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Gynecologic Cancers (LA Cantrell, Section Editor)

Review of Immune Therapies Targeting Ovarian Cancer

Cong (Ava) Fan, BS
Jocelyn Reader, PhD
Dana M. Roque, MD[*]

Address
[*]Division of Gynecologic Oncology, Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland-Baltimore, 22 S. Greene Street S3AX31, Baltimore, MD, 21201, USA
Email: droque@som.umaryland.edu

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Opinion statement

The rise of immunotherapy is the greatest advance in oncology to occur over the last several years, but applications in gynecologic malignancies lag behind other tumors. The term "immunotherapy" envelops monoclonal antibodies as receptor mediators, including immune checkpoint inhibitors (ICPI), cancer vaccines, and adoptive immunotherapies alone or in combination with other therapeutic approaches. The purpose of this review is to summarize the status of immunotherapy trials in ovarian cancer and to specifically highlight data published in the last 1–2 years.

Introduction

Ovarian cancer is the fifth most common cause of cancer-related deaths in women, surpassing that of any other gynecological cancer. In the USA, an estimated 22,240 new cases of ovarian cancer will be diagnosed in 2018, and an estimated 14,070 women will succumb to the disease in this year alone [1]. In addition, there are more than 200,000 new cases of ovarian cancer and more than 150,000 deaths per year worldwide [2]. Initial treatment options for epithelial ovarian cancer (EOC) include cytoreductive surgery followed by platinum and taxane chemotherapy [3, 4] or neoadjuvant chemotherapy followed by interval debulking surgery [5, 6]. Due to the late stage at time of diagnosis (80%) [7], a high rate of recurrence (70–80%), and few treatment options for patients who develop resistance to frontline therapies, prognosis for ovarian cancer is poor, and the overall 5-year survival rate is only 47.4%. Thus, there is a great need to improve therapies available for

ovarian cancer patients, particularly for patients with platinum-resistant disease.

Immunotherapy has shown promise in other cancers such as melanoma, bladder, lung, leukemia, and breast [8–10]. The tumor immune environment, such as the presence of CD3+ tumor-infiltrating T cells and intraepithelial CD8+ tumor-infiltrating lymphocytes (TILs), correlates with survival and progression in ovarian cancer [8, 11–14], indicating a role for modulation of the immune system in this disease site is possible. Current immunotherapeutic strategies for ovarian cancer consist mainly of (1) monoclonal antibodies as receptor mediators, including immune checkpoint inhibitors (ICPI); (2) cancer vaccines; or (3) adoptive immunotherapies alone or in combination with other approaches.

Immune checkpoint inhibitors for ovarian cancer ICPIs impede the ability of the tumor to activate checkpoint proteins on the surface of T cells, thereby preventing the cancer from evading immune response and allowing the immune system to generate an antitumor response [15, 16]. Immune regulatory checkpoints are essential for cultivating peripheral tolerance and prevention of autoimmunity. Among the most well understood are cytotoxic lymphocyte-associated antigen 4 (CTLA-4) and programmed death receptor (PD-1). CTLA-4 abrogates autoreactive T cells in lymph nodes early in T cell activation, while PD-1 regulates previously activated T cells in non-lymphatic tissues later in the immune response and controls apoptosis of regulatory T cells [17, 18]. PD-1 expression occurs in instances of high T cell stimulation, such as cancer. Binding of PD-1 to its antigens PD-L1 and PD-L2 inhibits T cell proliferation/survival, via changes in interferon (IFN)-gamma, tumor necrosis factor-alpha, and IL-2, as well as phosphorylation downstream of the TCR, and increases in regulatory T cells [19]. Blocking these immune checkpoints with monoclonal antibodies is an attractive strategy [20].

A variety of ICPCs have gained FDA approval, yet the study of ICPIs in gynecologic cancers lags behind other disease sites. Nivolumab (Bristol-Meyers-Squibb) and pembrolizumab (Merck) target PD1. Both are IgG4 complexes, but differ subtly in binding site (N-loop versus CD-loop) and affinity (Kd = 3.06 pM versus 29 pM) [21]. Nivolumab has indications in melanoma, lung, renal cell, Hodgkin's lymphoma, hepatocellular carcinoma, head and neck, urothelial, and MSI-high colorectal carcinomas. Pembrolizumab has indications in melanoma, lung, head and neck, Hodgkin's lymphoma, PD-L1-expressing cervical, or gastric cancers and is notable as the first drug to gain site agnostic approval for tumors that exhibit microsatellite instability. Ipilimumab (Bristol-Meyers-Squibb; targets CTLA-4, with indications in melanoma, urothelial, and lung cancers. Atezolizumab (Genentech-Roche), darvulamab (Astra-Zeneca), and avelumab (EMD-Serono) target PD-L1 and are approved for urothelial/lung cancers, bladder/lung, and for lung/Merckel cell cancers, respectively.

Multiple early-phase clinical trials are ongoing to examine ICPIs in ovarian cancer (Table 1). Preliminary results from the JAVELIN Solid Tumor [22••] clinical trial of avelumab (anti-PD-L1) in 124 patients with refractory/recurrent ovarian cancer found an overall response rate (ORR) of 9.7%; stable disease (SD) was observed in 55 patients (44.4%), yielding a DCR of 54.0%. Only 6.5% of patients experienced a grade 3/4 treatment-related adverse event (AE). PD-L1 expression was present in 77% of patients; ORR was 12.3% in PDL-1+ versus 5.9% in PD-L1- patients. Preliminary results from a trial of pembrolizumab in 16 patients with PD-L1+ advanced ovarian cancer reported an ORR of 11.5%, with 1 patient with a complete response (CR), 2 with partial responses (PR), and 6 with SD. Progression-free survival (PFS) was reported as 1.9 months and overall survival (OS) as 13.1 months, with 73.1% of patients experiencing an AE but only 1 patient with a grade 3 treatment-related AE. A phase II study of ipilimumab in 40 patients with recurrent platinum-sensitive ovarian cancer reported a best overall response rate (BORR) of 10.3% by RECIST 1.1 ($n = 39$); however, 50% (20/40) of the patients experienced a grade 3 or higher treatment-related AE [23•]. Toxicities related to ICPIs most commonly include skin (rash, pruritus), gastrointestinal tract (diarrhea), infusion-related reactions, and fatigue, which may limit the clinical effectiveness of this class of drugs [24, 25].

