Immuno-oncology for Gynecologic Malignancies

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Abstract

Patients with advanced and/or recurrent gynecologic cancers derive limited benefit from currently available cytotoxic and targeted therapies. Successes of immunotherapy in other difficult-to-treat malignancies such as metastatic melanoma and advanced lung cancer have led to intense interest in clinical testing of these treatments in patients with gynecologic cancers. Currently, in the realm of gynecologic oncology, the FDA-approved use of immune checkpoint inhibitors is limited to microsatellite instable cancers and PD-L1-positive cervical cancer. However, there has been an exponential growth of clinical trials testing immunotherapy approaches, both alone and in combination with chemotherapy and/or targeted agents, in patients with gynecologic cancers. This chapter reviews some of the major reported and ongoing immunotherapy clinical trials in patients with endometrial, cervical, and epithelial ovarian cancer.

Keywords

Endometrial cancer · Cervical cancer · Ovarian cancer · Immunotherapy · Immune checkpoint inhibitors · Cancer vaccines · Adoptive cell transfer

Introduction

Management of advanced and/or recurrent gynecological malignancies has been a challenge, because conventional therapy is often of limited and transient benefit [1–3]. In the search for more effective alternatives, attention has shifted more towards targeted and immune therapies. Recent immunotherapy trials have demonstrated significantly improved response rates in non-gynecologic cancers that were historically seen to be difficult to treat, such as metastatic melanoma and non-small cell lung carcinoma [4, 5]. Essential to protect the human body against foreign pathogens, the immune system also plays an integral role in eliminating cancerous cells through the process of immune surveillance [6]. Malignant cells may evade the immune system by several mechanisms which include activation of immune checkpoint pathways involving programmed cell death protein-1 (PD-1)/programmed cell death ligand (PD-L1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4),

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and various immunosuppressive cytokines. These mechanisms serve to suppress T-cell activity, thus promoting tumor tolerance and growth [7]. Treatment modalities in immunotherapy serve to augment the host's antitumor immune response and/or inhibit the immunosuppressive signals in the tumor microenvironment [6]. We will begin this chapter with a brief review of various immunotherapy approaches in use and under investigation for the treatment of gynecologic cancers including immune checkpoint inhibitors, cancer vaccines, and adoptive cell transfer (ACT) [8]. We will then summarize some of the major findings detailing outcomes of immunotherapy and ongoing clinical trials targeting different gynecologic cancers.

Immune Checkpoint Inhibitors

Regulated by a balance of co-stimulatory and inhibitory signals, immune checkpoints help the human immune system respond effectively to foreign pathogens while preventing overactivation that could result in autoimmunity or collateral tissue destruction [7]. At the initial antigen recognition by the T-cell receptor (TCR), CTLA-4 mitigates the amplitude of TCR-mediated signaling in cytotoxic T lymphocytes (CTLs) via counteracting CD28 co-stimulatory activity. Specifically, CTLA-4 sequesters CD80 and CD86 from binding to CD28 in CTLs while enhancing the immune-suppressive activity of regulatory T-cells. While CTLA-4 primarily acts on newly activated T-cells, PD-1 receptor activation via PD-L1 and PD-L2 functions to limit activation of CD-8+ effector T-cells mainly in peripheral tissue (due to the wide expression pattern of PD-1 ligands on a variety of normal and malignant cell types) to prevent collateral tissue damage. Tumor cells may overexpress PD-L1 either in response to inflammatory signals in the tumor microenvironment (adaptive immune resistance) or via upregulation through oncogenic signaling (innate immune resistance). In either situation, PD-1 downregulates effector T-cell response, and with chronic antigen exposure from tumor cells, this can result in T-cell anergy and self-tolerance.

Thus, immune checkpoint blockade via anti-CTLA-4 antibodies (e.g., ipilimumab, tremelimumab) and/or anti-PD-1/PD-L1 antibodies (e.g., pembrolizumab, nivolumab, durvalumab, avelumab, atezolizumab, and others) serve as potential therapeutic options to augment the antitumor activity of adaptive immunity.

Cancer Vaccines

The general principle of cancer vaccines is to elicit the host's adaptive immune response to target malignant cells and can be given either in the prophylactic or therapeutic setting [9, 10]. For prophylactic vaccines, these are typically given prior to exposure to the neoplastic-inducing antigen to prevent pre-malignant and malignant cellular transformation. One classic example is administration of the human papilloma virus (HPV) – vaccine series containing L1 virus-like particles specific high-risk carcinogenic HPV types (e.g. 16 and 18) to teenagers and adults in order to reduce HPV infection rates in order to reduce the incidence of cervical dysplasia or cervical cancer. In contrast, therapeutic vaccines consisting of tumor-specific antigens (as peptides or antigen-activated dendritic cells) are administered in patients with cancer in order to enhance the host's antitumor immune response [9]. As well, whole tumor antigen vaccines prepared via several approaches (including but not limited to free-thaw lysates, tumor cells treated with ultraviolet irradiation, RNA electroporation, or hypochlorous oxidation) is a novel technique that can potentially allow for a broad and stronger immune response given a higher number of tumor-associated antigens as opposed to a single antigen [11].

Adoptive Cell Transfer

In adoptive cell transfer (ACT), autologous T-cells are extracted (either from tumor tissue itself or from the peripheral blood) and are

subsequently expanded ex vivo, with or without genetic modification, and then re-infused back into circulation [12, 13]. Clinically used categories of ACT include tumor-infiltrating lymphocytes (TIL), genetically engineered T-cell receptors (TCR), and chimeric antigen receptor (CAR) T cell therapies [12, 13]. TIL therapy consists of several steps including surgical extraction of tumor tissue to gain access to a heterogeneous population of T lymphocytes that presumably recognize tumor-specific antigens [13, 14]. Isolation of TIL is subsequently followed by ex vivo cellular expansion, preconditioning lymphodepletion, TIL infusion, and adjuvant IL-2 to aid with in vivo TIL expansion and maintenance [14, 15]. Lymphodepletion is thought to be critical and improve the therapeutic responses to TIL immunotherapy through the elimination of both the endogenous T-lymphocytes that may compete with TIL for stimulatory cytokines/IL-2 and the regulatory T-cells that serve to inhibit the T-cell activity [13, 16]. In contrast to TIL (which are naturally occurring group of polyclonal T-lymphocytes with varying recognition of and affinities towards tumor-associated antigens), genetically engineered TCR and CAR T-cells are T-lymphocyte populations modified with the same high affinity tumor recognition moiety that are obtained from the peripheral blood [12, 13]. Following leukopheresis, the peripheral blood-derived T-lymphocytes are genetically modified (frequently via the use of retroviral vectors), to render specificity against a tumor-specific antigen, then subsequently expanded and re-infused back into the patient [12, 13]. These genetically modified T-cell approaches also frequently involve preconditioning using lymphodepleting chemotherapy. Important distinctions between CAR- and TCR-engineered T-cell therapies include the fact that TCR-modified T-cells recognize tumor-specific antigens in the context of a specific major histocompatibility complex (MHC) – 1 [12, 13]. Therefore, one of the limitations TCR T-cells in their utility is that the treatment is restricted to patients with common HLA types (typically HLA-A∗0201) used in engineering the TCR. Another limitation is the possibility of tumors downregulating the MHC protein expression and thereby decreasing tumor recognition. CAR T-cells address this limitation as these cells are genetically modified with an antigen-recognition moiety fused to intracellular T-cell signaling domains. This allows tumor antigen recognition by CAR T-cells to be independent of MHC proteins [17]. However, the major limitation of the CAR T-cell approach is the need for tumor antigen to be present on the cell surface.

In an era of precision medicine, immunotherapy represents one of the promising therapies that may be used to improve oncologic outcomes in gynecologic cancers. The following text will review the published, ongoing, and upcoming clinical trials in endometrial, ovarian, and cervical cancer.

Endometrial Cancer

Following the published results by the Cancer Genome Atlas Research Network, contemporary classification of endometrial cancer has shifted away from the traditional two histologic types (endometrioid vs. non-endometrioid; sometimes referred to as type I and type II cancers) and towards four types based on genomic sequencing: DNA polymerase epsilon (POLE) ultramutated, microsatellite instability hypermutated (MSI-H), copy-number low, and copy-number high [18]. Microsatellites are repeated sequences of DNA that become sites of DNA replication errors with "microsatellite instability" occurring in the setting of defects in the DNA mismatch repair (MMR) pathway. Defects of MMR function result in MSI in approximately 20–30% of endometrial tumors [18, 19]. Loss of MMR function is typically due to sporadic hypermethylation of the MLH1 promotor and less frequently due to germline mutations (i.e., hereditary nonpolyposis colon cancer (HNPCC) syndrome, also known as Lynch syndrome) [18, 20]. MMR-deficient and POLE-mutant endometrial tumors display a high number of tumor-infiltrating lymphocytes as well as a high neoantigen load (due to high somatic

tumor DNA mutational burden) giving the potential to elicit a strong antitumor immune response [18, 21–23].

Immune Checkpoint Inhibitors in Endometrial Cancer

There has been growing interest in the use of immune checkpoint inhibitors in MSI-H endometrial tumors since the landmark publication by Le and colleagues [24]. In this phase II study of MMR-deficient colorectal cancers and non-colorectal solid tumors and MMR-proficient colorectal cancers treated with pembrolizumab (anti-PD-1 antibody), patients with MMR-deficient cancers had clinically significant objective response rates (ORR) of 30–70% and an improved progression-free survival (PFS). Among the colorectal cancer patients, those with MMR-proficient tumors demonstrated no responses [24]. Although this cohort predominantly consisted of colorectal cancer patients, there were two MMR-deficient endometrial cancers that demonstrated favorable responses (one had a partial response and the other a complete response) [24]. In another study, Le and colleagues expanded their evaluation of pembrolizumab (10 mg/kg every 2 weeks) by examining the response in a cohort of 86 patients with 12 different cancer types with MMR deficiency who had progressive disease on at least one prior treatment (Table 7.1) [25]. Among the 15 endometrial cancer patients, there was a 53% ORR (three complete and five partial responses) with a 73% disease control rate (DCR) (20% had stable disease) [25]. MSI-H tumors display a higher expression of PD-L1 compared to microsatellite stable (MSS) tumors, and this expression appears to be correlated with improved response to PD-1 and PD-L1 inhibitors [23, 33]. In another trial, Fader et al. reported a 56% ORR with four partial responses and one complete response to pembrolizumab in MMR-deficient recurrent or persistent tumors as well as a DCR of 88.9% [26]. Given the above results, pembrolizumab was awarded US Food and Drug Association (FDA) approval for the use in treatment of MMR-deficient solid tumors following recurrence or progression on standard therapy in May 2017.

Another PD-1 inhibitor under investigation is nivolumab. In a Japanese, phase II multicenter study, nivolumab (240 mg IV every 2 weeks) was administered to mixed cohort of patients including advanced uterine cancer patients (clinical trial JapicCTI-163,212) [27]. In their preliminary results, Hasegawa and colleagues found an ORR of 22.7% in 23 uterine cancer patients with acceptable drug safety profile [27]. ORR was similar regardless of presence or absence of PD-L1 expression (25% vs. 21.4%, respectively) with all patients with MSI-H tumors experiencing partial responses [27]. For another PD-1 inhibitor, investigators administered dostarlimab (TSR-042) at 500 mg IV every 3 weeks for the first 4 cycles, then 1000 mg IV every 6 weeks in recurrent or advanced endometrial cancer patients (NCT02715284) [28]. In the preliminary results of 94 evaluable patients, the ORR was 27.7% (50% in MSI-H tumors and 19.1% in MSS tumors) and a DCR of 48.9%. The treatment-related adverse event (TRAE) rate was 61.8% with 11.8% with grade 3 or higher with the most common being increased aspartate aminotransferase [28].

