland AH, Pedersen M, Westergaard MCW, et al. Adoptive cell therapy in combination with checkpoint inhibitors in ovarian cancer. *Oncotarget*. 2020;11(22):2092-2105.
96. Chandran SS, Klebanoff CA. T cell receptor-based cancer immunotherapy: emerging efficacy and pathways of resistance. *Immunol Rev*. 2019;290(1):127-147.
97. Benard E, Casey NP, Inderberg EM, Wälchli S. SJI 2020 special issue: a catalogue of ovarian cancer targets for CAR therapy. *Scand J Immunol*. 2020;92(4):e12917.
98. Odunsi K, Cristea MC, Dorigo O, et al. A phase I/IIa, open label, clinical trial evaluating the safety and efficacy of autologous T cells expressing enhanced TCRs specific for NY-ESO-1 in patients with recurrent or treatment refractory ovarian cancer (NCT01567891) [ASCO abstract TPS3094]. *J Clin Oncol*. 2017;35(15)(suppl).
99. Stadtmauer EA, Fraietta JA, Davis MM, et al. CRISPR-engineered T cells in patients with refractory cancer. *Science*. 2020;367(6481):eaba7365.
100. Rafiq S, Hackett CS, Brentjens RJ. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. *Nat Rev Clin Oncol*. 2020;17(3):147-167.
101. Wu Z, Cheung NV. T cell engaging bispecific antibody (T-BsAb): from technology to therapeutics. *Pharmacol Ther*. 2018;182:161-175.
102. Hoffmann P, Hofmeister R, Brischwein K, et al. Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct. *Int J Cancer*. 2005;115(1):98-104.
103. Baeuerle PA, Kufer P, Bargou R. BiTE: teaching antibodies to engage T-cells for cancer therapy. *Curr Opin Mol Ther*. 2009;11(1):22-30.
104. Pons-Tostivint E, Latouche A, Vaflard P, et al. Comparative analysis of durable responses on immune checkpoint inhibitors versus other systemic therapies: a pooled analysis of phase III trials. *JCO Precis Oncol*. 2019;3(3):1-10.
105. Taube JM. Unleashing the immune system: PD-1 and PD-Ls in the pre-treatment tumor microenvironment and correlation with response to PD-1/PD-L1 blockade. *OncoImmunology*. 2014;3(11):e963413.

106. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
107. Taube JM, Anders RA, Young GD, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med*. 2012;4(127):127ra37.
108. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568-571.
109. McLaughlin J, Han G, Schalper KA, et al. Quantitative assessment of the heterogeneity of PD-L1 expression in non-small-cell lung cancer. *JAMA Oncol*. 2016;2(1):46-54.
110. Trujillo JA, Sweis RF, Bao R, Luke JJT. T cell-inflamed versus non-T cell-inflamed tumors: a conceptual framework for cancer immunotherapy drug development and combination therapy selection. *Cancer Immunol Res*. 2018;6(9):990-1000.
111. Chan TA, Yarchoan M, Jaffee E, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol*. 2019;30(1):44-56.
112. Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. *Science*. 2018;362(6411):eaar3593.
113. Ledermann JA, Colombo N, Oza AM, et al. Avelumab in combination with and/or following chemotherapy vs chemotherapy alone in patients with previously untreated epithelial ovarian cancer: results from the phase 3 javelin ovarian 100 trial. Scheduled for presentation at: SGO Annual Meeting on Women's Cancer; March 28-31, 2020; Toronto, Canada (meeting cancelled). Abstract LBA 25.
114. Landen C, Molinero L, Sehoui J, et al. Association of BRCA1/2, homologous recombination deficiency, and PD-L1 with clinical outcomes in patients receiving atezolizumab versus placebo combined with carboplatin, paclitaxel, and bevacizumab for newly diagnosed ovarian cancer: exploratory analyses [SGO Annual Meeting on Women's Cancer abstract 62]. *Gynecol Oncol*. 2021;162(1)(suppl).
115. Ayers M, Lunceford J, Nebozhyn M, et al. IFN-γ-related mRNA profile predicts clinical response to PD-1 blockade. *J Clin Invest*. 2017;127(8):2930-2940.
116. Ledermann JA, Shapira-Frommer R, Santin AD, et al. Association of gene expression signatures and TMB with response to pembrolizumab (pembro) in patients (pts) with recurrent ovarian cancer (ROC) enrolled in KEYNOTE-100 [ASCO abstract 843P]. *Ann Oncol*. 2020;31(4)(suppl).
117. Fattore L, Ruggiero CF, Liguoro D, et al. The promise of liquid biopsy to predict response to immunotherapy in metastatic melanoma. *Front Oncol*. 2021;11:645069.
118. Kilgour E, Rothwell DG, Brady G, Dive C. Liquid biopsy-based biomarkers of treatment response and resistance. *Cancer Cell*. 2020;37(4):485-495.
119. Snyder A, Morrissey MP, Hellmann MD. Use of circulating tumor DNA for cancer immunotherapy. *Clin Cancer Res*. 2019;25(23):6909-6915.
120. Huber V, Vallacchi V, Fleming V, et al. Tumor-derived microRNAs induce myeloid suppressor cells and predict immunotherapy resistance in melanoma. *J Clin Invest*. 2018;128(12):5505-5516.
121. Wu TD, Madireddi S, de Almeida PE, et al. Peripheral T cell expansion predicts tumour infiltration and clinical response. *Nature*. 2020;579(7798):274-278.
122. Capone M, Fratangelo F, Giannarelli D, et al. Frequency of circulating CD8+CD73+T cells is associated with survival in nivolumab-treated melanoma patients. *J Transl Med*. 2020;18(1):121.
123. Meyer C, Cagnon L, Costa-Nunes CM, et al. Frequencies of circulating MDSC correlate with clinical outcome of melanoma patients treated with ipilimumab. *Cancer Immunol Immunother*. 2014;63(3):247-257.
124. Zhou J, Mahoney KM, Giobbie-Hurder A, et al. Soluble PD-L1 as a biomarker in malignant melanoma treated with checkpoint blockade. *Cancer Immunol Res*. 2017;5(6):480-492.
125. Weber JS, Sznol M, Sullivan RJ, et al. A serum protein signature associated with outcome after anti-PD-1 therapy in metastatic melanoma. *Cancer Immunol Res*. 2018;6(1):79-86.
126. Sears CL, Pardoll DM. The intestinal microbiome influences checkpoint blockade. *Nat Med*. 2018;24(3):254-255.
127. Hayase E, Jenq RR. Role of the intestinal microbiome and microbial-derived metabolites in immune checkpoint blockade immunotherapy of cancer. *Genome Med*. 2021;13(1):107.
128. Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol*. 2017;28(6):1368-1379.
129. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science*. 2018;359(6371):97-103.
130. Lee KA, Luong MK, Shaw H, Nathan P, Bataille V, Spector TD. The gut microbiome: what the oncologist ought to know. *Br J Cancer*. 2021;125(9):1197-1209.
131. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*. 2018;359(6371):104-108.
132. Huang C, Li M, Liu B, et al. Relating gut microbiome and its modulating factors to immunotherapy in solid tumors: a systematic review. *Front Oncol*. 2021;11:642110.