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# Immunotherapy in Gynecologic Cancers: Are We There Yet?

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## Opinion statement

Immune-targeted therapies have demonstrated durable responses in many tumor types with limited treatment options and poor overall prognosis. This has led to enthusiasm for expanding such therapies to other tumor types including gynecologic malignancies. The use of immunotherapy in gynecologic malignancies is in the early stages and is an active area of ongoing clinical research. Both cancer vaccines and immune checkpoint inhibitor therapy continue to be extensively studied in gynecologic malignancies. Immune checkpoint inhibitors, in particular, hold promising potential in specific subsets of endometrial cancer that express microsatellite instability. The key to successful treatment with immunotherapy involves identification of the subgroup of patients that will derive benefit. The number of ongoing trials in cervical, ovarian, and endometrial cancer will help to recognize these patients and make treatment more directed. Additionally, a number of studies are combining immunotherapy with standard treatment options and will help to determine combinations that will enhance responses to standard therapy. Overall, there is much enthusiasm for immunotherapy approaches in gynecologic malignancies. However, the emerging data shows that with the exception of microsatellite unstable tumors, the use of single-agent immune checkpoint inhibitors is associated with response rates of 10– 15%. More effective and likely combinatorial approaches are needed and will be informed by the findings of ongoing trials.

### Keywords

Immunotherapy; Checkpoint inhibitor; Cervical cancer; Ovarian cancer; Endometrial cancer; PD1; PD-L1

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**Compliance with Ethical Standards**

**Conflict of Interest**

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This article does not contain any studies with human or animal subjects performed by any of the authors.

## Introduction

The treatment of many advanced, and historically difficult to treat malignancies, including melanoma and non-small cell lung cancer (NSCLC), has been revolutionized with the development of immune-based anti-tumor therapies. Such therapies, when active, have demonstrated impressive and durable responses. This has led to a growing interest in clinical testing of these therapies in other tumor types, including gynecologic malignancies. The purpose of this review is to present the emerging and preliminary data from trials evaluating immunotherapy approaches for the treatment of gynecologic cancers.

For an in-depth review of various immunotherapy approaches and their respective rationale, readers are referred to excellent reviews [1–3]. Here, we offer a focused overview, to familiarize those readers who may lack an extensive background in immunotherapy. In general, immunotherapies are utilized to reactivate the immune response and/or dampen tumor-directed immune inhibition. Early in the disease process, the tumor stimulates an immune response with activation of both innate and adaptive immune mechanisms [4••, 5]. Eventually, the tumor is able to evade these immune responses through multiple mechanisms [4••] including the activation of immune checkpoints that dampen and inhibit the immune system's ability to target the tumor [4••, 5]. In order to activate tumor-directed immune responses, recent immune therapies have consisted of several approaches, including adoptive cell transfer (ACT), cancer vaccines, and immune checkpoint inhibitors.

In ACT, autologous T cells can be collected from peripheral blood or directly from resected tumor tissue (tumor-infiltrating lymphocytes, TILs) which are then expanded and infused back into the patient for treatment [1]. ACT may also include the use of genetically modified T cells designed to recognize specific tumor-associated antigens. These include engineered T cell receptors (TCR) that recognize tumor-specific peptides bound to the major histocompatibility complex (MHC) or chimeric antigen receptors (CAR) that render T cells able to recognize tumor surface antigens independent of MHC using an antibody-like recognition module [1].

Another approach to immune activation is therapeutic tumor vaccines. These vaccines consist of tumor-specific antigens supplied as peptides or antigen-activated dendritic cells in combination with immune-stimulatory adjuvants, and work to stimulate T cell responses through activation from antigen-presenting cells [2].