There is immense interest in ICPIs in combination with poly-ADP-ribose polymerase inhibitors (PARPi) or vascular endothelial growth factor receptor (VEGF) inhibitors, including both monoclonal antibodies (e.g., bevacizumab) and small molecule inhibitors (e.g., cedirinib). There are currently numerous ongoing early-phase clinical trials focused on ICPIs in combination with these agents [26–30] (Table 1). A phase I study of durvalumab in combination with olaparib or cediranib in 26 patients with women's cancers found an 83% disease control rate (DCR) in patients who received durvalumab plus olaparib and a 75% DCR and 50% response rate in patients who received durvalumab plus

Table 1. Selected ongoing clinical trials of ICPIs in ovarian cancer

Drug	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
Ipilimumab (anti-CTLA-4) [Bristol-Meyers-Squibb]	monotherapy	10 mg/kg IV q 3 w x 4 doses (induction) then q 12 w (maintenance)	recurrent platinum sensitive ovarian cancer	grade 3 AEs within 90d induction	II	NCT01611558	active, not recruiting
	after allogenic stem cell transplant	dose escalation	persistent or progressive cancers, including EOC	grade 3/4 AEs, acute GVHD, autoimmune reaction within 60 d	I	NCT00060372	complete
Pembrolizumab (anti-CTLA-4) [Merck]	monotherapy	(KEYNOTE-100) 200 mg IV q 3 w x ≤ 2 y	recurrent, advanced disease (stratified across 1-3 and 4-6 prior lines)	ORR	II	NCT02674061	active, not recruiting
		200 mg IV q 3 weeks	advanced solid tumors, including EOC	genomic and immune biomarkers in blood and tumor	II	NCT02644369	active, not recruiting
		200 mg IV q 3 weeks	rare recurrent or relapsed tumors, including sex cord tumor, germ cell tumor, low-grade serous carcinoma, mucinous carcinoma, clear cell adenocarcinoma, small cell carcinoma, carcinosarcoma	ORR	II	NCT03012620	recruiting
		IV q 3 weeks x ≤ 1 year	metastatic, recurrent of locally advanced cancer with genomic instability (POLE/POLD1 or BRCA 1/2)	ORR	II	NCT03428802	recruiting
	+ cytotoxic	chemotherapeutics	carboplatin AUC 6 + paclitaxel 80 mg/m^2, pembrolizumab 200 mg starting cycle 2	stage IV EOC amenable to NACT		number of T-cells in peripheral blood	I/II
NCT03126812		recruiting					
		carboplatin AUC 6 d1 + paclitaxel 80 mg/m^2 IV d 1,8,15 q 21 d x 3 followed by IDS followed by re-initiation of chemotherapy +pembrolizumab 200 mg IV d1 q 21d x 3, followed by	stage III/IV EOC amenable to NACT	PFS	II	NCT02520154	recruiting

Table 1. (Continued)

Drug	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
		maintenance pembrolizumab x 20					
	carboplatin AUC 5-6, paclitaxel 175 mg/m^2, pembrolizumab 200mg IV q 21d followed by IDS then 3-4 additional cycles	stage III/IV EOC amenable to NACT	ORR	II		NCT02834975	recruiting
		pembrolizumab 200 mg IV, carboplatin AUC 5-6, paclitaxel 175mg/m^2 ± bevacizumab 15 mg/kg IV q 3 weeks x 4 followed by IDS and 2-5 cycles of adjuvant therapy	tage III/IV EOC amenable to NACT	complete resection rate at IDS	II	NCT03275506	not yet recruiting
		pembrolizumab 200 mg IV, carboplatin IV, paclitaxel 80 mg/m^2 IV d1 q 21 d followed by pembrolizumab IV q 21 d x 12 mo	suboptimally debulked EOC	PFS	II	NCT02766582	recruiting
		pembrolizumab IV over 30 min d1, carboplatin IV over 30 min d 8/15 x ≤ 2 years	recurrent platinum-sensitive EOC	PFS	I/II	NCT03029598	recruiting
		gemcitabine 750 mg + cisplatin 30 mg/m^2 d1 IV q 21d x 2 alone then in combination with pembrolizumab 200 mg IV q 21d	recurrent platinum-sensitive EOC	PFS	II	NCT02608684	recruiting
		paclitaxel 80 mg/m^2 + pembrolizumab 200 mg IV q 3 weeks* (KEYNOTE162)	platinum resistant EOC	PFS at 6 mo, AEs	II	NCT02440425	active, not recruiting
	+ PARPi	niraparib 200 mg po qd + pembrolizumab 200 mg IV q21 d	platinum-resistant EOC and triple negative breast cancer	DLTs, RP2D, ORR	I/II	NCT02657889	active, not recruiting; presented

Table 1. (Continued)