Other studies have shown more limited benefit of immune checkpoint inhibitors in patients with endometrial cancers. As an ongoing, open-label phase Ib trial, KEYNOTE-028 is evaluating the safety and efficacy of pembrolizumab on PD-L1-positive advanced solid tumors [29]. In this study, a cohort of 24 patients with advanced endometrial cancer and PD-L1 positivity were treated with pembrolizumab 10 mg/kg every 2 weeks for up to 24 months (or until progression or unacceptable toxicity) after failing 2 prior lines of therapy [29]. The DCR was 25% (n = 6) including 12.5% (n = 3) with partial responses. Progressive disease occurred in 54.2% (n = 13) and 20.8% (n = 5) could not be assessed. Of note, 19 of the 24 tumor samples were evaluable for MSI-H status with the sole patient with an MSI-H tumor having progressive disease. One of the three patients with a partial

Table 7.1 Reported immune checkpoint inhibitors studies in endometrial cancer

Study	Design	*N*	Patient population	Therapy	Results	TRAE
PD-1 inhibitors						
Le et al. 2017 [25]	Phase II	15	MMR-deficient endometrial cancer with progressive disease	Pembrolizumab (10 mg/kg IV q2 weeks)	ORR 53% (5 PR/3 CR) DCR 73%	Overall*: 74% (mainly rash/pruritus, fatigue, diarrhea/colitis). Grade 3–4: 20% (diarrhea/ colitis, pancreatitis, hyperamylasemia)
Fader et al. 2016 [26]	Phase II	9	Recurrent/ persistent MMR-deficient cancers	Pembrolizumab (10 mg/kg IV q2 weeks)	ORR 56% (4 PR/1 CR) DCR 88.90%, 12-month OS 89%	Mainly Grade 1–2; no TRAE higher than 3
Hasegawa et al. 2018 [27]	Phase II	23	Advanced/ recurrent EC	Nivolumab 240 mg IV q2 weeks	ORR: 23% (similar regardless of PD-L1 status), 3.4 month PFS, 12-mo OS 48.5%	Overall*: 56.3%, Grade 3–4 toxicities: 12.5% (mainly pruritus, increased lipase, diarrhea)
Oaknin et al. 2018 [28]	Phase I/II	94	Recurrent or persistent EC	Dostarlimab 500 mg IV q3 weeks for 4 cycles, then 1000 mg IV q6 weeks	ORR 27% (50% in MSI-H/19.1% in MSS). DCR 48.90%	Overall: 61.8%; Grade 3+ 11.8%, most common grade 3+ TRAE = AST increase
Ott et al. 2017 [29]	Phase IB	24	Locally advanced or metastatic PD-L1 positive with progression after standard therapy	Pembrolizumab (10 mg/kg q2 weeks) up to 24 months	ORR 12.5% (3 PR/0 CR), DCR 25%, PFS 1.8 months, 6- & 12-month PFS rate: 19.0% & 14.3%, 6- & 12-month OS rate: 67.0% & 51.0%	Overall: 54.2% (most common fatigue, pruritus, pyrexia, decreased appetite), Grade 3: 16.7% (asthenia, back pain; anemia, hyperglycemia, hyponatremia; chills and pyrexia, diarrhea)
PD-L1 inhibitors						
Fleming et al. 2017 [30]	Phase IA	15	Advanced and recurrent EC	Atezolizumab 1200 mg IV (or 15 mg/kg) q3 weeks	ORR 13% (2 PR/0 CR), DCR 26% mPFS 1.7 months, mOS 9.6 months	Overall: 47% (mainly grade 1–2)
Combination therapy						
Makker et al. 2019 [31]	Phase II	53	Metastatic endometrial cancer	Pembrolizumab 200 mg IV q3 weeks and Lenvatinib 200 mg po qday	ORR 39.6% (20 PR/ 1 CR) DCR 86.80% PFS 7.4 months	Overall: 94% (common: hypertension, diarrhea, fatigue, hypothyroidism), grade 3: 68%, serious TRAE: 30% with 1 death due to intracranial hemorrhage

(continued)

Table 7.1 (continued)

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Rubinstein et al. 2019 [32]	Phase II	28 per arm	Persistent or recurrent endometrial carcinoma and endometrial carcinosarcoma	Durvalumab 1500 mg IV q4 weeks vs. Durvalumab 1500 mg IV q4 weeks and Tremelimumab 75 mg IV q4 week	Monotherapy: ORR 14.8% (3 PR/1 CR), 24-week PFS 13.3% Combination: ORR 11.1% (1 PR/2 CR), 24-week PFS 18.5%	Grade 3 (7% vs. 32%, respectively) Grade 4 (4% vs. 11%, respectively)

AST aspartate aminotransferase, *DCR* disease control rate = stable disease + partial response + complete response rates, *mOS* median overall survival, *CR* complete response, *IV* intravenous, *MMR* mismatch repair, *mPFS* median progression-free survival, *MSI-H* microsatellite instability high, *MSS* microsatellite stable, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PO* oral, *q* every, *PR* partial response, *TRAE* treatment-related adverse events
*Includes other non-endometrial cancers

response was found to have a POLE-mutant tumor [29]. The high expression of a large set of immune-related genes and increased neoantigen load may explain the favorable response to immune checkpoint inhibitors in POLE-mutated tumors [18, 34]. Additionally, POLE-mutated tumors demonstrate a higher expression of PD-L1/PD-L2 proteins as well as a higher extent of T lymphocytic infiltration than MSI and MSS endometrioid tumors [18, 22, 23, 34]. Another PD-L1 inhibitor currently being investigated in endometrial cancer is atezolizumab. In a phase Ia study, atezolizumab (1200 mg IV every 3 weeks) was administered in advanced or recurrent endometrial cancer patients (NCT01375842) [30]. In their preliminary results of 15 patients, the ORR was 13% with 2 patients having partial response and a DCR of 26% without significant TRAE [30]. Response appeared to be higher in tumor PD-L1 expression and tumor lymphocytic infiltration [30].

The combination of immune checkpoint inhibitors and multi-tyrosine kinase inhibitors has been reported to result in higher response rates. In a phase Ib/II study, lenvatinib (inhibitor of vascular endothelial growth factor 1–3, fibroblast growth factor receptor 1–4, and other kinases) and pembrolizumab were administered a mixed cohort of MSI-H/MSS advanced endometrial cancer patients (NCT02501096) [31]. Among 53 evaluable patients, tumors were primarily MSS (85%) with an overall ORR of 39.6% (1 complete response and 20 partial responses) at 24 weeks of treatment and DCR of 86.8%. Although impressive tumor responses were seen, the TRAE rate was high (94%) with grade 3 TRAE rate of 68% (most common being hypertension and diarrhea) [31]. Serious TRAE occurred in 30% of patients with one treatment-related death due to intra-cranial hemorrhage) [31]. A phase III trial investigating lenvatinib/pembrolizumab versus physician's choice is currently underway (NCT03517449). At the 2019 American Society of Clinical Oncologists Meeting, the preliminary results of a phase II trial of durvalumab (PD-L1 inhibitor) with or without tremelimumab (CTLA-4 inhibitor) in persistent/recurrent endometrial cancer were presented (NCT03015129) [32]. Twenty-eight patients were enrolled in each treatment arm. The durvalumab monotherapy group had an ORR of 14.8% (1 complete response and 3 partial responses) with PFS of 13.3% at 24 weeks [32]. The combination group had an ORR of 11.1% (2 complete responses and 1 partial response) with a PFS of 18.5% at 24 weeks [32]. Grade 3 and 4 TRAE were 7% and 4% in the monotherapy group and 32% and 11% in the combination group, respectively [32]. Numerous ongoing trials utilizing combination therapy are shown in Table 7.2.

Table 7.2 Ongoing studies for immune checkpoint inhibitors in endometrial cancer

Study	Design	Patient population	Therapy	Endpoints	Study status
MK-3475-158/ KEYNOTE-158 (NCT02628067)	Phase II	Advanced (unresectable and/or metastatic) disease that have progressed on standard of care therapy	Pembrolizumab	Primary: ORR	Recruiting
NCT02549209	Phase II	Advanced or recurrent disease	Pembrolizumab + carboplatin + paclitaxel	Primary: ORR, AE	Recruiting
NCT02899793	Phase II	Persistent, recurrent, or metastatic POLE-mutation and/or MMR-deficient endometrial tumors with prior treatment	Pembrolizumab	Primary: ORR, frequency and severity of AE Secondary: PFS, OS	Recruiting
NCT02982486	Phase II	Locally advanced non-operable or metastatic endometrial carcinoma with somatic-deficient MMR with at least 1 prior failed systemic therapy	Nivolumab + ipilimumab	Primary: ORR Secondary: PFS, OS	Not recruiting yet
NCT02912572	Phase II	POLE-mutated, MSS, and MSI-H persistent or recurrent tumors with prior therapy	Avelumab +/− talazoparib	Primary: Drug activity Secondary: PFS, OS, TRAE, immune-related objective response	Recruiting
KEYNOTE-775 (NCT03517449)	Phase III	Advanced, recurrent, or metastatic with at least 1 failed prior line of systemic therapy	Pembrolizumab + lenvatinib vs. investigator's choice of chemotherapy	Primary: PFS, OS Secondary: ORR, HRQoL, AEs	Recruiting
NCT03526432	Phase II	Advanced, recurrent, or persistent with at least 1 prior platinum-based chemotherapy regimen	Bevacizumab + atezolizumab	Primary: ORR Secondary: OS/ PFS, safety, Immune related response	Recruiting

AE adverse event, *HRQoL* Health-related quality of life, *IV* intravenous, *MMR* mismatch repair, *MSI-H* microsatellite instability high, *MSS* microsatellite stable, *q* every, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *POLE* DNA polymerase epsilon, *TRAE* treatment-related adverse events

Vaccines in Endometrial Cancer

One of the identified tumor-associated antigens that have been utilized, as a target for therapeutic vaccinations, is a product of the Wilm's tumor gene: WT1 [35, 36]. Classically categorized as a tumor-suppressor gene, WT1 may instead perform oncogenic functions in many malignancies and is highly expressed in multiple cancers including gynecologic malignancies [36]. In a phase II clinical trial, Ohno et al. utilized a WT1 peptide vaccine on 12 patients with HLA-A∗2402-positive gynecologic cancers resistant to standard therapy (Table 7.3) [36]. Two of endometrial cancer patients (carcinosarcoma and endometrioid adenocarcinoma histologic subtypes) both had progressive disease after 3 months but the treatment was otherwise well tolerated [36]. In another phase I/II study, a mixed cohort of end-stage serous endometrial carcinoma ($n = 3$) and leiomyosarcoma ($n = 3$) patients received four weekly vaccines of autologous dendritic cells electroporated with WT1 mRNA [37]. Although all three serous endometrial carcinoma patients (two HLA-A2 positive and one HLA-A2 negative)

