Chapter

Immunotherapy in Gynecological Malignancies

Neha Sharma and Deepti Sharma

Abstract

Cancer immunotherapy is one of the most upcoming treatment strategies emerging as a fascinating option in the management of advanced gynecological malignancies. The development of immune-based antitumor approaches has led to safer treatment options that give fruitful results in these malignancies. In this chapter, we are focusing on immune-based treatment in the management of gynecological cancers like cervical cancer, endometrial cancer, ovarian cancer, and vaginal and vulvar cancer. We are also discussing the clinical studies that have been conducted or are currently underway which are exploring these immune strategies that are developing as a logical overture for the treatment of advanced cancers including gynecological cancers.

Keywords: gynecological malignancy, immunotherapy, immune checkpoint inhibitors, cervical cancer, ovarian cancer, endometrial cancer

1. Introduction

Cancer immunotherapy is emerging as an attractive strategy among different therapeutic options over the past years, and also the treatment of many advanced malignancies has been revolutionized with the development of immune-based antitumor therapies. The advent of targeted immune therapies leading to successful outcomes in other malignancies has led to an increase in the number of clinical trials using these interventional strategies in patients with gynecological cancer. Generally, the role of immunotherapy is either to reactivate the immune response or to diminish the tumor-directed immune inhibition.

There are three stages of the dynamic process of immunoediting, also known as the three Es: an early elimination phase with the activation of an innate and adaptive immune response, an equilibrium phase where the isolated tumor cells are able to endure immune incursion, and an immune escape phase that the cancer cell variants can alter their genomic or antigenic phenotype or they are under the control of immunoregulatory phenomena to survive in the immunosuppressive medium. 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.

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. The implementation of antiangiogenic therapy has greatly improved the
treatment for relapsed/advanced disease over the last 5 years. Several clinical trials including CheckMate 358 and KEYNOTE-028 and KEYNOTE-158 are evaluating the role of immune checkpoint inhibitors in the treatment of cervical cancer.

In endometrial cancer, patients with advanced or disseminated recurrent disease have a poor prognosis, 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. So there is a need for development of more effective treatment for patients having advanced disease.

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

For several reasons ovarian cancer is an ideal tumor type for which to consider an immunomodulatory management approach. Firstly, there is no negative impact of cancer itself on immunoregulatory cells that may be present within the bone marrow or other body locations. Secondly, while standard cytotoxic therapy of ovarian cancer can result in a depression in the number of immunoregulatory cell, these effects are generally modest in extent and short in duration. Lastly, it is common for patients with ovarian cancer to maintain a quite reasonable performance status and satisfactory nutrition.

A majority of ovarian cancer patients respond to cytotoxic chemotherapy and invariably are free from disease for periods varying from months to several years. This time interval can be exploited for required “activation” of immune defense mechanisms, either by using a tested vaccination strategy or any other form of immune modulation.

Multiple studies involving immune checkpoint inhibitors, conducted in advanced endometrial cancer, ovarian cancer, and cervical cancer, have shown promising preliminary results. But 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.

The immune system plays an important role in cancer pathogenesis. Numerous clinical trials and multiple researches dedicated to study therapies that involve the immune system to favorably impact the disease course in various malignancies have not only shown improved patient survival but also diversified the whole cancer management scenario by approval of the use of various immunotherapeutic agents in advanced malignancies [1].

Since cancer immunotherapy has emerged as an effective and appealing therapeutic option among other different therapeutic strategies and has been proven competent against multiple malignancies, it has led to an increase in research on immunomodulatory approaches in gynecological malignancies [2].

The ongoing research on the understanding of tumor biology and immunology has led to improved comprehension of mechanisms of immune recognition, regulation, and tumor escape that has provided new approaches for cancer immunotherapy [3].