Exploitation of immune checkpoints has been a compelling recent development and heralded a renaissance in the field of cancer immunotherapy. Immune checkpoint proteins are expressed on cytotoxic T cells upon activation and work as a "negative feedback loop" to inhibit the tumor-directed immune response in order to minimize damage to normal tissues. However, these pathways are frequently co-opted by tumors to evade immune surveillance [3]. Monoclonal antibodies against the immune checkpoints cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death (PD-1) and the PD-1 ligands (PDL-1) are currently being used in clinical settings [6–8]. Examples of such agents are shown in Table 1. Immune checkpoint-inhibiting agents can also be used alone or in combination [9].

With the recent promising results in other tumor types, adaptation of immunotherapy to gynecologic malignancies has begun. Although in the early stages, numerous trials in cervical, ovarian, and endometrial cancer are underway. Here, we review the recent work with immunotherapy in gynecologic malignancies, as well as, ongoing and upcoming clinical trials. Ongoing clinical trials are highlighted in Table 2.

## Ovary

### Immune checkpoint inhibitors

**Reported trials—**In ovarian cancer, there are few published studies utilizing immunotherapies. A phase II Japanese study of nivolumab (an anti-PD-1 antibody) in 20 patients with platinum-resistant epithelial ovarian cancer (EOC) showed a response rate of 15% (3/20) and a disease control rate of 45% [10•]. Two patients experienced a complete response, one with serous and one with clear cell histology. Although small, the presence of complete responses in a heavily pretreated group of patients with an overall poor prognosis is promising. This study also suggested that a 3 mg/kg dose may be preferred over a 1 mg/kg dose of nivolumab as there was improved response and similar toxicities in the higher dose group. More recently, at the ASCO 2015 annual meeting, a study assessing the safety and activity of an anti-PD-L1 antibody (avelumab) in platinum-resistant ovarian cancer showed an objective response rate (ORR) of 9.7% and a stable disease (SD) rate of 44.4% (NCT01772004) [11]. At this same meeting, single-agent pembrolizumab was shown to have an 11.5% ORR and 34.6% SD rate in advanced ovarian cancer with positive PD-L1 status (NCT02054806) [12].

In those patients with a BRCA mutation and ovarian cancer, immune checkpoint inhibitors are being investigated in combination with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors. This combination is thought to potentially increase the efficacy of PARP inhibitors alone. Specifically, a phase I study of olaparib (PARP inhibitor) and durvalumab (anti-PD-L1) found an ORR of 17% but a disease control rate of 83% [13].

**Ongoing trials—**Currently, multiple studies are further investigating the role of immune checkpoint inhibitors in ovarian cancer. The major focus of many of these trials has been in platinum-resistant disease in which an anti-PD-1/PD-L1 agent is combined with standard chemotherapeutic agents. A phase III study design reported at the 2016 ASCO annual meeting is investigating pegylated liposomal doxorubin (Doxil) with an anti-PD-L1 agent (avelumab) versus Doxil alone (NCT02580058) [14]. Other studies are also adding bevacizumab to a Doxil and anti-PD-L1 (atezolizumab) combination compared to Doxil and atezolizumab or Doxil and bevacizumab alone (NCT02839707). Another phase II study presented at the 2016 ASCO annual meeting is evaluating the combination of weekly paclitaxel and an anti-PD-1 (pembrolizumab) (NCT02440425) [15]. The primary endpoint of this study is a 6-month progression-free survival rate. Additionally, pembrolizumab is also being investigated in combination with gemcitabine and cisplatin with overall response as the primary objective (NCT02608684). In this study, patients receive six cycles of gemcitabine and cisplatin. Pembrolizumab is added with cycle number three and continued as maintenance therapy up to 1 year. The role of immune checkpoint inhibitors in recurrent

platinum-sensitive disease is also being studied in a phase III French trial in which patients receive a platinum-based therapy with bevacizumab and are randomized to either additional anti-PD-L1 therapy (atezolizumab) or placebo (NCT02891824).