Table 7.3 Reported vaccine therapy trials in endometrial cancer

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Ohno et al. 2009 [36]	Phase II	2	HLA-A∗2402-positive endometrioid adenocarcinoma and carcinosarcoma resistant to standard therapy	Intradermal injections of 3.0 mg of HLA-A∗2402-restricted adjuvant modified 9-mer WT1 peptide emulsified with Montanide ISA51 adjuvant administered q week for 12 weeks	ORR 0%, DCR 0%	Mild erythema at injection site with no grade 3–4 toxicities
Coosemans et al. 2013 [37]	Phase I/II	3	Advanced uterine cancer	4 weekly vaccines of autologous dendritic cells electroporated with WT1 mRNA	ORR 0%, DCR 0%, Increase in WT1-specific T-cells and NK cells in HLA-A2 positive endometrial cancers	Mild erythema at injection site with no grade 3–4 toxicities
Jager et al. 2006 [38]	Phase I	1	Advanced NY-ESO-1 cancers	2 vaccinations with rV-NY-ESO-1 at a dose of 3.1×10^7 pfu followed by 2 vaccinations with rV-NY-ESO-1 at a dose of 7.41×10^7 pfu at 4-week intervals	ORR = 0%, DCR = 0%, humoral and cellular responses increased as indicated by NY-ESO-1-specific antibody production and CD4/CD8 response	Mild erythema at injection site with no grade 3–4 toxicities
Kaumaya et al. 2009 [39]	Phase I	2	Recurrent and/or metastatic disease	Combination vaccines of a mixture of two B-cell epitopes of HER2 fused to a T-cell epitope with nor-muramyl-dipeptide (n-MDP) adjuvant emulsified in Montanide ISA 720 at 0.25 or 0.5 mg IM q3 weeks × 3, additional vaccinations given later based on if there were toxicity	ORR 50% (1 PR / 0 CR), DCR = 50%	Grade 3*: 12.5%, (diarrhea, pain, hyperglycemia)

(continued)

Table 7.3 (continued)

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Jackson et al. 2017 [40]	Phase I/IIa	Treatment group ($n = 6$) Controls ($n = 3$)	Endometrial cancer patients at risk of recurrence with HLA-2+ patients after primary treatment	HLA-A2 restricted, FBP-derived peptide (1.5 ml) vaccine administered at several doses: 100 mcg/0.5 ml, 500 mcg/0.5 ml, 1000 or mcg/0.5 ml + 250 mcg/1.0 ml GM-CSF intradermally	2-year DFS rate 43% vs. 33.6% ($p = 0.36$); for 1000 mcg dosage: 2-year DFS 85.7% vs. 33.6% ($p = 0.02$), recurrence rate 41.4 vs. 54.6% ($p = 0.35$); for 1000 mcg group 13.3% vs. 54.6%, $p = 0.01$	Most common: induration at injection site, erythema, and pruritus; 1 grade 3 toxicity but no grade 4 or 5

CR complete response, *DCR* disease control rate = stable disease + partial response + complete response rates, *DFS* disease-free survival, *FBP* Folate-binding protein, *HLA* human leukocyte antigen, *IV* intravenous, *NK cells* natural killer cells, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *Pfu* plaque-forming units, *PR* partial response, *q* every, *TRAE* treatment-related adverse events, *WT1* Wilm's tumor gene
*Includes other non-endometrial cancers

demonstrated disease progression, some immunological activity was present in the HLA-A2 positive patients as noted by an increase in WT1-specific T-cells and NK cells [37]. However, the two HLA-A2 positive leiomyosarcomas demonstrated some disease control (one with stable disease but eventually progressed and another had a mixed response prior to progression) [37].

Another targeted epitope is associated with NY-ESO-1, which is classified as a "cancer germline antigen" (an antigen expressed in the germ cells and multiple different types of malignancies). In a series of 36 patients with various stage III/IV NY-ESO-1 expressing malignancies, the patients were administered a recombinant vaccinia/fowlpox-NY-ESO-1 vaccine series [38]. In the only endometrial cancer patient, the vaccine mounted both humoral and cellular responses indicated by NY-ESO-1-specific antibody production and CD4/CD8 response although the patient ultimately had progressive disease [38].

Human epidermal growth factor-2, HER2, is overexpressed in many epithelial-derived cancers (often with breast cancers) and has been the target for vaccination in other malignancies [39]. In a phase I clinical study, patients with various metastatic cancers received combination vaccines of a mixture of two B-cell epitopes of HER2 fused to a T-cell epitope [39]. Of the 24 patients enrolled, two endometrial cancer patients had received the vaccines after 2 failed chemotherapy treatments with 1 of the patients demonstrating high antibody production and partial response [39].

Folate-binding protein (FBP) is another immunogenic protein overexpressed in endometrial (as well as ovarian) cancer [41]. In the interim analysis of a phase I/IIa trial by Jackson and colleagues, a mixed cohort of 51 patients with either endometrial or ovarian cancer received an HLA-A2 restricted, FBP-derived peptide vaccine to prevent recurrence (NCT01580696) [40]. The vaccine was well tolerated and resulted in a lower risk of recurrence in the higher dosage treatment group (1000 mcg) compared to the control group (13.3% vs. 55%, respectively; $p = 0.01$), and a higher estimated 2-year disease-free survival (85.7% vs. 33.6%, respectively; $p = 0.021$) [40].

ACT in Endometrial Cancer

Although there are no reported studies discussing TIL, TCR-T, or CAR-T therapy in endometrial cancer at the time of this chapter's preparation, another ACT therapeutic option involves lymphokine-activated killer (LAK) cells. This process involves collection of peripheral blood containing mononuclear cells that are stimulated in vitro with IL-2 to become LAK cells [42]. These LAK cells are re-infused into the patient and are capable of lysing tumor cells without MHC restriction while sparing normal tissue [42]. In a study by Steis et al., they selected patients with various cancers that had metastatic disease restricted to the peritoneal cavity [43]. These patients received IL-2 (100,000 U/kg IV every 8 hours) for 3 days, followed by leukapheresis for 5 days [43]. LAK cells were expanded in vitro by incubating the peripheral blood mononuclear cells in IL-2 for 7 days, then administered IP for 5 days with IL-2 (25,000 U/kg IP every 8 hours) [43]. In the cohort, there was only one endometrial cancer patient but that patient failed to respond to therapy with the therapy overall having multiple side effects including intraperitoneal fibrosis [43]. In another study, Santin et al. observed stable disease in a patient with endometrial cancer with unresectable, chemo-resistant liver metastases who was treated with infusion of peripheral T-cells stimulated with tumor lysate-pulsed autologous dendritic cells [44].

Cervical Cancer

The carcinogenesis of cervical cancer evokes great interest in immunotherapeutic options. Chronic HPV infection is attributed as the etiologic agent for the development of cervical cancer in nearly all cases. Although the majority of HPV-infected people do not develop cervical cancer (due to HPV clearance by a competent immune system), chronic HPV infections results in the expression of oncoproteins E6 and E7 that bind and inactivate the TP53 and Rb tumor suppressor gene product, respectively. Immunotherapeutic options for cervical cancer will be reviewed.

Immune Checkpoint Inhibitors in Cervical Cancer

Several studies have demonstrated relatively high PD-1/PD-L1 expression on cervical tumors (as high as 95% in cervical intraepithelial neoplasia and 80% of squamous cell carcinomas) and thus these cancers are potential targets for immune checkpoint inhibitors [45–47]. In KEYNOTE-028, the cervical cancer subgroup consisted of 24 patients with advanced disease and PD-L1-positive tumors that had progressed on prior standard therapy [48]. Following the administration of pembrolizumab (10 mg/kg every 2 weeks up to 24 months), the subgroup had an ORR of 17% (4 patients with partial response) with a DCR of 17% (Table 7.4) [48]. In an interim analysis in the KEYNOTE-158 phase II, open-label trial, 98 cervical cancer patients received pembrolizumab (200 mg every 3 weeks), including 83.7% of patients who had PD-L1-expression in their tumors and 78.6% who had prior lines of chemotherapy for recurrent or advanced disease (NCT02628067) [49]. Among these patients, the ORR was 12.2% (9 had a partial response and 3 had a complete response) with responders all having PD-L1-positive tumors (including one patient with adenocarcinoma). The DCR was 30.6% including 15 of the 18 (83.3%) patients with stable disease who had PD-L1-positive tumors [49]. Since June 2018, the FDA has approved pembrolizumab in advanced cervical cancer expressing PD-L1 with disease progression during or after chemotherapy.

Another PD-1 inhibitor reported in the cervical cancer literature is nivolumab and has demonstrated promising results. For neuroendocrine cervical cancer known to be an aggressive cervical cancer subtype, two case reports have demonstrated complete response to nivolumab monotherapy (despite being PD-L1 negative) and a near complete response (95% resolution of target lesions) when nivolumab was combined with

Table 7.4 Reported immune checkpoint inhibitors studies in cervical cancer

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Monotherapy						
Frenel et al. 2017 [48]	Phase IB	24	PD-L1 advanced cervical cancer that progressed on prior therapy	Pembrolizumab 10 mg/kg q2 weeks up to 24 months	ORR 17% (4 PR/ 0 CR) DCR 17%, mPFS = 2 months, 6- and 12-month PFS = 21% & 4%, mOS = 11 months, 6- and 12-month OS = 67% & 40%	Overall: 75%, mainly rash and pyrexia Grade 3: rash and proteinuria
Chung et al. 2019 [49]	Phase II	98	Previously treated advanced cervical cancer	Pembrolizumab 200 mg q3 weeks for 24 months	ORR 12.2% (9 PR/ 3 CR) DCR 30.60%, mPFS = 2.1 months, 6-month PFS = 25%, mOS 9.4 months, 6- and 12-month OS 75.2% and 41.4%	Overall: 65.3%, most common being hypothyroidism, decreased appetite, and fatigue Grade 3–4: 12.2%
Hollebecque et al. 2017 [50]	Phase I/II	19	Recurrent or metastatic cervical cancer with up to two failed systemic therapies	Nivolumab 240 mg q2 weeks	ORR 26.3% (4 PR/ 1 CR) DCR 70.8%*, mPFS 5.5 months	Overall 70.8% Grade 3–4 12.5%
Santin et al. 2018 [51]	Phase II	25	Persistent or recurrent cervical cancer	Nivolumab 3 mg/kg every 2 weeks for up to 46 doses over 92 weeks	ORR 4% (1 PR/0 CR) DCR 40%, 6-month PFS rate 16%, 6-month OS rate 78.4%	Overall: 84% Grade 3: 24% Grade 4: 8%
Lheureux et al. 2018 [52]	Phase I/II	42	Metastatic or recurrent cervical cancer	Ipilimumab 3 mg/kg q3 weeks × 4 cycles or (10 mg/kg q3 weeks for 4 cycles and 4 cycles of maintenance q12 weeks)	ORR 2.9% (1 PR/ 0 CR) DCR 32.40% mPFS 2.5 months mOS 8.5 months	Grade 3 TRAE: 11.7% (mainly diarrhea and colitis)
Combination therapy						
Mayadev et al. 2017 [53]	Phase I	19	Stage IB2 - IVA cervical cancer with node positive disease undergoing chemoradiation	Cisplatin (40 mg/M^2) q week × 6 + extended field radiation, then sequential ipilimumab was given at 3 mg/kg, 10 mg/kg, and expansion cohort of 10 mg/kg	DCR 74% DFS survival of 74% at 1 year	Mostly grade 1–2 (most common being GI distress, rash & endocrinopathies). Grade 3: 16%, transient which resolved (lipase, neutropenia, and rash)
Friedman et al. 2019 [54]	Phase II	10	Recurrent, persistent, or metastatic cervical cancer	Atezolizmab 1200 mg IV q3 weeks and bevacizumab 15 mg/kg IV q3 weeks	DCR 50% mPFS 2.9 months mOS 9 months	TRAE 3: 23% (arachnoiditis, sensorineural hearing loss, lower extremity weakness, thrombosis, rectal bleed)

AE adverse event, *CR* complete response, *ORR* objective response rate, *DCR* disease control rate = stable disease + partial response + complete response rates, *DFS* disease-free survival, *IV* intravenous, *mOS* median overall survival, *mPFS* median progression-free survival, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *q* every, *TRAE* treatment-related adverse events

*Includes 5 vaginal and vulvar cancers

stereotactic body radiation [55, 56]. In a larger study, nivolumab (240 mg every 2 weeks) was tested in 5 HPV-associated malignancies including cervical, vulvar, and vaginal cancers that previously had up to two failed prior systemic therapies (CheckMate358; NCT02488759) [50]. In the preliminary results of this ongoing phase I/II multicohort study, the majority of the cohort consisted of cervical cancer patients (19 of 24) with the rest having vaginal or vulvar cancer. The overall ORR was 20.8% with a DCR of 70.8% (15 of 24) and was well tolerated [50]. Response to therapy was only noted in the cervical cancer patients (ORR 26.3%) with one complete and four partial responses, regardless of PD-L1 status [50]. In the preliminary phase II results of another trial with nivolumab (NRG-GY002; NCT02257528), the agent was demonstrated to have poor response rate with an ORR of 4% (1 partial response) with a DCR 40% in a cohort of 25 cervical cancer patients with persistent or recurrent disease who failed at least one prior line of systemic therapy [51].