Drug	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
							at ASCO 2018
	+ bevacizumab and	cyclophosphamide	pembrolizumab IV + bevacizumab IV day 1 and cyclophosphamide po qd q 3 w x 12 mo	recurrent EOC	PFS	II	NCT02853318
recruiting							
	+ trebananib	dose escalation	advanced solid tumors, including platinum-resistant EOC	DLTs	I	NCT03239145	recruiting
	single-dose	200 mg pembrolizumab IV 14-21 d prior to surgery	chemo-naïve EOC scheduled for primary debulking surgery	fold-change in tumor infiltrates	I	NCT02728830	recruiting
Nivolumab (anti-PD-1) [Bristol-Meyers-Squibb]	+ cytotoxic	chemotherapeutics	carboplatin AUC 5-6, paclitaxel 80 mg/m^2, nivolumab 360 mg IV q 3 followed by IDS and adjuvant therapy for 6-8 total cycles, then maintenance nivolumab qmo x ≤ 12 mo	stage III/IV EOC amenable to NACT	DLTs	I	NCT03245892
recruiting							
		IP over 90 minutes on d 1/15,/29 q 6w	platinum-resistant/refractory EOC, uterine/cervical cancer progressive on a second-line regimen	DLTs, RP2D	I	NCT03508570	not yet recruiting
	± ipilimumab	nivolumab IV over 60 min ± ipilimumab IV over 90 min q 3w x 4 (induction) followed by nivolumab IV over 60 min q 2 w	persistent or recurrent EOC	ORR	II	NCT02498600	active, not recruiting
		nivolumab 240 mg IV q 2 w ± ipilimumab 1mg/kg q 6 w	clear cell EOC	ORR	II	NCT03355976	recruiting
		nivolumab 240 mg IV q 2 w + ipilimumab 1mg/kg q 6 w x 4	platinum resistant EOC, chemo-naïve breast amenable to NACT, advanced gastric tumors	ORR, AEs	II	NCT03342417	recruiting
		nivolumab IV over 30 min d1/15/29, + ipilimumab IV over 60 min d1 q 42d	rare tumors, including ovarian germ cell tumors, carcinosarcoma, adenosarcoma	ORR	II	NCT02834013	recruiting

Table 1. (Continued)

Drug	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
	+ anti-CD27	varlilumab 3 mg/kg q 2 w, 3 mg/kg q 12 w, or 0.3 mg/kg q 4 w, plus nivolumab 240 mg q 2 w	recurrent EOC	AEs, ORR	II	NCT02873962	active, not recruiting
	± PARPi	placebo alone, oral rucaparib bid alone, nivolumab IV q 4 w, alone, or rucaparib +nivolumab in combination	EOC treated with front line platinum therapy for maintenance therapy	PFS	III	NCT03522246 (ATHENA)	not yet recruiting
	+ anti-angiogenics	nivolumab + bevacizumab IV q 2 w	platinum sensitive or resistant EOC ≤3 prior lines	ORR	I/II	NCT02335918	recruiting
Atezolizumab (anti-PD-L1) [Genentech-Roche]	+ anti-angiogenics and acetylsalicylic acid	bevacizumab, bevacizumab + atezolizumab, atezolizumab, atezolizumab + acetylsalicylic acid	recurrent platinum- resistant EOC	PFS	II	NCT02659384	recruiting
	+ cytotoxic	chemotherapeutics	carboplatin AUC 5 + cyclophosphamide 600 mg/m^2 IV d1, atezolizumab 840 mg IV d1/15 q28d	recurrent EOC (JAVELIN Solid Tumor), M1			
cervical/breast cancer, stage IV		cervical/endometrial cancers	PFS	I		NCT02914470	active, not recruiting
Avelumab (anti-PD-L1) [EMD-Serono]	monotherapy	dose-finding	(JAVELIN Solid Tumor)	DLTs, ORR	I	NCT01772004	active, not recruiting
	+ cytotoxic	chemotherapeutics	carboplatin and paclitaxel (qw or q 21d) ± avelumab q 3 wk ± maintenance q 2 w	previously untreated EOC (JAVELIN Ovarian 100)	PFS	III	NCT02718417
active, not recruiting							
		avelumab 10 mg/kg d1/15 q 2 w, PLD 40 mg/m2 d1 q 28d, or in combination	platinum resistant/refractory EOC (JAVELIN Ovarian 200)	OS, PFS	III	NCT02580058	active, not recruiting
	± HDAC inhibitor	avelumab d1 q 14d ± entinostat d1/8 q 14	refractory or recurrent EOC	AEs, PFS	I/II	NCT02915523	completed
	+ RT	avelumab dose not specified	recurrent EOC with 2 non-CNS metastasis and one outside radiation field	ORR	II	NCT03312114	recruiting
	+ PARPi	dose-finding		DLTs, ORR	Ib/II		recruiting

Table 1. (Continued)

Drug	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
			recurrent platinum-sensitive EOC, other metastatic/locally advanced solid tumors			NCT03330405 (JAVELIN PARP Medley)	
	+ other	immunotherapies	• A: avelumab + utomilumab (4-1BB agonist mAb) • B: avelumab + PF-04518600 (OX40 agonist mAb) • C: avelumab + PD 0360324 (M-CSF mAb) • D: avelumab + utomilumab + PF-04518600				
platinum-resistant EOC, other locally advanced or metastatic solid tumors	DLTs, ORR	Ib/II	NCT02554812 (JAVELIN Medley)	recruiting			
Durvalumab (anti-PD-L1)	+ cytotoxic	chemotherapeutics	carboplatin AUC6 + paclitaxel 80 mg/m2 d1/8/15 + durvalumab 750 mgd1/15 q 21d; maintenance durvalumab q 2w q 28d x cycles 7-13	frontline EOC			
		(non-mucinous)	biomarkers	I/II		NCT02726997	recruiting
investigator's choice chemotherapy versus durvalumab 1500mg IV q 28d	recurrent ovarian clear cell carcinoma	PFS	II	NCT03405454		recruiting	
	+ PLD	recurrent platinum-resistant EOC	MTD, PFS	I/II		NCT02431559	active, not recruiting
		durvalumab 1.12g IV d1 + eribulin 1.1 -1.4 mg/m^2 IV d8 q 21d	recurrent EOC, triple-negative breast cancer	DLTs	I	NCT03430518	recruiting
	+ cytotoxic	chemotherapeutics and ± other immunotherapies	carboplatin AUC 5 IV + paclitaxel 175 mg/m^2 IV + durvalumab 1125 mg IV ± tremelimumab 75 mg/m^2 (if residual disease at IDS)	EOC amenable to NACT	DLTs	I/II	NCT03249142 (INeOV)
recruiting							
	paclitaxel + carboplatin IV with durvalumab	advanced solid tumors, including EOC	laboratory findings, AEs,	I		NCT02658214	recruiting