Combination immune checkpoint inhibitor therapy may also improve low response rates to single-agent therapy and is an area of active investigation. For example, the BMS-sponsored CheckMate 032 study is a phase I/II study of nivolumab monotherapy or nivolumab plus ipilimumab in advanced solid malignancies (NCT01928394). This study includes an ovarian cancer cohort as well as different schedules and doses of ipilimumab and nivolumab in the combination cohorts. A similar study at the National Cancer Institute is comparing nivolumab alone versus combination with ipilimumab in platinum-resistant ovarian cancers. This trial also includes a maintenance phase of nivolumab for both groups (NCT02498600). At MD Anderson, we recently started an investigator-initiated adaptively randomized study, testing the combination of an anti-CTLA-4 antibody (tremelimumab) with an anti-PD-L1 antibody (durvalumab) versus their sequential use in platinum-resistant EOC (NCT03026062).

In the upfront setting, several studies are currently including immune checkpoint inhibitors in the initial therapy to help improve progression-free survival. One such study is incorporating an anti-PD-L1 (durvalumab) with standard carboplatin and paclitaxel (NCT02726997). Similarly, another study combines an anti-PD-1 (pembrolizumab) with standard carboplatin and paclitaxel therapy (NCT02520154). In this study, patients receive neoadjuvant carboplatin and paclitaxel followed by interval tumor reductive surgery. Pembrolizumab is then added to the treatment regimen as adjuvant therapy after surgery. Yet, another study uses pembrolizumab in the neoadjuvant setting with carboplatin and paclitaxel prior to interval debulking surgery (NCT02834975). The GOG Foundation, in partnership with Genetech—Roche, is investigating carboplatin, paclitaxel, and bevacizumab with or without atezolizumab (anti-PD-L1) in patients either undergoing neoadjuvant treatment or with residual disease after primary debulking surgery (NCT03038100). The role of maintenance therapy with immune checkpoint inhibitors is also under investigation with a phase III study of avelumab (anti-PD-L1) as maintenance after standard therapy or in combination with standard therapy and then continued as maintenance treatment (NCT02718417).

## Cancer vaccines

Various types of cancer-specific vaccines have been trialed in ovarian cancer, and continue to be an area of active investigation. The cancer-testis antigen, NY-ESO-1, is frequently expressed in EOC, making it a suitable candidate for targeted vaccine therapies. Early vaccine trials with this agent demonstrated induced T cell-specific immunogenicity [16]. To further improve NY-ESO-1 presentation, epigenetic modulators that inhibit DNA methylation have also been combined with the NY-ESO-1 vaccine and standard chemotherapy in those with recurrent disease [17]. This regimen was found to increase the presence of NY-ESO-1 antibodies and T cell responses, and resulted in stable disease and partial clinical response (CR) in 6/10 patients. Other attempts to increase immunogenicity to this agent have included the addition of immune modulation agents to the vaccine

preparation such as Montanide and immunostimulants such as the toll-like receptor (TLR) ligand poly-ICLC (polyinosinic-polycytidylic acid—stabilized by lysine and carboxymethylcellulose) [18]. The addition of combination immune modulators seems to enhance the immune-specific response to NY-ESO-1.

Her2/neu is another tumor-associated antigen under active investigation as it is expressed in approximately 90% of recurrent ovarian cancers. In a small study of 11 patients, autologous dendritic cells loaded with the Her2/neu antigen, as well as human telomerase reverse transcriptase (hTERT) and pan-DR peptides (PADRE) antigens, were administered to patients with advanced ovarian cancer in remission [19]. This study demonstrated a 90% 3-year overall survival. Other autologous dendritic cell vaccine studies have also shown prolonged disease-free intervals when used in the maintenance setting and with concurrent IL-2 infusion [20].