Another immune checkpoint inhibitor under investigation in patients with cervical cancer is ipilimumab (CTLA-4 inhibitor). In the phase I study (GOG 9929), ipilimumab was administered after chemoradiation for patients with stage IB2-IIB or IIIB-IVA cervical cancer with node positive disease (NCT01711515). Preliminary results in the 19 evaluable subjects demonstrate a 1-year disease-free survival of 74% with tolerable side effects [53]. In another phase I/II clinical trial, 42 patients with metastatic cervical cancer (squamous cell or adenocarcinoma) with progression on at least 1 line of platinum chemotherapy received ipilimumab [52]. Among the 34 evaluable patients, the ORR was 2.9% (1 partial response) with DCR of 32.4% and a median PFS and OS of 2.5 months and 8.5 months, respectively [52]. Expression of CD3, CD4, CD8, FoxP3, indoleamin 2,3-dioxygenase, and PD-L1 expression did not predict benefit [52].

In a phase II study by Friedman et al., atezolizumab (1200 mg IV every 3 weeks) and bevacizumab (15 mg/kg IV every 3 weeks) were administered to patients with recurrent, persistent, or metastatic cervical cancer (NCT02921269) [54]. There were 10 evaluable patients with no confirmed responses and a DCR of 50% [54]. The median PFS was 2.9 months and overall survival was 9 months with 23% of patients having grade 3 TRAE [54]. A number of ongoing trials are testing the efficacy of immune checkpoint inhibitors as a part of various combinations regimens (Table 7.6).

Vaccines in Cervical Cancer

Given the role of chronic HPV infection in the carcinogenesis of cervical cancer, and the success of prophylactic HPV vaccines for prevention of dysplasia and cervical cancer, there is great interest in development of therapeutic HPV vaccines that typically target the E6 and E7 oncoproteins. In a phase II study, amalimogene filolisbac (ADXS11-001) (live, attenuated Listeria monocytogenes (Lm) vaccine containing the HPV-16 E7 oncoprotein) was administered by random assignment with or without cisplatin to 109 recurrent or treatment-refractory cervical cancer patients in India. The response rate was similar between both groups (17.1% vs. 14.7%) with comparable survival rates but the combination group experienced more adverse events that were not related to the study drug [57]. ADXS11-001 was also examined in the GOG/NRG0265 phase II study (NCT01266460) (Table 7.5) [58]. In the preliminary results of the trial, ADXS11-001 was administered as monotherapy to 50 patients with persistent or recurrent metastatic cervical cancer who progressed on at least one prior line of systemic chemotherapy [58]. The 12-month OS was 38% with a ORR of 2% (1 complete response) and DCR of 32% [58]. TRAE occurred in 96% of patients with the most frequent being fatigue, chills, anemia, and nausea; grade 3 and 4 TRAE were present in 39% and 4% of patients, respectively [58]. Another phase I/II study examined the safety and efficacy of durvalumab (anti-PD-1 inhibitor) with or without ADSX11-001 in previously treated recurrent or metastatic cervical cancer and other HPV-related squamous

Table 7.5 Reported vaccine therapy and adoptive cell therapy trials in cervical cancer

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Basu et al. 2018 [57]	Phase II	Mono ($n = 35$) combo ($n = 34$)	Recurrent or treatment-refractory	ADXS11-001 1 cycle (3 infusions) (1×10^9 CFUs as an 80-mL IV infusion over 15 minutes on day 1, 29, and 57) and combo therapy = ADX-011 (day 1 only) + cisplatin weekly (40 mg/m^2) post-vaccine 4 weeks × 5 weeks, then 1 cycle of ADS11-011 (3 infusions)	ORR: 17.1% (3 PR/3 CR) [mono] vs. 14.7% (2 PR/3 CR) [combo], mPFS 6.08 months (mono) vs. 6.44 months (combo), mOS 8.28 (mono) vs. 8.78 (combo) months	More TRAE in the combination group (46.3% in combo group and 36.4% in mono group). Most common were chills and pyrexia
Huh et al. 2017 [58]	Phase II	50	Persistent or recurrent metastatic cervical cancer	ADXS11-001 (1×10^9 CFU) q3 weeks × 3 doses for stage 1 or until 1 year for stage 2 of the trial	2% (0 PR / 1 CR) 12-month OS was 38%	Overall: 96% (most frequent being fatigue, chills, anemia, and nausea) Grade 3 & 4: 39% and 4%, respectively
Slomovitz et al. 2016 [59]	Phase I/II	5	Recurrent or metastatic cervical cancer	ADXS11-001 q4 weeks and durvalumab (3 mg/kg or 10 mg/kg) q2 weeks	ORR 40% (1 PR/1 CR)	*Overall: 91%. The most frequent was chills/rigors, fever, nausea, hypotension, diarrhea, fatigue, tachycardia, and headache. Grade 3 & 4: 27% and 9%, respectively
Stevanovic et al. 2019 [60]	Phase II	18	Metastatic cervical cancer after standard therapy	Single infusion of E6 and E7 reactive TILs following lymphodepletion chemotherapy	ORR 28% (3 PR/2 CR)	*Grade 3–4: conditioning agent (myelosuppression and infection)
Jazaeri et al. 2019 [61]	Phase II	27	Recurrent, metastatic, or persistent squamous cell/adenosquamous or adenocarcinoma	After non-myeloablative lymphodepletion, patients were infused with their autologous TIL (LN-145) followed by IL-2 administration	ORR 44% (11 PR/1 CR) DCR 89%	TRAE generally consistent with the underlying advanced disease and the profile of the lymphodepletion and IL-2 regimens
Lu et al. 2017 [62]	Phase I	3	Metastatic or locally advanced/recurrent cancer. HLA-DPB1∗0401 positive and with tumors that contained 50% MAGE-A–positive tumor cells	Non-myeloablative chemotherapy preparative regimen followed by a single intravenous infusion of autologous TCR-transduced CD4+ T cells. A cell dose escalation starting at 10^7 total cells and escalating at half-log increment (highest 10^{11} cells). Post-infusion high-dose IL-2 intravenously at 720,000 IU/kg every 8 hours to physiologic tolerance	ORR 33% (0 PR/1 CR)	Transient grade 3 and from chemotherapy and high-dose IL-2. Prolonged high fever (39.0–40.0 °C) after cell infusion

AE adverse event, *CFU* colony-forming units, *Combo* combination therapy, *CR* complete response, *DCR* disease control rate = stable disease + partial response + complete response rates, *IV* intravenous, *Mono* monotherapy, *OS* overall survival, *mOS* median overall survival, *mPFS* median progression-free survival, *ORR* objective response rate, *PFS* progression-free survival, *PR* partial response, *q* every, *TRAE* treatment-related adverse events

*Includes other cancers

Table 7.6 Ongoing trials in cervical cancer

Study	Design	Patient population	Agent and dosing	Endpoints	Study status
KEYNOTE-826 (NCT03635567)	Phase III	Persistent, recurrent, or metastatic cervical cancer without treatment with systemic chemotherapy and is not amenable to curative treatment with surgery and/or radiation	Pembrolizumab + investigator's choice of chemotherapy vs. placebo + investigator's choice chemotherapy	Primary: PFS, OS Secondary: ORR, DOR, 12-month PFS, AE	Recruiting
BEATcc (NCT3556839)	Phase III	Persistent, recurrent, or metastatic cervical cancer is not amenable to curative treatment	Cisplatin + paclitaxel + bevacizumab vs. cisplatin + paclitaxel + bevacizumab + atezolizumab	Primary: OS Secondary: RFS, ORR, DOR, TRAE	Recruiting
NCT03614949	Phase II	Persistent, recurrent, or metastatic cervical cancer	Stereotactic body radiation therapy + atezolizumab	Primary: ORR Secondary: PFS, OS	Recruiting
NCT03508570	Phase Ib	Cervical cancer with metastatic peritoneal carcinomatosis and recurred after or progressed on frontline and 1–2 second line standard treatments	IP nivolumab +/− IP ipilimumab	Primary: MTD, RP2D Secondary: PK, toxicities, and IrAE, ORR	Recruiting
NCT02164461	Phase I/II	Persistent, metastatic, or recurrent cervical cancer	ADXS11-001 × 10^{10} CFU	Primary: MTD, AE Secondary: Changes in clinical immunology in serum and ORR	Awaiting results
AIM2CERV (NCT02853604)	Phase III	High-risk locally advanced cervical cancer	ADXS11-001 q3 weeks × 3 doses for the first 3 months in the adjuvant setting following chemoradiation	Primary: DFS; safety and tolerability	Active but not recruiting

ADXS11-001 axalimogene filolisbac, *AE* adverse events, *CFU* colony-forming units, *DOR* duration of action, *DCR* disease control rate = stable disease + partial response + complete response rates, *IrAE* Immune-related adverse events, *MTD* maximum tolerated dose, *OS* overall survival, *ORR* objective response rate, *PFS* progression-free survival, *PK* Pharmacokinetics, *RFS* recurrence-free survival, *RP2D* recommended phase II dose, *TIL* tumor-infiltrating lymphocytes, *TRAE* treatment-related adverse events

cell carcinomas of the head and neck (NCT02291055) [59]. In the phase I portion of the trial, combination therapy was examined with 8 cervical cancer patients treated [59]. Among the 5 evaluable patients, the ORR and DCR was 40% (1 partial and 1 complete response) with TRAE present in 91% of patients and grade 3 and 4 TRAE present in 27% and 9%, respectively. The most frequent TRAE were chills/rigors, fever, nausea, hypotension, diarrhea, fatigue, tachycardia, and headache. Additional studies examining ADSX11-011 use are currently under investigation (Table 7.6).