Table 1. (Continued)

Drug	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
	IV + tremelimumab IV (for EOC cohort) + PARPi and other	immunotherapies	olaparib po bid with tremelimumab IV + durvalumab IV d1 q 28d; olaparib for ≤≤ 12 mo, tremelimumab x ≤ 4, durvalumab x ≤ 13	recurrent or refractory EOC with BRCA1/2 mutation	DLTs, PFS	I/II	NCT02953457
recruiting							
	+ other	immunotherapies	MEDI0562 (OX40) + tremelimumab combination, MEDI0562 (OX40) + durvalumab, MEDI9447 (CD73) + durvalumab	relapsed EOC	DCR	II	NCT03267589
recruiting							
		durvalumab + tremelimumab	recurrent or refractory ovarian, colorectal, non-triple negative breast cancer, renal cell, cervical cancer, with at least one lesion measurable by irRC not previously irradiated	AEs	I	NCT01975831	active, not recruiting
		bi-shRNAfurin + GMCSF autologous tumor cell immunotherapy + durvaluman 1500 mg IV q 4 w	recurrent, platinum resistant EOC	AEs	I/II	NCT02725489	recruiting by invitation
	sequential: tremelimumab 3 mg/kg IV q4w x ≤4 followed by durvalumab 1.5 g IV q4w x ≤ 9 doses upon progression concurrent: tremelimumab 1 mg/kg IV + durvalumab 1.5g IV q4w for up to 4 doses followed by	recurrent high-grade EOC	irPFS	II		NCT03026062	recruiting

Table 1. (Continued)

Drug	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
	durvalumab monotherapy 1.5 g IV q4w x ≤ 9						
	+ other	immunotherapies and RT	durvalumab q4w x ≤ 13 + tremelimumab q 4w x ≤ 4 +RT	advanced solid tumors, including EOC	MTD	I/II	NCT03277482
recruiting							
	+ PARPi and anti-angiogenics	olaparib po (200 mg or 300 mg) bid q 28d ± durvalumab 3mg/kg or 10mg/kg IV) ± cediranib po qd (15, 20, or 30 mg daily)	advanced or recurrent EOC	RP2D, ORR	I/II	NCT02484404	recruiting
		durvalumab IV q 4 w + olaparib po bid ± bevacizumab IV q 2 w	recurrent EOC	DCR, DTLs		NCT02734004	recruiting

*Abbreviations: EOC- epithelial ovarian cancer; ICPI- immune checkpoint inhibitor; AE- adverse events; GVHD- graft versus host disease; IV- intravenous; ORR- overall response rate; PFS- progression-free survival; irPFS- immune-related progression-free survival; irRC- immune related response criteria; DLT- dose-limiting toxicities; RP2D- recommended phase II dose; po- per os; ASCO- American Society of Clinical Oncology; AUC- area under the curve; IDS- interval debulking surgery; NACT- neoadjuvant chemotherapy; min- minutes; d- day; w- week; mo- month; y- year; PARPi- poly-ADP-ribose polymerase inhibitor; IP- intraperitoneal; bid- twice daily; HDAC- histone deacetylase; RT- radiation therapy; DCR- disease control rate; * first cycle is 28 d with pembolizumab given d8 in order to determine tolerance of weekly paclitaxel*

trial of atezolizumab (anti-PD-L1) versus placebo with standard frontline chemotherapeutics and bevacizumab on yet untreated patient with advanced EOC and fallopian or primary peritoneal cancers (NCT03038100) [32].

Biomarkers to predict response to ICPI in ovarian cancer must be validated. The definition of PD-L1 "positivity" varies greatly. Microsatellite instability (MSI) leading to high mutational burden was first shown to be predictive of response to ICPIs in colorectal carcinomas [33]. Rates of MSI may vary by histologic subtype of ovarian cancer. One group identified a subset of ovarian clear cell carcinomas, typically characterized by worse prognosis compared to other histological subtypes, associated with increased MSI and increased tumor immunogenicity [34]. *BRCA1/2* mutations may also be associated with increased mutation load, immunogenicity, and greater expression of PD-1/PD-L1, indicating that these patients may respond well to ICPIs [35]. Others have suggested that whole exome sequencing may also identify disruptions of the PD-L1 gene, signifying that genetic characteristics may, one day, be used to identify ICPI responsiveness [36]. Such observations underscore the need for further study of the effects of genomic instability, homologous recombination status, or *BRCA 1/2* mutations on ICPI outcome [29, 37, 38].

Vaccination strategies for ovarian cancer The first attempt to use vaccination to stimulate immune function occurred in 1891 when William Coley injected *Streptococcus pyogenes* and *Serratia marcescens* intratumorally, after observing regression of sarcoma in a patient with erysipelas [39]. Modern cancer vaccines consist of autologous whole cells, dendritic cells loaded with autologous tumor-specific antigens, or plasmids that result in antigen expression and immune activation after repeated exposure. Each vaccination strategy may be further augmented by a variety of immune-modulatory agents.

Engineered autologous tumor cell immunotherapy represents an elegant approach to restoration of T cell effector function. This may involve transfection of autologous irradiated tumor cells with a plasmid encoding for the upregulation of immunostimulants and downregulation of immunosuppressants. One notable example is Vigil® (Gradalis, Carrollton, TX), containing a proprietary plasmid leading to up regulation of granulocyte-monocyte colony stimulating factor (GM-CSF) and silencing of furin, an enzyme that activates transforming growth factor (TGF)-ß1/2. Expression of GM-CSF stimulates antigen presentation; inhibition of TGF-ß1/2 allows antigen-presenting cells to recognize tumor antigens. Early studies showed that response to vaccination (as manifested by positivity in gamma-interferon) using $\geq 10^7$ cells with the construct for up to 12 monthly injections in solid tumors correlated with survival (25.7 versus 11.6 months) [40]. In 2017, similar immune results were found using a 1-log lower-dose formulation in a study of 15 patients, including 40% with heavily pre-treated ovarian cancer [41], which suggests smaller tumor samples are required for initial engineering. Additional studies of this technology as maintenance therapy remain in progress (NCT02346747, NCT01309230) [42, 43].