Additionally, whole tumor cell vaccines are being utilized, as it is theorized, that this will allow for an induced immunologic response to a wider array of antigens rather than a single tumor-associated antigen [21]. This method may also induce a more broad immune response with both cytotoxic T cell (CTL) and CD4 T cell responses [21]. Similarly, personalized peptide vaccines have also been trialed in which anti-cancer vaccine composition is selected based on the HLA type of the patient as well as the IgG levels for other tumor-associated antigens in the individual tumor [22]. This study was conducted in patients with both platinum-sensitive and platinum-resistant disease showing an overall survival (OS) of 39.3 and 16.2 months, respectively, and was felt to be secondary to stabilization of disease and prolongation of tumor progression rather than disease regression. The Vigil autologous whole tumor vaccine administered to patients after primary tumor debulking and six cycles of standard chemotherapy preliminarily showed improved disease-free interval in those receiving the vaccine compared to the placebo group (19.3 vs 12.4 months) (NCT01309230). These phase II results were presented at the 2015 Society of Gynecologic Oncology annual meeting. The follow-up phase III trial (NCT02346747) is nearing completion. Although the studies for ovarian cancer vaccines are small, the findings are intriguing and warrant further investigation.

## Adoptive cell transfer

Adoptive cell immunotherapy using TILs consists of isolation of TILs from fresh tumor biopsy and expansion to large numbers ex-vivo with subsequent administration of the expanded TIL product to the patient. TIL infusion is preceded by lymphodepletion chemotherapy to reduce the number of regulatory T cells. As with other immunotherapy approaches, TIL therapy has been most extensively utilized in melanoma where response rates of approximately 50% have been reported [23••, 24–25]. There are only a handful of reports on TIL therapy in ovarian cancer, and all of these studies predated the recognition of the crucial importance of lymphodepleting chemotherapy prior to TIL infusion [26–29]. However, when ovarian cancer TIL therapy was administered after surgery and primary adjuvant chemotherapy (a situation analogous to the use of lymphodepleting chemotherapy), the results showed 100% 3-year survival in patients who received TIL versus 67.5% in those who did not [28]. In summary, there is strong biological and clinical rationale for testing TIL

therapy in ovarian cancer and several ongoing and planned trials will be investigating this approach.

## Cervix

Cervical cancer is unique among gynecologic malignant tumors because of its well-established and causative risk factor, chronic HPV infection. The infectious etiology of cervical cancer has led to effective vaccines for prevention; however, advanced stage/metastatic disease remains a principal cause of gynecologic cancer mortality in much of the world.

### Immune checkpoint inhibitors

**Reported trials—**In patients with advanced and recurrent cervical cancer, few substantial treatment options are available which make alternative treatment options like immunotherapy appealing. Preliminary results from the cervical cancer cohort of the KEYNOTE-028 study were recently presented and included patients with recurrent squamous cell carcinoma (SCC) of the cervix (NCT 02054806) [30]. In this study, treatment with anti-PD-1 therapy (pembrolizumab) demonstrated a 12.5% objective response rate with 3/24 patients having stable disease. The KEYNOTE-158 trial is further investigating pembrolizumab in this population, as well as, other solid tumors in a phase II trial (NCT02628067). Preliminary results of this trial showed a 17% ORR independent of tumor PD-L1 status [31]. The CheckMate 358 study investigating response to anti-PD-1 therapy with nivolumab in cervical, vaginal, and vulvar cancer demonstrated a preliminary objective response rate of 20.8% and a disease control rate of 70.8% in 24 patients (NCT02488759) [32]. All patients with response had a diagnosis of cervical cancer, and progression-free survival was 5.5 months. Although the response to immune checkpoint therapies in these studies is promising, the responses were low overall with a short disease progression-free interval, and further investigation is warranted.

Aggressive subtypes of cervical cancer, such as neuroendocrine tumors, have shown some responses to immune checkpoint inhibitors in case reports. In one such report, a patient with recurrent small cell neuroendocrine carcinoma of the cervix experienced a complete and lasting response to anti-PD-1 therapy [33]. The rarity of these tumors, however, makes large randomized trials challenging.