ACT in Cervical Cancer

In their phase II study, Stevanovic and colleagues administered a single infusion of E6 and E7 reactive TIL following lymphodepletion chemotherapy in patients with metastatic HPV-associated cancers following at least one prior

standard chemotherapy or chemoradiotherapy regimen [60, 63]. In the cervical cancer subcohort, the ORR and DCR was 28% (5 out of 18) including two patients who had complete responses after 22 and 15 months of treatment with no evidence of disease after 67 and 53 months, respectively (Table 7.5) [60, 63]. The proportion of HPV-reactive T-cells in peripheral blood post-infusion was positively correlated with improved clinical response [63]. Interestingly, analysis of the tumor antigens targeted by the TIL administered in patients who had complete objective responses demonstrated persistence of TIL that recognized neoantigens and cancer germline antigens in addition to the expected HPV viral antigens [64]. Given these promising results, there is another ongoing phase II, multicenter study to evaluate TIL therapy in patients with recurrent, metastatic, or recurrent cervical cancer (NCT03108495). The preliminary results of this trial presented at 2019 annual American Society of Clinical Oncology Meeting showed an ORR of 44% (1 complete and 11 partial responses) with a DCR of 89%, but with a short follow-up period (median follow-up of 3.5 months) [61].

Using ACT with genetically modified T-cells, Lu and colleagues administered dose-escalating autologous purified CD4+ T-cell therapy using an MHC class II-restricted, TCR that recognizes the cancer germline antigen, melanoma-associated antigen-A3 (MAGE-A3) to a cohort of 17 patients with various cancers [62]. In the preliminary results, although two of the three cervical cancer patients did not demonstrate a response to therapy, one of the patients who received 2.7×10^9 cells had a complete objective response at 29 months [62].

Ovarian Cancer

Immunotherapy represents a potentially promising alternative therapy in ovarian cancer for several reasons. PD-L1 expression appears to be highly prevalent in ovarian cancer compared to other malignancies with high expression associated with worse survival [65]. Furthermore, with a high prevalence of TIL and select groups with high neoantigen load, ovarian tumors are potential targets for therapeutic vaccines and ACT as well [66, 67].

Immune Checkpoint Inhibitors in Epithelial Ovarian Cancer

In a multicenter phase I trial, Brahmer et al. administered an anti-PD-L1 antibody to a heterogeneous cohort of advanced cancers, including 17 ovarian cancer patients [68]. In the ovarian cancer cohort, the ORR was 6% (1 partial response) with a DCR of 23.5% (Table 7.7) [68]. In an open-label, phase II trial, Hamanishi and colleagues administered up to 6 cycles of nivolumab to advanced or recurrent, platinum-resistant ovarian cancer [69]. In a cohort of 20 patients, nivolumab demonstrated an ORR of 15% (1 partial and 2 complete responses) and DCR of 45%. The median PFS was 3.5 months and median OS was 20 months [69]. In KEYNOTE-028, 26 patients with PD-L1-positive advanced, metastatic ovarian cancer received pembrolizumab with the majority of patients having at least 3 prior lines of systemic therapy [70]. The ORR was 11.5% (2 partial and 1 complete response) with a DCR of 38.5% and acceptable side effect profile [70]. In KEYNOTE-100 study, 376 patients with advanced, recurrent ovarian cancer were administered pembrolizumab and divided into two cohorts (A, $n = 285$ or B, $n = 91$) based on the history of number of prior lines of systemic therapy and treatment-free interval [71]. The ORR in cohort A was 7.4% (16 partial and 5 complete responses), while in cohort B it was 9.9% (7 partial and 2 complete responses) while the DCR was 37.2% and 37.4%, respectively. Higher PD-L1 expression (as measured as combined positivity score (CPS) ≥ 10) appeared to be correlated with higher clinical response (ORR 17.1% vs. 5.2% vs. 5.0% for CPS ≥ 10, 1–10, <1, respectively) [71].

The JAVELIN trials have investigated the use of avelumab in epithelial ovarian cancer. In the phase IB JAVELIN Solid Tumor study, avelumab was administered to 125 patients with advanced,

recurrent, or refractory ovarian cancer [72]. The ORR was 9.6% (including 1 complete and 11 partial responses) and DCR of 52% [72]. The 1-year PFS rate was 10.2% with a median OS was 11.2 months and acceptable side effect profile [72]. The study authors did not find an association between PD-L1 nor BRCA status and treatment response [72]. In JAVELIN Ovarian 200, 566 platinum-resistant/refractory ovarian cancer patients were randomized to one of 3 treatment arms: avelumab alone, pegylated liposomal doxorubicin alone, or both (NCT02580058) [74]. Preliminary results demonstrated that avelumab monotherapy resulted in the worst PFS, and there was no additional benefit with the combination of avelumab to pegylated liposomal doxorubicin (1.9 vs. 3.5 vs. 3.7 months, respectively). Similar results were seen with OS (11.8 vs. 13 vs. 15.7 months) [74]. However, subgroup analyses demonstrated that PD-L1 positivity was associated with slight clinical benefit with combination therapy in terms improved PFS (3.7 vs. 3.0 months; HR 0.65, 95% CI 0.46–0.92) with a trend towards improved OS (17.7 vs. 13.1 months; HR 0.72, 95% CI 0.48–1.08) [74]. Grade 3 TRAE were highest in the combination arm (42.9%) followed by PLD alone (31.6%) and avelumab alone (16.0%) [74].

In a phase I study by Infante and colleagues, atezolizumab was administered to 12 patients with advanced ovarian cancer with the majority having at least 2 prior lines of therapy [73]. In preliminary results of the 9 patients with an evaluable response, there was a 22% ORR and DCR (2 patients with partial response) [73].

Combination Therapy: Immune-chemotherapy

Given the strength immunosuppressive tumor microenviroment and modest response to single-agent immune checkpoint inhibitor therapies, interest has grown to utilize combination therapy in ovarian cancer. Wenham and colleagues presented their preliminary findings at the 2018 International Gynecologic Cancer Society Meeting where platinum-resistant recurrent ovarian cancer patients were treated with weekly paclitaxel and pembrolizumab (NCT02440425) [75]. In the 37 evaluable patients, the ORR was 51.4% (all partial responses) with DCR of 86.5%. The 6-month PFS rate was 64.5% and median PFS 7.6 months with a median OS of 13.4 months [75].

Combination Therapy: Immune-targeted Therapy

In a phase I study by Lee and colleagues, durvalumab was administered with either olaparib (poly-ADP-Ribose inhibitor) or cediranib (vascular endothelial growth factor receptor 1–3 inhibitor) to 26 patients with various cancers, the majority of which was ovarian (73%) [76]. In the 10 evaluable recurrent ovarian cancer patients who received durvalumab and olaparib, the ORR was 20% (two partial responses) with a DCR of 90% [76]. Durable responses in this treatment group were not explained by homologous recombination DNA repair pathway defects and none of the patients had germline BRCA mutations (two patients with somatic BRCA mutations had stable disease). For the 6 evaluable patients who received durvalumab and intermittent cediranib and were assessed for response, the ORR was 50% (all partial responses) and had a DCR of 83% [76]. Although the doublets overall had an acceptable safety profile, daily dosing cediranib treatment was not tolerated due to recurrent grade 2 and non-dose limiting toxicity grade 3 and 4 TRAE [76]. A biomarker analysis of a subset of the tumors demonstrated some clinical benefit correlated with tumoral PD-L1 expression [82]. In a larger cohort of recurrent, platinum-resistant ovarian cancer patients (majority consisting of BRCA wild types), Lee and colleagues found that durvalumab and olaparib had an ORR of 14.7% (5 partial responses; 2 with germline BRCA mutated and 3 with BRCA wild type) and DCR of 52.9% (NCT02484404) [77]. In another durvalumab/olaparib study, Drew et al. administered olaparib followed by maintenance olaparib and durvalumab therapy in platinum-sensitive ovarian cancer patients with germline BRCA mutations (MEDIOLA study; NCT02734004)

Table 7.7 Reported immune checkpoint inhibitors studies in epithelial ovarian cancer

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Monotherapy						
Brahmer et al. 2012 [68]	Phase I	17	Progressive disease with advanced or metastatic ovarian cancer	Anti-PD-L1 3 mg/kg or 10 mg/kg up to 16 cycles	ORR 6% (1 PR/0 CR), DCR 23.50% (DCR only seen at 10 mg/kg dose)	∗Overall: 61% (fatigue, infusion reactions, diarrhea, arthralgia, rash, nausea, pruritus, and headache) Grade 3 or 4 TRAE in 9%
Hamanishi et al. 2015 [69]	Phase II	20	Platinum-resistant ovarian cancer	Nivolumab 1 or 3 mg/kg q2 weeks up to 6 cycles	ORR 15% (1 PR/ 2 CR), DCR 45% mPFS 3.5 months, mOS 20 months	Most common: increased serum AST, hypothyroidism, lymphocytopenia, decreased albumin, fever, increased serum ALT, maculopapular rash, arthralgia, arrhythmia, fatigue, and anemia Grade 3–4: 40%
Varga et al. 2019 [70]	Phase IB	26	Advanced ovarian cancer with failure of previous therapy and PD-L1 positivity	Pembrolizumab 10 mg/kg q2 weeks for up to 24 months	ORR 11.5% (2 PR/ 1 CR), DCR 38.50% mPFS 1.9 months, mOS 13.8 months	Overall: 73.1% (most commonly arthralgia, nausea, pruritus). One grade 3 TRAE
Matulonis et al. 2019 [71]	Phase II	Cohort A ($n = 285$ Cohort B ($n = 91$)	Advanced recurrent ovarian cancer. Cohort *A* = 1–3 prior lines of treatment & TFI 3–12 months; cohort *B* = 4–6 prior lines of therapy and TFI of at least 3 months	Pembrolizumab 200 mg IV q3 weeks up until 2 years	ORR Cohort A: 7.4% (16 PR/5 CR); Cohort B: 9.9% (7 PR/2 CR), DCR 37.2% vs. 37.4%. CPS ≥ 10 is correlated with higher clinical response, mPFS 2.1 months for both; mOS not reached for cohort A and 17.6 months for cohort B	Overall: 73.1%. Grade 3–5: 19.7% (Most common fatigue 2.7%, 2 deaths due to Stevens-Johnson syndrome and one hypoaldosteronism). Ir-AEs: 22.6% with most common being hypo/ hyperthyroidism, grade 3–5 severity: severe skin reaction and colitis
Disis et al. 2019 [72]	Phase IB	125	Platinum-resistant ovarian cancer	Avelumab 10 mg/kg q2 weeks until progression or withdrawal	ORR 9.6% (11 PR/1 CR), DCR 52% mPFS 2.6 months, 6- and 12-month PFS rate 16.1% and 10.2%, respectively, mOS 11.2 months, 12-month OS rate 47% PD-L1 status nor BRCA status was associated with response	Overall: 68.8% Grade 3–4: 7.2%

(continued)

Table 7.7 (continued)