An antigen of recent interest in gynecologic malignancies is folate receptor (FR)-α (also known as folate-binding protein, FBP), as it is highly overexpressed in ovarian and type 2 endometrial cancers, coinciding with increased DNA production and turnover. Jackson and colleagues (2017) recently published results of a phase I/IIa trial employing E39 (GALE 301), an HLA-A2 restricted, FRα peptide in women without evidence of disease following treatment of initial disease ($n = 24$ with 16 controls) or recurrence ($n = 5$ with 6 controls). A total of 6 monthly injections (100, 500, or 1000 μg) with granulocyte macrophage-colony stimulating factor (GM-CSF) were provided. Delayed-type hypersensitivity increased in a dose-dependent fashion (13.3% vs 55% CG, $p = 0.01$). Estimated 2-year disease-free survival (DFS) was 85.7% in the 1000 μg group vs 33.6% in controls ($p = 0.021$). A subsequent phase Ib study of breast and ovarian cancer patients evaluated six serial immunizations using E39 and an attenuated variant (E39′) (E39 × 6, versus E39 × 3 then E39′ × 3, E39′ × 3 then E39 × 3). This study suggested benefit to incorporation of attenuated vaccine with no new safety signals [44]. Immune response was successfully generated without significant AEs in 90% of patients in a related phase I trial of 22 patients with a history of ovarian cancer or breast cancer and no evidence of disease who were treated with metronomic cyclophosphamide then vaccinated 6 times monthly [45••]. While this provides biologic plausibility, there is presently no estimate on clinical efficacy of this approach.

Of note, FRα is also the target for mirvetuximab soravtansine (IMGN853), a humanized monoclonal antibody attached via a disulfide-containing linker to the cytotoxic maytansinoid, DM4. Once released within the target cell, DM4 acts as an anti-mitotic agent that

inhibits tubulin polymerization and microtubule assembly, resulting in cell cycle arrest and apoptosis. A phase III study of mirvetuximab soravtansine versus investigator's choice chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan) in platinum-resistant ovarian cancer is currently ongoing (FORWARD1, NCT02631876) [46]. Mirvetuximab soravtansine is not independently cytotoxic to FRα-negative endometrial cells in vitro; however, bystander killing on FRα-negative cells in co-culture with FRα-positive cells does occur [47]. This effect is presumably secondary to diffusion of metabolites to adjacent cells following lysosomal processing post-internalization [48]. Thus, antibody-drug conjugation may offer prominent advantages relative to other FRα-targeting strategies including farletuzumab (MORAb-003; Morphotek, Inc., Exton, PA), which relies only upon antibody-dependent cellular and complement-dependent cytotoxicity.

Other tumor-associated antigens (TAA) of interest in ovarian cancer belong to cancer-testis family and p53, the latter of which is nearly universally mutated in ovarian cancers [49]. Vaccination strategies targeting cancer-testis antigen (e.g., MAGE, NY-ESO) are reviewed extensively elsewhere [50]. Despite much early excitement surrounding various vaccination strategies targeting various TAAs, phase III trials have historically been disappointing. One notable example is vaccination with anti-idiotypic antibodies against glycoprotein CA-125, an FDA-approved serum biomarker to monitor clinical response to therapy in ovarian cancer, which failed at the phase III level for reasons still not fully understood, but which remain under active investigation [51]. Recently, a phase I trial of a modified vaccinia ankara vaccine delivering wild-type human p53 (p53MVA) in combination with gemcitabine chemotherapy in patients with platinum-resistant ovarian cancer showed longer PFS in patients with p53 reactive CD4+/CD8+ T cells but unacceptable toxicity with chemotherapy administration [52•]. These studies serve as a humbling reminder of the complexity of the immune response in disease.

Adoptive immunotherapy in ovarian cancer Adoptive immunotherapy is based on the infusion of autologous or allogeneic neoplastic targeting immune cells that have been expanded and/or activated ex vivo [53, 54]. Adoptive immunotherapy can be based on antigen-independent (innate immunity, e.g., natural killer (NK) and cytokine-induced killer (CIK) cells) or antigen-dependent (adaptive immunity, e.g., TILs, chimeric antigen receptor (CAR) T cells) strategies [53].

NK cells can kill tumor cells without prior sensitization or need for MHC expression and have an important role in tumor immunosurveillance. Individuals with impaired NK cell function display an increased risk of cancer development [55, 56]. Initial clinical trials involving NK cells focused on response modifiers and cytokine therapy to potentiate autologous antitumor response in vivo and demonstrated conflicting results [55].

Most of the clinical trials using NK cells remain in early-phase development; however, data thus far suggest that administration of large numbers of donor NK cells is safe, feasible, and efficacious in patients with leukemia and solid tumors (NCT01212341) [57, 58]. Administration of lymphodepleting chemotherapy and T cell suppression with allogenic NK cells has been shown to increase TTP from 52 days with fludarabine, cyclophosphamide, cyclosporine, NK cells, IL-2 (Arm 1) to 98 and 100 days using this regimen plus 10 mg methylprednisolone (Arm 2) or 1 mg methylprednisolone (Arm 3), respectively (NCT01105650). Arm 2 experienced a decrease in disease progression (33%, 1/3) compared to Arm 1 (67%, 2/3) and Arm 3 (71%, 5/7) suggesting benefit from higher doses of methylprednisolone. Both Arm 2 (1/3) and Arm 3 (3/7) treatments resulted in improved OS at 1 year compared to Arm 1 (0/3). CAR-NK cells, chimeric antigen receptor-engineered NK cells, have also been explored in vitro and in hematologic and MUC1-positive solid tumors, but have yet to be tested clinically in ovarian cancer [59, 60]. While data from many NK cell clinical trials demonstrates that this treatment is safe, one trial (NCT00652899) was terminated early due to toxicity.