**Ongoing trials—**Other ongoing studies are evaluating the role of immune checkpoints with chemoradiation. One such study is looking at an anti-CTLA-4 inhibitor (ipilimumab) after primary chemoradiation in stage IB2-IIB or IIIB-IVA cervical cancer with positive pelvic and/or para-aortic nodes (NCT01711515). Preliminary results of this study were recently presented and demonstrated a 1-year disease-free survival of 74%, and therapy was well tolerated overall. Yet, another phase II study is comparing concurrent pembrolizumab with chemo-radiation to sequential therapy (chemoradiation followed by pembrolizumab) (NCT02635360).

### Cancer vaccines

**Reported trials—**Cancer-associated vaccines have been used to provoke immune-mediated anti-tumor activity, and in cervical cancer, HPV-specific proteins have been utilized to target HPV-infected cells. Specifically, a live attenuated Listeria monocytogenes (Lm) vaccine containing an HPV-16-E7 fusion protein was initially used in a phase II study by a group in India [34]. In this study, 110 patients with recurrent squamous cell carcinoma (SCC) of the cervix were randomized to three doses of the vaccine alone versus four doses of the vaccine with concurrent cisplatin chemotherapy. The clinical response rate was 11% with the response lasting an average of 10.5 months. There was also a 12-month survival of 36% and 18-month survival of 28%. There was no difference seen between those who received concurrent cisplatin therapy.

In response to the promising activity in this study, the NRG/GOG created an Lm cancer vaccine trial for those with persistent or recurrent SCC of the cervix who had at least one prior line of chemotherapy (GOG/NRG-0265) [35]. The vaccine was used as monotherapy every 28 days, and over half of the patients had been previously treated with bevacizumab. Preliminary results were presented at the 2017 Society of Gynecologic Oncology (SGO) annual meeting, and they demonstrated a 12-month overall survival (OS) rate of 38% with 50 enrolled patients. This compares to a 30% 12-month OS previously seen with bevacizumab therapy in those with persistent or recurrent SCC of the cervix [36]. Given the overall poor prognosis of these patients, the activity and durable responses seen in this study are promising.

**Ongoing trials—**Other vaccine trials in cervical cancer are ongoing using HPV 16- and 18-specific vaccines for recurrent disease that has failed standard chemotherapy (NCT02866006) or combining therapeutic HPV 16-directed vaccines to standard chemotherapy (carboplatin and paclitaxel with or without bevacizumab) in advanced or recurrent HPV-positive disease (NCT02128126).

## Endometrial

In endometrial cancer, patients with advance or disseminated recurrent disease have a poor prognosis [37] and most patients with peritoneal recurrence are considered incurable. Platinum and taxane chemotherapy produces response rates of 40–60%, which decreases to 20% for second-line drugs [37, 38]. This represents a critical need to identify more effective treatments for those patients with advanced disease.

### Immune checkpoint inhibitors

Approximately 25% of endometrial tumors are characterized by defects in the DNA mismatch repair (MMR) system manifested by errors in DNA replication of trinucleotide repeat regions, commonly referred to as microsatellite instability (MSI). These MMR defects also result in a high somatic mutation rate and accordingly increased number of neoantigens in these MMR-deficient (MMRD) tumors [39•, 40]. In endometrial cancer, the presence of high microsatellite instability (MSI-H) has become an area of interest for use of immune checkpoint inhibitors. This is due to the results of a phase II trial of anti-PD-1

therapy (pembrolizumab) in MSI-H tumors that demonstrated a 71% immune-related objective response rate in non-colorectal tumors [41]. Interestingly in this study, two patients with MSI-H endometrial cancer were included with one having a partial response and the other a complete response. Another phase Ib study (KEYNOTE-028) evaluating anti-PD-1 (pembrolizumab) therapy in PD-L1-positive solid tumors analyzed a subgroup of patients with advanced endometrial cancer (MSI testing was not performed) [42]. Patients in this study had failed standard therapy and received at least two prior lines of treatment. Additionally, the tumors were required to have positive PD-L1 expression defined as at least 1% positive staining by immunohistochemistry. Out of 24 patients, three had a partial response and three had stable disease. This group included patients with all histologies and only one patient had an MSI-H tumor, however, they were only able to evaluate MSI status in 18 cases. Pembrolizumab was well tolerated in this study with no patients discontinuing treatment due to toxicity, but about half of the patients experienced a treatment-related adverse event. These results are promising given the poor prognosis for those with endometrial cancer that fail standard therapy. Additionally, pembrolizumab was recently granted FDA approval for use in MSI-H solid tumors that have progressed on standard therapy and have no alternate therapeutic options.