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Infante et al. 2016 [73]	Phase 1A	9	Advanced, recurrent ovarian cancer	Atezolizumab 0.3 mg/kg, 10 mg/kg, or 15 mg/kg q3 weeks	ORR 22.2% (2 PR/0 CR) DCR 22.20% mPFS 2.9 months, mOS 11.3 months	Overall: 91.7% and mainly grade 1–2 fatigue and pain. Grade 3: 17% (autoimmune hepatitis and maculopapular rash)
Combination therapy: immune-chemotherapy						
Pujade-Lauraine et al. 2019 [74]	Phase III	566	Platinum-resistant/ refractory ovarian cancer patients	Randomized 1:1:1 ARM#1: avelumab alone ARM#2: PLD alone ARM#3: avelumab + PLD	ORR 3.7% vs. 4.2% vs. 13.3% PFS 1.9 vs. 3.5 vs. 3.7 months OS 11.8 vs. 13 vs. 15.7 months	Grade 3 or more: highest in ARM#3 (42.9%) followed by ARM#2 (31.6%) and ARM#1 (16.0%). PPE syndrome (9.9%), neutropenia & rash (9.3% each), fatigue (7.1%), and stomatitis (5.5%)
Wenham et al. 2018 [75]	Phase II	37	Recurrent EOC platinum resistant, at most 3 prior therapies	Weekly paclitaxel (80 mg/ m^2) with pembrolizumab 200 mg IV q3 weeks	ORR 51.4% (PR only), DCR 86.50%, 6-month PFS 64.5%, mPFS 7.6 months, mOS 13.4 months	Most common = anemia, fatigue, neutropenia, nausea, edema, diarrhea, dyspnea, leukopenia, neuropathy, vomiting, abdominal pain, lymphopenia, cough, hypomagnesemia. Grade 3 or 4 AE: leukocytosis, anemia, neutropenia, lymphopenia; neutropenia, glucose intolerance, hyponatremia
Combination therapy: immune-targeted therapy						
Lee et al. 2017 [76]	Phase I	Arm#1 ($n = 10$) Arm#2 ($n = 9$)	Eligible patients had recurrent or metastatic ovarian cancer	Dose escalation ARM#1: Durvalumab (10 mg/kg q2 weeks – 1500 mg q4 weeks) + olaparib (200–300 mg BID) ARM#2 Durvalumab (10 mg/kg q2 weeks – 1500 mg q4 weeks) + cediranib (30 mg qday or 20 mg with 5 days on/2 days off)	ORR: ARM#1 20% (2 PR/0 CR); ARM#2 50% (3 PR /6 CR) DCR: ARM#1 90%; ARM#2 83%	ARM#1 grade 3 included anemia and lymphopenia. ARM#2: grade 3 fatigue and grade 4 hypertension. Daily cediranib treatment was not tolerated due to recurrent grade 2 and non-dose limiting toxicity grade 3 and 4 AE
Lee et al. 2018 [77]	Phase II	35	Recurrent, platinum resistant ovarian cancer	Durvalumab 1500 mg IV q4 weeks and olaparib 300 mg BID	ORR 14.7% (5 PR/ 0 CR), DCR 52.90%	Grade 3 or 4: anemia, lymphopenia. Olaparib dose reduction due to anemia, atrial fibrillation, and nausea refractory to supportive care

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Drew et al. 2018 [78]	Phase II	32	gBRCAm platinum-sensitive relapsed ovarian cancer	Olaparib 300 mg po BID × 4 weeks, then olaparib 300 mg po BID + durvalumab 1.5 g IV q4 weeks	ORR 63% (14 PR/ 6 CR) DCR 81%	Grade 3 AE = anemia, increased lipase, increased amylase, and neutropenia
Konstantinopoulos et al. 2019 [79]	Phase I/II	60	Recurrent ovarian cancer	Pembrolizumab 200 mg q3 weeks + niraparib 200 mg q day	ORR 18% (8 PR/ 3 CR), DCR 65%, mPFS 3.4 months, 6- and 12-month PFS 31% & 12%. ORR consistent across platinum-based chemo sensitivity, previous bevavcizumab, somatic BRCA mutations or HRD biomarker status	Most common: fatigue, nausea, anemia, constipation. Grade 3: myelosuppression
Liu et al. 2018 [80]	Phase II	38	Platinum sensitive and resistant ovarian cancer	Bevacizumab 10 mg/kg and nivolumab 240 mg every 2 weeks until progression	ORR 26.3% (10 PR/0 CR), DCR 34.2%, mPFS 9.4 months	Most common = fatigue, AST/ALT elevation, myalgia, and skin changes
Combination therapy: immune-immunotherapy						
Burger et al. 2018 [81]	Phase II	Arm#1 ($n = 49$) Arm#2 ($n = 51$)	Recurrent ovarian cancer	ARM#1: nivolumab 3 mg/kg IV then q2 weeks × 4 then maintenance 3 mg/kg IV q2 weeks for up to 42 doses. ARM#2: nivolumab 3 mg/kg IV + ipilimumab 1 mg/kg q3 weeks × 4 then maintenance nivolumab 3 mg/kg IV q2 weeks	ORR 31.4% vs. 12.2%, mOS 28.1 months vs. 21 months	AE: more frequently from ARM#2 vs. ARM#1 Grade 3 or more: 67% (ARM#2) vs. 55% (ARM#1)

AE adverse events, *CPS* combined positivity score, *CR* complete response, *DCR* disease control rate = stable disease + partial response + complete response rates, *gBRCAm* germline BRCA mutated, *IrAE* Immune-related adverse events, *mOS* median overall survival, *mPFS* median progression-free survival, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PPE* palmar-plantar erythrodysesthesia, *PR* partial response, *RFS* recurrence-free survival, *TRAE* treatment-related adverse events

[78]. In the 32 patients, there was an ORR of 63% (14 partial and 6 complete responses) with a DCR of 81% at 12 weeks and tolerable safe profile [78]. In TOPACIO/KEYNOTE-162, the investigators examined another PARPi/immune checkpoint inhibitor combination in a different patient population consisting of recurrent, platinum-resistant ovarian cancer patients with enrollment regardless of BRCA mutational status [79]. In this phase I/II study, niraparib and pembrolizumab was given to a cohort of 67 patients with ovarian or triple-negative breast cancer [79]. In the 60 evaluable ovarian cancer patients, the ORR was 18% (8 partial and 3 complete responses) and the DCR was 65% with acceptable treatment side effect profile [79]. The ORRs were seen to be consistent regardless of platinum-based chemotherapy sensitivity, previous bevacizumab, somatic BRCA tumor mutation, or homologous recombination defect biomarker status [79].

In another combination doublet study, Liu and colleagues tested nivolumab plus bevacizumab in a mixed cohort of platinum-sensitive and platinum-resistant ovarian cancer patients [80]. In the preliminary analyses of 38 patients, there was an ORR of 26.3% (10 partial responses with the majority in platinum-sensitive patients) with a DCR of 34.2% and tolerable side effect profile (NCT02873962) [80].

Combination Therapy: Immune-immunotherapy

Immunotherapy doublet therapy for ovarian cancer is currently being investigated in the phase II NRG-GY003 trial (NCT02498600) [81]. Burger and colleagues presented their preliminary findings at the 2018 International Gynecologic Cancer Society Meeting where 100 recurrent ovarian cancer patients were randomized to either nivolumab alone or nivolumab/ipilimumab followed by maintenance nivolumab [81]. Although the trial was not powered to detect a difference in overall survival (median OS 28.1 months vs. 21 months, respectively), ORR at 6 months was higher in the combination group than the monotherapy group (31.4% vs. 12.2%, respectively; OR 3.28, $p = 0.034$) [81]. Adverse events were higher in the combination group than the monotherapy group but were overall well tolerated [81]. There are a plethora of ongoing studies utilizing immune checkpoint inhibitors in combination with other agents in ovarian cancer (Table 7.10).

Vaccines in Epithelial Ovarian Cancer

Vaccines have been a point of interest in ovarian cancer to target tumor-associated antigens. NY-ESO-1 is expressed in >40% of advanced epithelial ovarian cancers and is one of the tumor-associated antigens of interest for vaccine therapy [83] (Table 7.8). In a study by Diefenbach et al., high-risk ovarian cancer patients with HLA-A∗0201 positivity had the administration of a NY-ESO-1b peptide and Montanide vaccination series following primary debulking and chemotherapy [84]. In the 9 patients evaluated, the vaccine series was overall well tolerated and appeared to mount a T-cell immunity response regardless of tumor expression of NY-ESO-1; 3 patients with NY-ESO-1 negative tumors having clinical remission at 25, 38, and 52 months [84]. In another phase I study, the addition of NY-ESO-1 vaccine and decitabine (DNA methylation inhibitor) following doxorubicin chemotherapy for 10 patients with recurrent epithelial ovarian cancer demonstrated increased antibody production and T-cell responses with an ORR of 10% (1 partial response) and DCR of 60% [85]. A phase I trial by Sabbatini et al. demonstrated that vaccine adjuvants to NY-ESO-1 such as Montanide-ISA-51 preparation and toll-like receptor ligand poly-ICLS (polyinosinic-polycytidylic acid-stablized by lysine and carboxymethylcellulose) can generate a stronger immune response in terms of antibody and CD8+ activity [86].

Dendritic cell vaccines have also been used in several trials. In a phase I/II trial, 11 ovarian cancer patients in their first or second clinical remission received monocyte-derived dendritic (DC)

loaded with Her2/neu (highly expressed in ovarian cancers), human telomerase reverse transcriptase, and pan-DR peptide antigens with or without cyclophosphamide chemotherapy prior to administration [87]. Overall 3-year survival was 90% with a trend towards survival in those who received cyclophosphamide therapy prior to vaccination [87]. In a phase I/II study, Baek et al. administered autologous dendritic-cell vaccination with IL-2 consolidation following debulking and chemotherapy and demonstrated good tolerability in 10 patients [88]. Three patients had maintenance of complete remission after vaccination for 83, 80.9, and 38.2 months and one patient had complete response for 50.8 months [88]. Increased immune response and reduced immune-suppressive factor secretion was also evident [88]. Another study compared autologous dendritic cell vaccine with chemotherapy to chemotherapy alone for recurrent platinum-sensitive ovarian cancers and demonstrated a trend towards improved ORR (87.5% vs. 62.5%, respectively) for the vaccine cohort (NCT02107950) [89]. A European multicenter, phase II study found that sequential administration of dendritic vaccines following primary cytoreductive surgery and chemotherapy had a trend of improved PFS compared with concomitant administration with adjuvant chemotherapy (24.3 vs. 18.3 months, $p = 0.05$) (NCT02107937) [90].

Kuwano et al. investigated the use of personalized vaccination based on HLA-type and pre-existing host immunity (by IGG response levels to tumor-associated antigens) and have demonstrated some disease stabilization with good tolerability [91]. Personalized vaccine generated by autologous dendritic cells pulsed with oxidized autologous whole-tumor cell lysate also demonstrated broad antitumor immune response activity [92].

In the DeCidE trial, DPX-Survivac (vaccine containing mix of HLA class I peptides against survivin antigen), low dose cyclophosphamide, and epacadostat (selective inhibitor of indoleamine 2,3-dioxygenase 1) were administered to stage IIC-IV recurrent ovarian cancer patients (NCT02785250) [93]. Preliminary results in the 10 evaluable patients demonstrated an ORR of 30% (3 partial responses) and DCR of 60% with good treatment tolerability [93].

Clinical trials utilizing autologous whole tumor vaccines are currently underway for high-risk stage III/IV ovarian cancer patients as adjuvant therapy (NCT01309230) or maintenance therapy (NCT02346747) (Table 7.10).