While clinical trials involving cytokine-induced killer (CIK) cells are numerous for other cancers, data are much more limited for ovarian cancer. In one study, stage II ovarian cancer patients receive radiofrequency ablation (RFA) with and without autologous transfer of CIKs (Table 2). Several studies have been published analyzing the efficacy of CIK cells in the treatment of solid tumors including ovarian cancer [61–63]. Liu et al. in a phase II study tested the role of CIK cells in maintenance therapy after first-line treatment in advanced epithelial ovarian cancer [61]. Ninety-two patients underwent cytoreductive surgery followed by 6–8 courses of carboplatin and paclitaxel chemotherapy and

Table 2. Selected ongoing clinical trials of biologicals in ovarian cancer

Cell	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
	NK cells ± cyrosurgery	8-10 billion cells (I.V.) x 3	recurrent ovarian cancer	ORR (3 months)	I/II	NCT02849353	recruiting
	allogenic NK Cells ± cyclophosphamide and fludarabine	IP delivery	recurrent ovarian fallopian tube, primary peritoneal carcinoma	AE (6 months)	I	NCT03539406	not yet recruiting
NK	FATE-NK100 (donor activated NK cells) with IL-2	IP delivery, single infusion	recurrent EOC, fallopian tube/ primary peritoneal cancer	MTD	I	NCT03213964	recruiting
	allogeneic NK cells, fludarabine, cyclophosphamide, IL-2, INCB024360 - IDO inhibitor	IP delivery, single infusion	recurrent EOC, fallopian tube cancer, primary peritoneal cancer	MTD	I	NCT02118285	complete
	allogenic NK cells, cyclophosphamide, cyclosporine, IL-2, methylprednisolone	NK cells with lymphodepleting chemotherapy and T-cell suppression (CsA (Arm1)/ CsA + 10 mg methylprednisolone (Arm 2) / CsA + 1 mg methylprednisolone(Arm 3))	recurrent EOC, fallopian tube, primary peritoneal cancer, metastatic breast cancer	ORR	II	NCT01105650	complete
CIK	RFA ±CIK	RFA along or RFA + CIK, one IV infusion one weeks after RFA	FIGO stage II ovarian cancer	RFS	II	NCT02487693	active, not recruiting
TIL	TILs and pembrolizumab after cyclophosphamide	cyclophosphamide 60 mg/kg or 30 mg/kg per day for 2 days followed by TILs IV 1x10^10-1.6x10^11 cells, IL-2 subQ daily and pembrolizumab 200mg IV q 3 weeks	advanced ovarian cancer, metastatic melanoma	SAE within 35 days of TIL infusion	I	NCT03158935	recruiting
	restimulated TILs/ autologous dendritic cells after cyclophosphamide treatment	cyclophosphamide 30mg/kd/day for 2 days dose escalation of IV TILS subQ IL-2 x 4 days during 1st week and x5 days during 2nd week	recurrent, platinum-resistant high grade serous ovarian, fallopian tube, or primary peritoneal cancer	AE	I	NCT01883297	recruiting
	TILS after cyclophosphamide and fludarabine with prior treatment with	1x ipilimumab 3mg/kg 14 d prior to TIL harvesting, cyclophosphamide 60 mg/kg IV x2, fludarabine	metastatic ovarian, fallopian tube, or primary peritoneal cancer	AE	I/II	NCT03287674	recruiting

Table 2. (Continued)

Cell	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
	ipilimumab and nivolumab	25 mg/m2 x2, 1x IV TILS, IL-2 subQ daily x14 days					
	TILs after fludarabine and total body radiation	fludarabine 25 mg/m2 x 3d, TBR x 1d, TILS, IL-2 every 8 hours to tolerance, max 10 doses	metastatic epithelial ovarian cancer, fallopian tube, primary peritoneal carcinomatosis	ORR, AE	II	NCT03412526	not yet recruiting
	CD8+ T cells and utomilumab, cyclophosphamide	CD8+ T cells IV following anti-CD137 at 0, 0.3 mg/kg or 1.2 mg/kg IV, cyclophosphamide 300 mg/m2 IV, IL-2 subQ every 12 hours x 14 days (28 doses)	platinum-resistant high grade ovarian cancer	AE, duration of *in vivo* persistence	I	NCT03318900	not yet recruiting
Engineered T-cells: TCR	cyclophosphamide and TAEST16001 (NY-ESO-1 specific TCR-T cell)	2x 1g/ day of cyclophosphamide, 1 x IV anti-NY-ESO-1 TCR, IL-2 subQ x 14 d	ovarian, bone sarcoma, soft tissue sarcoma, melanoma, liver, esophageal, breast and thyroid cancers that failed multi-line treatment	AE (30 days)	I	NCT03159585	recruiting
	cyclophosphamide and TBI-1301 (NY-ESO-1 specific TCR gene transduced autologous T lymphocytes	cyclophosphamide IV 750 mg/m2/d x 2, TBI-1301	NY-ESO- expressing solid tumors in HLA-A2 patients, metastatic or recurrent unresectable solid tumor, synovial sarcoma, melanoma, esophageal, ovarian, lung, bladder, liver cancers	AE, RP2D	I	NCT02869217	recruiting
	cyclophosphamide, fludarabine, anti-NY ESO-1 TCR-transduced T cells	cyclophosphamide 60 mg/kg/day IV x2, fludarabine 25 mg/m2/day IV x4, anti-NY ESO-1	NY-ESO- expressing solid tumors in HLA-A2 patients, ovarian cancer, bladder, breast, other metastatic solid cancers	AE (8 weeks)	I	NCT02457650	recruiting
	NYESO-1c259 T cells	cytoreductive chemotherapy followed by 1 x IV NYESO-1(C259) transduced T cells (5 x 10^9 cells, min 1x10^9 cells, max 6 x 10^9 cells)	recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma with refractory or platinum resistance disease and/ or >/= 2 lines chemotherapy and HLA A*0201, HLA-A*0205, and/or	AE > or = grade 3 (30 days ± 10 days)	I/II	NCT01567891	active, not recruiting