These results have inspired ongoing clinical trials with immune checkpoint inhibitors in endometrial cancer patients as shown in Table 2. These agents are being investigated in combination with standard therapies (carboplatin and paclitaxel) for those with recurrent or advanced disease (NCT02549209). Other studies are focusing on the use of immune checkpoint inhibitors in patients with POLE or MSI-H tumors (NCT02899793), as this group was shown to be a promising targeted cohort of endometrial cancer patients [41]. Combination immune checkpoint inhibitors (anti-PD-1 and anti-CTLA-4) are also being investigated in patients with advanced grade 3 endometrial cancers and high-risk histologies (serous, clear cell, mixed histology) (NCT02982486).

## Conclusion

Immunotherapy has begun to make a major impact on multiple cancer types, and the efficacy of immunotherapy in gynecologic malignancies is under active investigation. Immune checkpoint inhibitors have shown promising preliminary results in advanced endometrial cancer, ovarian cancer, and cervical cancer. Similar to that seen in other tumor types, continued work will need to focus on identifying those subsets of patients that will benefit from these therapies as these treatments are not without significant toxicities. With the notable exception of MSI tumors, low response rates with single-agent checkpoint inhibitor therapies highlight the importance of research aimed at identifying rational combination immunotherapies for gynecologic cancers.

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**Table 1**

Immune checkpoint drugs and associated targets

| Drug name | Immune checkpoint target |
|---|---|
| Ipilimumab | CTLA-4 |
| Tremelimumab | CTLA-4 |
| Pembrolizumab | PD-1 |
| Nivolumab | PD-1 |
| Avelumab | PD-L1 |
| Durvalumab | PD-L1 |
| Atezolizumab | PD-L1 |

*CTLA-4* cytotoxic T lymphocyte-associated antigen 4, *PD-1* programmed cell death 1, *PD-L1* programmed cell death ligand 1