ACT in Epithelial Ovarian Cancer

Multiple trials have examined ACT in ovarian cancer. The first trial was by a 1991 study by Aoki et al. who examined TIL therapy without IL-2 infusion in advanced or recurrent ovarian cancer with or without cisplatin-containing combination chemotherapy [94]. In the TIL group without chemotherapy, there was an ORR of 71.4% (1 complete and 4 partial responses) while the group with both TIL and chemotherapy had a 90% ORR (7 with complete response and 2 with partial responses) where 4 of the 7 patients with complete responses did not have recurrence for >15 months of follow-up (Table 7.9) [94]. Another study by Ikarashi et al. demonstrated that TIL therapy may also induce increased cytotoxic T-cell and natural killer cell activity [95]. Another study by Fujita and colleagues compared patients with EOC following primary debulking and chemotherapy who were treated with TIL therapy without IL-2 infusion compared to controls. In their small study, they found that those who received TIL therapy had a better 3-year overall survival (100% vs. 65.5%) and PFS (82.1% vs. 54.5% respectively) rate compared with the control group [96]. In contrast to the above previous 3 studies, Pedersen et al. utilized an IL-2 infusion following TIL therapy in 6 patients with progressive platinum-resistant disease [97]. The DCR was 100% with 5 patients who had a reduction in size of target lesions (but did not meet partial response criteria) and antitumor reactivity seen in the TIL infusion products

Table 7.8 Reported vaccine therapy trials in epithelial ovarian cancer

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Diefenbach et al. 2008 [84]	Phase I	9	HLA-A*0201, positive and high-risk epithelial ovarian cancer (defined by suboptimal initial debulking surgery, failure to normalize CA-125 after 3 cycles of chemotherapy, or positive second-look surgery)	HLA-A*0201–specific NY-ESO-1b peptide with Montanide-ISA-51 vaccine q3 weeks × 5 doses	ORR 33.33% (0 PR /3 CR. DCR 33.33% T-cell immunity in both NY-ESO-1 positive and negative tumors	Fatigue, anemia, pruritus, myalgias, and hyper- or hypothyroidism. No grade 3–4 AE
Odunsi et al. 2014 [85]	Phase I	10	Women with relapsed EOC, who normally receive doxorubicin as salvage therapy for recurrent disease.	Decitabine, doxorubicin, & vaccination (NY-ESO-1 peptide + Montanide-ISA-51 + GM-CSF) × 4 cycles	ORR 10% (1 PR/0 CR) DCR 60%	Mainly injection side reactions. Grade 3 or 4: neutropenia, injection site reactions
Sabbatini et al. 2012 [86]	Phase I	Arm#1 ($n = 4$) Arm#2 ($n = 13$) Arm#3 ($n = 11$)	Stage II to IV histologically documented epithelial carcinoma arising in the ovary, fallopian tube, or peritoneum in 2nd or 3rd remission	ARM#1: NY-ESO-1 OLP only ARM#2: NY-ESO-1 OLP + Montanide-ISA-51 ARM#3: NY-ESO-1 OLP + Montanide-ISA-51 + Poly-ICLC	NY-ESO-1–specific Antibodies and CD8 + T cells: Undetectable after vaccination in ARM#1, 46% & 62%, respectively, with ARM#2, 91% & 91%, respectively, with ARM#3. Montanide ISA-51 increased NY-ESO-1–specific CD4 + T cells frequency and polyclonality. Poly-ICLC accelerated the induction of immune responses	Injection site reactions and fatigue that were definitely or possibly related, respectively
Chu et al. 2011 [87]	Phase I/II	5 per ARM	HLA-A2+ stages II–IV disease with no clinical evidence of disease after primary debulking surgery and chemotherapy, or those with stages I–IV disease with no clinical evidence of disease after secondary surgical treatment for a first recurrence diagnosed after a progression-free interval of at least 2 years	ARM#1: Mature autologous Dendritic cells pulsed with HLA-A2-restricted hTERT 988Y, Her2/neu 369V2V9, Her2/neu 689, and PADRE peptides (PolyPeptide laboratories, San Diego, CA) with cyclophosphamide ARM#2: as above without cyclophosphamide	PFS 40% (ARM#1) vs. 80% (ARM#2) ($p = 0.17$) ARM#2 had no change in total lymphocytes or regulatory cells. Modest T-cell response to vaccine but less than normal response to control vaccine (diphtheria conjugate protein CRM197)	Most common: erythema, induration, pruritus, and pain at the site of injection, fever and fatigue. No grade 3–4 toxicities

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Baek et al. 2015 [88]	Phase I/II	10	DC vaccination was introduced as a consolidation therapy in patients initially treated with debulking surgery and chemotherapy	Autologous monocyte-derived DCs pulsed with autologous tumor lysate and KLH at 4-week intervals	DCR 50%, PFS 21.7 months, OS 43.8 months, Increased NK activity, Interferon-gamma secreting T cells, immune-stimulatory cytokine secretion and reduced immune-suppressive factor secretion	Most common: flu-like symptoms
Cibula et al. 2018 [89]	Phase II	32 per ARM	Platinum-sensitive recurrent advanced stage EOC	ARM#1: Chemo + DCVAC. DCVAC (1×10^7 DCs/dose). ARM#2: Chemo only	ORR 87.5% vs. 62.5%, mPFS 10.9 vs. 9.4 months for ARM#1 and #2, respectively	Most AE: related to chemo. No grade 3 based on vaccines
Rob et al. 2018 [90]	Phase II	Arm#1 ($n = 34$) Arm#2 ($n = 34$) Arm#3 ($n = 31$)	Stage III EOC (serous, endometrioid, or mucinous), PS 0–2, post-PDS with <1 cm maximal residuum and no prior systemic therapy	ARM#1: combo DCVAC (1×10^7 DCs/dose) + chemo, ARM#2: Sequential chemo then DCVAC ARM#3: Chemo alone	mPFS 18.3 vs. 24.4 vs. 18.6 months; gain in PFS in ARM#2 ($p = 0.05$) and similar trend in OS	No grade 3 TRAE related to DCVAC
Kawano et al. 2014 [91]	Phase II	42	Platinum-sensitive and platinum-resistant recurrent ovarian cancer	Personalized vaccine based on peptides selected in consideration of the HLA-type and pre-existing host immunity, as assessed by IgG levels against each of the 31 different vaccine candidates + Montanide ISA-51 (Seppic, Paris, France) +/− chemo (if tolerable by patient)	ORR 2.3% (0 PR /1 CR), DCR 7.10% mOS 19.1 months	Mainly grade 1 or 2 dermatological reaction at the injection sites except one grade 3 leg infection. Severe adverse events associated with chemotherapy, rather than directly associated with the vaccinations
Tanyi et al. 2018 [92]	Phase I	25	Platinum-treated, immunotherapy-naïve, recurrent ovarian cancer patients	ARM#1: OCDC only ARM#2: OCDC + bevacizumab ARM#3: OCDC + bevacizumab + cyclophosphamide	ORR 0% vs. 10% vs. 10% DCR 30% vs. 50% vs. 70% Vaccination induced T-cell responses to autologous tumor antigen, which were associated with significantly prolonged survival	Mainly grade 1 or 2 AE, most common being pain

(continued)

Table 7.8 (continued)

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Dorigo et al. 2018 [93]	Phase I/II	10	Subjects with advanced ovarian cancer (stage IIc-IV with evidence of disease progression)	DPX-Survivac (dose escalation) + metronomic CPA + epacadostat	ORR 30% (3 PR/0 CR) DCR 60%	Well-tolerated

AE adverse events, *Chemo* chemotherapy, *Combo* combination, *CR* complete response, *DCR* disease control rate = stable disease + partial response + complete response rates, *DCVAC* dendritic-cell vaccine, *RP2D* recommended phase II dose, *HLA* human leukocyte antigen, *IL-2* interleukin-2, *KLH* keyhole limpet hemocyanin, *mOS* median overall survival, *mPFS* median progression-free survival, *MTD* maximum tolerated dose, *OCDC* oxidized autologous whole-tumor cell lysate injected intra-nodally, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *RFS* recurrence-free survival, *TRAE* treatment-related adverse events

Table 7.9 Reported trials in adoptive cell therapy in epithelial ovarian cancer

Study	Design	*N*	Patient population	Therapy	Results	TRAE
Aoki et a. 1991 [94]	Phase I	TIL only ($n = 7$) TIL + chemo ($n = 10$)	Advanced or recurrent EOC	ARM#1: TIL (at least 1×10^{10} cells); no IL-2 infusion ARM#2: cisplatin-containing chemo followed by TIL infusion; no IL-2 infusion	ORR: 71.4% (4 PR/1 CR) (mono) vs. 90% (2 PR/7 CR) (combo) DCR: 85.7% (mono) vs. 100% (combo)	Fever and chills in 30%
Ikarashi et al. 1994 [95]	Phase I	TIL ($n = 12$) Controls ($n = 10$)	Epithelial ovarian cancer of advanced stage (International Federation of Obstetrics and Gynecology Stage II, III, or IV) following PDS	PDS then cisplatin-containing chemo followed by TIL (5×10^8 cells) without IL-2 vs. PDS + chemo	Increased CD8+ cells, cell-mediated immunity, and NK cell activity with CD16 and CD56 APCs)	Toxicity mainly from chemo (nausea/vomiting, alopecia, myelosuppression)
Fujita et al. 1995 [96]	Phase I	TIL + chemo ($n = 13$) Chemo only ($n = 11$)	Epithelial ovarian cancer of advanced stage (International Federation of Obstetrics and Gynecology Stage II, III, or IV) following PDS without residual tumor	PDS then cisplatin-containing chemo Followed by TIL (5×10^8 cells) without IL-2 vs. PDS + chemo	3 year PFS = 82.1% (combo) vs. 54.5% (mono), $p < 0.05$. 3 year OS of disease-free patients = 100% (combo) vs. 67.5% (mono) respectively (= < 0.01)	Toxicity mainly from chemo, e.g., nausea/vomiting, alopecia, myelosuppression
Pedersen et al. 2018 [97]	Phase I	6	Progressive platinum-resistant metastatic ovarian cancer	Standard lymphodepleting chemotherapy followed by TIL therapy and decrescendo IL-2 stimulation	ORR 0%, DCR 100% mPFS 3 months, mOS 10 months, high expression of LAG-3) and PD-1	Mild TRAE; hypophosphotemia, fever, hypokalemia, anemia, lymphocytopenia, thrombocytopenia
Freedman et al. 1994 [98]	Phase I	8	Advanced epithelial ovarian carcinoma, and who were refractory to platinum-based chemotherapy	IP TIL + IP IL-2 infusion	ORR 0% ascites regression (two patients), tumor and CA-125 reduction (one patient), and surgically confirmed stable tumor and CA-125 values (one patient)	Grade 3: anemia and peritonitis

AE adverse events, *CFU* colony-forming units, *Chemo* chemotherapy, *Combo* combination therapy, *CR* complete response, *DCR* disease-control rate = CR rate + PR rate + stable disease rate, *DOR* duration of action, *IL-2* interleukin-2, *IrAE* Immune-related adverse events, *LAG3* Lymphocyte activation gene 3, *Mono* monotherapy, *MTD* maximum tolerated dose, *ORR* objective response rate, *OS* overall survival, *PD-1* programmed cell death protein 1, *PDS* primary debulking surgery, *PK* Pharmacokinetics, *PFS* progression-free survival, *PR* partial response, *PROs* patient-reported outcomes, *TIL* tumor-infiltrating lymphocytes, *TRAE* treatment-related adverse events, *RFS* recurrence-free survival, *RP2D* recommended phase II dose, *WT1* Wilm's tumor gene