Table 2. (Continued)

Cell	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
			HLA-A*0206 positive with tumors expressing NY-ESO-1 tumor antigen				
	Individual patient TCR-transduced PBL, cyclophsphamide, fludarabine, aldesleukin	cyclophosphamide IV 60 mg/kg/day x 2 days with D5W with mesna 15 mg/kg/day over 1 hour x 2 days, fludarabine 25 mg/m2/day x 4, aldesleukin 720,000 IU/kg IV every 8 hours x 4 days (max 10 doses) or 72,000 IU/kg IV, TCR-transduced PBL IV 1.5E11	gastrointestinal and genitourinary cancers (metastatic), breast and ovarian, and other solid cancers (metastatic), non-small cell lung cancer (NSCLC) (metastatic), glioblastoma	ORR	II	NCT03412877	recruiting
	genetically engineered NY-ESO-1-specific lymphocytes, aldesleukin, cyclophosphamide, decitabine	course 1: decitabine IV daily days 1-3, cyclophosphamide IV days 5-6, and genetically engineered NY-ESO-1-specific T lymphocytes IV and IP day 9. Patients also receive aldesleukin SC BID on days 10-23. course 2: decitabine IV daily days 31-33, genetically engineered NY-ESO-1-specific T lymphocytes IV and IP on day 37, and aldesleukin SC BID on days 38-51	recurrent or refractory epithelial ovarian, primary peritoneal or fallopian tube carcinoma, if plantinum sensitive disease, have received >= 2 lines of chemotherapy. Subjects may have received PARP inhibitators, bevacizumab or immunotherapy.	AE (28 days)	I	NCT03017131	recruiting
	TBI-1201 (MAGE-A4-specific TCR transduced T lymphocyes), cyclophosphamide, fludarabine	dose escalation TBI-1201 with cyclophosphamide 750 mg/m^2/day x 2 days IV and with (experiment 3) fludarabine (20mg/m^2 x 5 days IV	metastatic or recurrent solid tumor, refractory to standard treatment, unresectable, HLA-A*24:02 positive tumor, MAGE-A4-expression	AE, appearance of replication competent retrovirus, appearance of clonality, kinetics of TBI-1201 in blood	I	NCT02096614	recruiting
		IV x 1 of T cells	ovarian, urinary bladder, melanoma, head and	AE/ SAE (3.5 years), DLT, persistence	I	NCT03132922	recruiting

Table 2. (Continued)

Cell	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
	autologous genetically modified MAGE-A4c1032 T cells		neck, non-small cell lung, esophageal, gastric, synovial, myxoid round cell liposarcoma, HLA-A*02 positive and subject's tumor shows expression of the MAGE-A4 RNA or protein	of genetically modified T cells, RCL (replication competent lentivirus) in genetically modified T cells			
	Mov-gamma chimeric receptor gene (chimeric antigen receptor against folate-binding protein), aldesleukin, therapeutic allogeneic lymphocytes	dose escalation of Mov-PBL ±IL-2	recurrent, resected recurrent or residual ovarian epithelial cancer, failed SoC, tumor positive for folate-binding protein (MOv18 antibody test)	MTD	I	NCT00019136	complete
	4H11-28z/fIL-12/EGFRt+ Genetically-modified T cells, cyclosphosphamide, fludarabine	dose escalation of T cells (cohort I), cyclophosphamide750 mg/m^2 or cyclophosphamide 300 mg/m^2 x 2 days with fludarabine 25-30 mg/m^2 x 3 days	solid tumors - tumors must express MUC16ecto	MTD (2 years), DLT	I	NCT02498912	recruiting
Engineered T-cells: CAR	anti-meso-CAR vector transduced T cells	dose escalation using anti-meso-CAR vector transduced T cells	chemotherapy refractory or relapsed mesothelin positive ovarian, triple negative breast cancer, endometrial, pancreatic, malignant mesothelioma	AE (up to 24 weeks ≥ grade 3	I	NCT02580747	recruiting
	anti-mesothelin CAR transduced PBL, cyclophosphamide, fludarabine	dose escalation to determine MTD for T cells, fludarabine 25 mg/m^2/day IVPB x5, cyclophosphamide IV 60 mg/kg/day x 2, transduced T cells IV x1, aldesleukin 72,000 IU/kg IV every 8 hours x 5 days (max 15 doses)	metastatic or unresectable measurable cancers expressing mesothelin, ovarian, pancreatic, mesothelioma, lung, cervical cancers	AE (5 years), ORR	I/II	NCT01583686	recruiting
	Hu-CART meso cells	dose escalation ± cyclophosphamide	metastatic or recurrent lung adenocarcinoma, persistent or recurrent	AE (2 years)	I	NCT03054298	active, not recruiting

Table 2. (Continued)

Cell	Therapy	Dosing	Eligibility Criteria	Primary Endpoint(s)	Phase	Clinical Trial Identifier	Recruitment Status
			serous EOC, peritoneal or fallopian tube carcinoma, malignant pleural and peritoneal mesothelioma				
	anti-hCD70 CAR PBL with cyclophosphamide, fludarabine, aldesleukin	cyclophosphamide 60 mg/kg/day IV x2, fludarabine 25 mg/m2/day IV x4, aldesleukin every 8 hours x 3 days (max 9 doses), anti-hCD70 CAR PBL IV x1	ovarian, pancreatic, renal, breast cancer, melanoma (tumors must express CD70)	MTD, ORR	I/II	NCT02830724	recruiting
	anti-CD133 CAR vector-transduced T cells	dose escalation with anti-CD133-CAR T cells	chemotherapy- refractory or relapsed CD133-positive ovarian, pancreatic, liver, brain, breast, colorectal, acute myeloid and lymphoid leukemia	AE	I	NCT02541370	recruiting
	NKG2D CAR-T cells	dose escalation - NKR-2 cells every 2 weeks (3 total infusions within 4 weeks)	ovarian, colorectal, urothelial, triple negative breast, pancreatic cancers, acute myeloid leukemia/ myelodysplastic syndrome, multiple myeloma	AE/SAE	I/II	NCT03018405	recruiting
	anti-HER2 CAR-T cells	infusion of HER-2 targeting T cells	ovarian, breast, lung, gastric, colorectal, glioma, pancreatic cancers (HER2 positive cancers)	AE	I/II	NCT02713984	recruiting