**Table 2**

Ongoing immunotherapy trials in gynecologic malignancies

| Trial | Study population | Phase | Intervention | Primary outcome | Status |
|---|---|---|---|---|---|
| Ovary | | | | | |
| NCT02580058 JAVELIN Ovarian 200 | Platinum-resistant/refractory EOC | III | Arm 1: Avelumab<br>Arm 2: avelumab + Doxil<br>Arm 3: Doxil | OS; PFS | Recruiting |
| NCT02839707 | Platinum-resistant EOC | II/III | Arm 1: Doxil + atezolizumab<br>Arm 2: Doxil + atezolizumab + bevacizumab<br>Arm 3: Doxil + bevacizumab | DLTs, PFS | Recruiting |
| NCT02440425 | Platinum-resistant EOC | II | Weekly paclitaxel + pembrolizumab | PFS; AEs | Recruiting |
| NCT02608684 PemCiGem | Platinum-resistant EOC | II | Gemcitabine + cisplatin + pembrolizumab | ORR | Recruiting |
| NCT02891824 ATALANTE | Recurrent platinum-sensitive EOC | III | Arm 1: placebo + bevacizumab + platinum chemo<br>Arm 2: atezolizumab + bevacizumab + platinum chemo | PFS | Recruiting |
| NCT01928394 CheckMate 032 | Advanced or metastatic solid tumors | I/II | Arm 1: nivolumab<br>Arm 2: nivolumab + ipilimumab<br>Arm 3: nivolumab + ipilimumab + cobimetinib | ORR | Recruiting |
| NCT02498600 | Recurrent or persistent EOC | II | Arm 1: nivolumab + nivolumab maintenance<br>Arm 2: nivolumab + ipilimumab + nivolumab maintenance | ORR | Recruiting |
| NCT03026062 | Platinum-resistant and platinum refractory EOC | II | Arm 1: sequential tremelimumabfollowedby durvalumab<br>Arm 2: combination tremelimumab + durvalumab | irPFS | Recruiting |
| NCT02726997 | Advanced EOC with no prior treatment | I/II | Carboplatin + paclitaxel + durvalumab | Pharmacodynamics changes | Recruiting |
| NCT02520154 | Advanced EOC with no prior treatment | II | Neoadjuvant carboplatin + paclitaxel followed by interval TRS and adjuvant carboplatin + paclitaxel + pembrolizumab | PFS | Recruiting |
| NCT02834975 | Advanced EOC with no prior treatment | II | Neoadjuvant pembrolizumab + carboplatin + paclitaxel following by interval TRS and adjuvant pembrolizumab + carboplatin + paclitaxel | ORR | Recruiting |
| NCT03038100 IMagyn050 | EOC with no prior treatment | III | Arm 1: carboplatin + paclitaxel + bevacizumab + atezolizumab<br>Arm 2: carboplatin + paclitaxel + bevacizumab + placebo | PFS; OS | Recruiting |
| NCT02718417 JAVELIN OVARIAN 100 | Advanced EOC with no prior treatment | III | Arm 1: carboplatin + paclitaxel<br>Arm 2: carboplatin + paclitaxel + avelumab maintenance<br>Arm 3: carboplatin + paclitaxel + avelumab + avelumab maintanence | PFS | Recruiting |
| Cervix | | | | | |

| Trial | Study population | Phase | Intervention | Primary outcome | Status |
|---|---|---|---|---|---|
| NCT02628067 KEYNOTE 158 | Advanced solid tumors | II | Pembrolizumab | ORR | Recruiting |
| NCT02488759 CheckMate 358 | Squamous cell carcinomas of the cervix, vulva, and vagina plus other virus-associated malignancies | I/II | Arm 1: neoadjuvant/metastatic nivolumab<br>Arm 2: nivolumab + ipililumab<br>Arm 3: nivolumab + BMS-986016<br>Arm 4: nivolumab + daratumumab | Safety and tolerability; ORR; rate of surgery delay | Recruiting |
| NCT01711515 | Advanced cervical cancer stage IB-IIB with positive PA nodes only and stage IIB/IIIB/IVA with positive nodes | I | Primary chemoradiation followed by ipilumumab | DLTs | Active, not recruiting |
| NCT02635360 | Locally advanced cervical cancer | | Arm 1: chemoradiation followed by pembrolizumab<br>Arm 2: chemoradiation with concurrent pembrolizumab | Immune markers; DTLs | Recruiting |
| NCT02866006 | Metastatic, progressive, or recurrent HPV 16/18 cervical cancer after failed standard therapy | I | BVAC-C vaccine | DTLs, AEs | Recruiting |
| NCT02128126 | Advanced, metastatic, or recurrent cervical cancer and HPV16positive | I/II | ISA101/ISA101b vaccine | HPV-specific immune response | Recruiting |
| Uterus | | | | | |
| NCT02549209 | Stage III/IV or recurrent endometrial cancer | II | Carboplatin + paclitaxel + pembrolizumab | ORR | Not yet recruiting |
| NCT02899793 | Recurrent endometrial cancer | II | Pembrolizumab | ORR; AEs | Recruiting |
| NCT02982486 | Non-resectable/metastatic sarcoma or high-grade endometrial cancer with MSI | II | Nivolumab + ipilimumab | ORR | Not yet recruiting |

*EOC* epithelial ovarian cancer, *OS* overall survival, *PFS* progression-free survival, *AEs* adverse events, *ORR* overall response rate, *irPFS* immune-related progression-free survival, *TRS* tumor reductive surgery, *PA* para-aortic, *DLTs* dose-limiting toxicities, *MSI* microsatellite instability

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