Table 7.10 Ongoing clinical trials for epithelial ovarian cancer

Study	Design	Patient population	Agent and dosing	Endpoints	Study status
NCT02839707	Phase II/III	Recurrent, platinum-resistant high-grade ovarian cancer	ARM#1: Atezolizumab + PLD ARM#2: Atezolizumab + Bevacizumab + PLD, ARM#3: PLD + Bevacizumab	Primary: MTD, PFS, OS Secondary ORR, AE, PROs, PD-L1 expression	Suspended for scheduled interim monitoring
PemCiGem (NCT02608684)	Phase II	Recurrent ovarian cancer	Gemcitabine/cisplatin/pembrolizumab then pembrolizumab maintenance	Primary: ORR Secondary: PFS, time to progression, DOR, OS, AE	Active but not recruiting
ATLANTE (NCT02891824)	Phase III	Progressive non-mucinous EOC, fallopian tube, and primary peritoneal cancer (platinum sensitive relapse)	ARM #1: placebo + bevacizumab + platinum-based chemotherapy ARM#2: atezolizumab + bevacizumab + platinum-based chemotherapy	Primary: PFS Secondary: OS, PROs, AE	Recruiting
NCT01928394	Phase I/II	Advanced or metastatic ovarian cancer	Nivolumab +/− Ipilimumab +/− cobimetinib	Primary: ORR Secondary: PFS, TRAE, OS	Active but not recruiting
NCT03026062	Phase II	Platinum-resistant or refractory high-grade epithelial ovarian, peritoneal, or fallopian tube cancer	ARM#1: Sequential tremelimumab then durvalumab ARM#2 combination tremelimumab + durvalumab	Primary: Immune-related progression-free survival Secondary: TRAE, OS, ORR	Recruiting
NCT02726997	Phase I/II	Newly diagnosed Stage III-IV ovarian, primary peritoneal, or fallopian tube cancer	Addition of durvalumab to neoadjuvant and/or adjuvant carboplatin/paclitaxel with maintenance durvalumab monotherapy	Primary: pharmacodynamic changes by treatment Secondary: PFS, feasibility of treatment	Recruiting
NCT02520154	Phase II	Stage III-IV ovarian, primary peritoneal, or fallopian tube cancer	Addition of pembrolizumab to neoadjuvant and/or adjuvant carboplatin/paclitaxel with maintenance pembrolizumab monotherapy	Primary: PFS, Response rate Secondary: feasibility of treatment, AE, OS	Recruiting
NCT02834975	Phase II	Stage III-IV ovarian, primary peritoneal, or fallopian tube cancer	Addition of pembrolizumab to neoadjuvant chemotherapy	Primary: pathologic ORR Secondary: PFS, safety, and tolerability of combination therapy	Recruiting
NCT03038100	Phase III	Stage III-IV ovarian, primary peritoneal, or fallopian tube cancer	Addition of atezolizumab to adjuvant carboplatin, paclitaxel, and bevacizumab following PDS	Primary: PFS, OS Secondary: OR, DOR, PROs, HRQoL, AE	Active but not recruiting
NCT03330405	Phase II	Recurrent platinum sensitive ovarian cancer	Avelumab + talazoparib	Primary: DLT, OR Secondary: PK, ORR, tumor marker levels, PD-L1 biomarker in tumor tissue	Recruiting

Study	Design	Patient population	Agent and dosing	Endpoints	Study status
KEYLYNK-001/ ENGOT-ov43 (NCT03740165)	Phase III	First-line treatment of women with BRCA non-mutated advanced epithelial ovarian cancer	First-line chemotherapy (carboplatin/ paclitaxel) +/− pembrolizumab +/− olaparib (+/− placebo for each or both)	Primary: PFS, OS Secondary: PFS, TRAE, treatment discontinue rate, QoL, pathologic CRR	Recruiting
ENGOT-0 V44 The FIRST Study (NCT03602859)	Phase III	First-line treatment of stage III or IV non-mucinous epithelial ovarian cancer	ARM#1: chemotherapy + dorstarlimab placebo + maintenance placebo ARM#2: chemotherapy + dorstarlimab placebo + maintenance niraparib + maintenance dorstarlimab placebo ARM#3: chemotherapy + dorstarlimab + maintenance niraparib + dorstarlimab	Primary: PFS Secondary: OS, TRAE, ORR	Recruiting
NCT03598270	Phase III	Patients with recurrent ovarian, tubal, or peritoneal cancer and platinum treatment-free interval (TFIp) >6 months	ARM#1: Investigator's choice chemotherapy + atezolizumab + maintenance atezolizumab and niraparib ARM#2: investigator's choice chemotherapy + maintenance niraparib + placebo	Primary: PFS Secondary: OS, TRAE, PROs, HRQoL, ORR, DOR, PK	Recruiting
DUO-O (NCT03737643)	Phase III	Newly diagnosed stage III-IV ovarian, primary peritoneal, or fallopian tube cancer	ARM#1: carboplatin/paclitaxel/bevacizumab + durvalumab placebo + maintenance bevacizumab + placebo maintenance durvalumab & olaparib ARM#2: carboplatin/paclitaxel/bevacizumab + durvalumab placebo + maintenance bevacizumab & durvalumab + placebo maintenance olaparib ARM#3: carboplatin/paclitaxel/bevacizumab + durvalumab placebo + maintenance bevacizumab, durvalumab, & olaparib.	Primary: PFS Secondary: OS, HRQoL, pathological CRR, PK, ORR, DOR, safety and tolerability	Recruiting
ATHENA (NCT03522246)	Phase III	Newly diagnosed advanced (FIGO stage III-IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer	Maintenance rucaparib +/− nivolumab following primary or interval cytoreductive surgery	Primary: PFS Secondary: OS, ORR, DOR, TRAE, AE,	Recruiting

(continued)

Table 7.10 (continued)

Study	Design	Patient population	Agent and dosing	Endpoints	Study status
NCT03508570	Phase Ib	Platinum-resistant or refractory ovarian cancer with metastatic peritoneal carcinomatosis and recurred after or progressed on frontline and 1–2 second-line standard treatments	IP nivolumab +/− IP ipilimumab	Primary: MTD and P2PD Secondary: PK, IrAE, ORR	Recruiting
NCT01309230	Phase II	Stage III/IV papillary serous or endometrioid ovarian cancer following primary debulking and complete response to treatment	Intradermal autologous Vigil™ (1.0×10^7 cells/injection; maximum of 12 vaccinations)	Primary: Time to recurrence Secondary: immune function (surrogate markers, TIL, TAM, safety)	Recruiting
NCT02346747	Phase II	Stage IIIb-IV high-grade ovarian, fallopian tube or primary peritoneal following optimal PDS and chemotherapy	Vigil ® Ovarian (gemogenovatucel-T) engineered autologous tumor cells (EATC): receive 1.0×10^7 cells of gene transfected, irradiated, autologous tumor cells via intradermal injection once a month vs. placebo	Primary: PFS	Active but not recruiting
NCT00562640	Phase I	Recurrent platinum resistant or refractory ovarian cancer	WT1-peptide-sensitized T cells infusion when administered alone or with non-myelosuppressive chemotherapy (Cyclophosphamide) in patients	Primary: safety and tolerability, mean tolerated dose, quantitation of alterations in concentration of peptide-specific T-cells post infusion, response	Active but not recruiting
NCT01174121	Phase II	Chemorefractory ovarian cancer on at least second-line chemotherapy	Arm#1: CD8+ enriched TIL. ARM #2: unselected TIL. ARM#3: unselected TIL + Pembrolizumab prior to administration +3 cycles after ARM#4: unselected TIL + Pembrolizumab at progression for up to 8 cycles	Primary: Response rate Secondary: Frequency and severity of TRAE, safety and efficacy of pembrolizumab following TIL therapy	Recruiting
NCT01883297	Phase I	Recurrent platinum resistant high grade serous ovarian, fallopian tube, or primary peritoneal cancer, with evidence of disease progression from previous line of treatment	Conditioning with cyclophosphamide then re-stimulated TIL and IL-2 infusion	Primary: AE Secondary: clinical response to treatment, immune response	Recruiting
NCT02876510	Phase I	HLA-positive phenotype with advanced/metastatic ovarian cancer with up to 1 previous failed therapy	Conditioning with cyclophosphamide + fludarabine + autologous T-cell products (ACTolog® (IMA101–101)) with IL-2 +/− atezolizumab	Primary: AE; Secondary: feasibility of treatment, peripheral T-cell persistence, T-cell functionality, incidence of clinical responders, OS, PFS	Recruiting

Study	Design	Patient population	Agent and dosing	Endpoints	Study status
NCT03412526	Phase II	Platinum-resistant or platinum refractory disease	Conditioning with cyclophosphamide + fludarabine then total body radiation then unselected or 4-1BB-enriched TIL+ IL-2 infusion	Primary ORR, AE Secondary: OS, response rate, PFS, QoL	Recruiting

AE adverse events, *CFU* colony-forming units, *DOR* duration of action, *HLA* human leukocyte antigen, *IL-2* interleukin-2, *IrAE* Immune-related adverse events, *MTD* maximum tolerated dose, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PK* Pharmacokinetics, *PROs* patient reported outcomes, *QoL* Quality of life, *RFS* recurrence-free survival, *RP2D* recommended phase II dose, *TIL* tumor-infiltrating lymphocytes, *TRAE* treatment-related adverse events, *WT1* Wilm's tumor gene

[97]. However, they noted that the lack of better therapeutic response may be due to high expression of lymphocyte-activation gene 3 (LAG-3) and PD-1, which are both involved in immune inhibitory signaling when interacting with MHCII and PD-L1, respectively [97]. Another study by Freedman et al. examined the administration of intraperitoneal TIL therapy with IL-2 in 11 patients and found clinical activity in 4 patients: ascites regression (2 patients), tumor and Ca-125 reduction (1 patient), and stable tumor and CA-125 levels in 1 patient [98].

Given the encouraging results, there is a plethora of ongoing clinical trials employing ACT for the treatment of ovarian cancer which are listed in Table 7.10.

Other Gynecologic Malignancies

There are few immunotherapy studies in other gynecologic malignancies. Quéreux and colleagues examined patients with metastatic or unresectable vulvar and vaginal melanomas who received immune checkpoint inhibitors in a retrospective review [99]. In the 6 patients that received ipilimumab, there were 4 patients with progressive disease, 1 stable response, and 1 patient who had a partial response but 89% reduction in tumor volume and a survival of 31 months [99]. In the 8 patients that were treated with nivolumab, there were partial responses in 4 patients [99]. One vaginal melanoma patient had received both ipilimumab and nivolumab and had a partial response [99].

Conclusion

Immunotherapeutic options hold modest but promising results in gynecologic cancers. Although a number of early studies have found limited clinical efficacy of vaccines as a monotherapeutic strategy, therapeutic vaccines may be useful as an adjunct in oncologic treatment as we await future trial results. Demonstrating impressive clinical responses in other solid tumors (e.g., metastatic melanoma), ACT and its utilization in gynecologic cancers are growing, and this approach has demonstrated promising early results in cervical and ovarian cancer. Additionally, immune checkpoint inhibitors have demonstrated durable clinical responses in various clinical trials, and this has resulted in granting approval for select patient population (e.g., pembrolizumab for MMR-deficient or MSI tumors and PD-L1-positive cervical cancers). Although immune checkpoint inhibitors have been the focus of interest in immunotherapy, there has been an explosion of new clinical trials in the recent years to investigate other modalities as well. With the modest results of using one immunotherapeutic agent, combination therapy utilizing agents from various immunotherapeutic/cytotoxic/targeted modalities is being investigated in multiple trials and to determine the optimal treatment regimens for right subset of patients. However, with a wealth of new immunemodulatory drugs, there will need to be a rethinking and innovation of clinical testing and trial design to optimize financial and clinical resources in pursuit of improved oncologic outcomes.

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