Abbreviations: AE- adverse events; SAE- severe adverse events; MTD- maximum tolerated dose; IV- intravenous; IP- intraperitoneal; RFS- relapse free survival; DLT- dose limiting toxicity; PD- progressive disease; CR- complete response; CT- computed tomography; SoC- standard of care; RECIST- response evaluation criteria in solid tumors; CTCAE- common terminology criteria for adverse events; CSA- cyclosporine; NK- natural killer; CIK- cytokine induced killer; ORR- objective response rate; TIL- tumor infiltrating lymphocytes; RFA- radiofrequency ablation; RP2D- recommended phase 2 dose; CAR- chimeric antigen receptor; EOC- epithelial ovarian cancer

1 month after the last course half of the patients received monthly infusions of autologous CIK cells with the remaining patients receiving no treatment [53, 61]. In patients treated with CIK therapy, an increase in median PFS was observed (37.7 vs 22.2 months, $p = 0.004$) while OS differences did not reach statistical significance. Zhang et al. demonstrated that pre-treating CIK cells with an immunological adjuvant PA-MSHA (*Pseudomonas aeruginosa*-mannose-sensitive hemagglutinin) led to improved function of CIK cells; patients treated with PA-MSHA-stimulated CIK cells plus chemotherapy achieved PR or SD (with only one patient exhibiting PD), whereas no patients in the CIK plus chemotherapy group achieved partial remission [63].

Ovarian cancer is not generally considered an immunogenic cancer, however, evidence of immune evasion, clinical response to immunotherapy, and the correlation of CD8+ CD3+ T cells with improved survival suggest otherwise [64]. TILs (tumor-infiltrating lymphocytes) are endogenous autologous T cells derived from resected tumors or the peripheral blood of naïve or vaccinated patients and expanded ex vivo [64]. Non-reactive autologous T cells can be stimulated by tumor antigen-specific stimulation in vitro or by genetic engineering to express either an exogenous tumor antigen-specific T cell receptor (TCR) or chimeric antigen receptor (CAR).

TILs have been explored in clinical trials since the 1990s with early human trials showing mixed results [65]. Prospective studies demonstrate spontaneous recognition of tumor neo-epitopes in immunotherapy naïve ovarian cancer patients validating the resurgence of TIL clinical trials [66•, 67]. Results for a pilot study determined that TIL treatment for platinum-resistant metastatic ovarian cancer with a decrescendo IL-2 was feasible and tolerable. All patients had SD for a minimum of 3 months (NCT02482090) [68]. TIL therapy in combination with checkpoint inhibitors or new methods for TIL expansion could results in improved clinical responses in ovarian cancer.

Numerous clinical trials using engineered T cells, TCR, and CAR-T cells to target antigens such as HER2, NY-ESO-1, FR-alpha, MSLN, MUC16, and p53 are currently recruiting. These TAAs are also targets in cancer vaccine development [64]. ALT-801 is a biologic compound composed of IL-2 genetically fused to a humanized soluble T cell receptor directed against p53-derived antigen which recognized an epitope displayed on cancer cells in the context of HLA-A*0201 [69]. In patients with progressive metastatic malignancies, this regimen was well tolerated and elicited a clinical antitumor response at the three doses analyzed (0.015 mg/kg, 0.040 mg/kg, and 0.080 mg/kg, the 0.040 mg/kg demonstrated the highest production of IFN-gamma and immunogenicity titer (NCT00496860).

A variant of adoptive T cell immunotherapy, CAR-T cell immunotherapy allows for the combination of antigen specificity through conjugation of a specific antibody with T cell activating properties in a single fusion molecule [70]. CARs bypass the immune escape mechanism of cancer cells because they endow T lymphocytes with cytotoxic effector features in an MHC-unrestricted manner. The current CAR-T cell trials mainly target antigens mesothelin and HER2. In a trial of CAR-T cells directed against mesothelin (CART-meso) (NCT02159716) [71], six recurrent serous ovarian cancer patients were treated with either a single dose ($3 \times 10\text{^}7$ cells/m^2) of CART-meso or CART-meso ($3 \times 10\text{^}8$ cells/m^2) with or without lymphodepletion. This therapy was found to be safe and feasible with patients showing SD after 1 month of treatment. Preclinical data demonstrated that established and primary ovarian cancer cells were recognized and reacted against by anti-HER2-CAR-T cells with little to no reactivity to normal ovarian surface epithelium, thus showing feasibility for the current HER2 clinical trials [72].

Cytokine release syndrome is a potentially severe systemic toxicity seen after adoptive T cell therapy caused by T cell activation and proliferation. It is associated with elevated levels of circulating cytokines and has been previously described as a systemic response in hematologic malignancies. Tanyi et al. (2017) described a new phenomenon, compartmental cytokine release syndrome, in a patient with advanced recurrent serous ovarian cancer treated with autologous mesothelin-redirected CAR-T cells [73]. This was thought to arise from antigen-specific T cell activation and innate immune activation targeted to the site of tumor in the pleural cavity rather than other compartments that harbored tumor or compartments in which CART-meso cells were detected. The unique nature of ovarian cancer growth and spread could therefore lead to unexpected responses to CAR-T cell therapy compared to other solid tumors.

Conclusions

Immunotherapeutic strategies for the treatment of ovarian cancer must be explored and refined to improve morbidity and mortality of this disease and render therapies available to these patients which are on par with those available to other tumor sites.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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