2. Role of immune system in cancer

The principal role of the immune system is against foreign pathogens and infections. It is further classified as cellular and humoral immune systems, mediated by T and B lymphocytes and their products, respectively.
The initial innate immunity is nonspecific, and the adaptive immune response is the specialized defense. Both the strategies work in different manner. They employ the cellular immunity which has a rather fast response in eradicating intracellular microbes through the recognition of antigens, activation of antigen-presenting cells (APCs), and activation and proliferation of T cells. They also need humoral immunity mediated via antibodies produced by B cells for neutralizing toxins and act against infections. Where innate immunity works by releasing signals essential to stimulate responses from both T cells and B cells [4], the adaptive immune system is mainly consists of B cells, CD8+ cytotoxic T cells, as well as CD4+ helper T cell [5].

The immune system in tumor cells has a dynamic relationship, in which either it can identify or control tumor cells in a process called cancer immunosurveillance or cause tumor progression through chronic inflammation, immunoselection of poorly immunogenic variants, and suppressing antitumor immunity [6]. There are three stages of this dynamic process called immunoediting. The first is the elimination phase in which innate and adaptive immunity works together to identify and eliminate the cancer cells before they become clinically apparent [7]. If the cancer cells are not eliminated, they enter the second phase which is equilibrium. It can last from months to years. Here the cancer cells persist, but outgrowth is prevented by the immune system. Lastly the escape phase is in which either the cancer cell variants survive in the immunosuppressive microenvironment by altering genetic or antigenic phenotype or under the control of immunoregulatory phenomena. [8] 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.

Gynecological cancers are a group of malignancies that involve different organs that comprise the female reproductive system. The most common types of gynecologic malignancies are cervical cancer, ovarian cancer, and endometrial cancer. Other less common gynecological malignancies arise from the vagina, vulva, and fallopian tubes [9].

3. Cervical cancer

Cervical cancer represents 6.6% of all female cancers. It is the fourth most common cancer in women with an estimated 570,000 new cases in 2018. Approximately 90% of deaths from cervical cancer occur in underdeveloped and developing countries [10]. Cervical cancer has emerged as a preventable disease due to currently employed screening tests which have highlighted HPV infection as an etiological factor. Although significant progress has been made in screening and prevention of cervical cancer, the 5-year overall survival remains 66% [11]. For cases diagnosed at an early stage, the recurrence rates vary between 10 and 20%, but for advanced cases, the rate of recurrence reaches up to 70% [12]. There is a need to improve outcomes, and immunotherapy could offer this possibility. The recognition of human papilloma virus as an etiological agent has greatly improved the understanding of the disease and led to improved strategies in prevention of cervical cancer [13]. 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. Currently there are three licensed HPV prophylactic vaccines, namely, bivalent vaccine cervarix against HPV16/18, Gardasil against HPV-6/11/16/18, and Gardasil9, a nonavalent HPV-6/11/16/18/31/33/45/52/58 vaccine. All are based on on-infectious recombinant type-specific L1 capsid proteins assembled into viral-like particles (VLPs) as immunogens [14].
There is a huge unmet need for the treatment for women having advanced/recurring cancer after standard chemotherapy and immunotherapy aims to fill that void, through therapies that harness a patient's own immune system to attack the cancer.

4. Cancer vaccines in cervical cancer

Cancer vaccines are used to mediate immune response by activating T cells which can specifically recognize cancer cells by tagging them with tumor-specific antigens E6 and E7. These antigen-tagged tumor cells are recognized by antigen-presenting cells and killed by cytotoxic T cells [15].

Live vector vaccines are highly immunogenic vaccines which can stimulate mucosal as well as humoral and/or cellular systemic immunity. They present E6 and E7 to APC to cause immune response through major histocompatibility complex MHC I [16]. Although they are attenuated vaccines, still care has to be taken before administering it in immunocompromised individuals. ADXS11-001 is a type of live attenuated vaccine that uses *Listeria monocytogenes* (Lm), a gram-positive intracellular bacterium as bacterial vector. It secretes HPV-16 E7 antigen fused to a nonhemolytic fragment of Lm protein listeriolysin O [17].

The following studies have been conducted (Table 1):

| Study name | Patient cohort | Treatment schedule | Response | Toxicity |
|------------|----------------|--------------------|----------|----------|
| Maciag et al. [18] Phase I trial | n = 15 Recurrent or metastatic disease | DL1: ADXS11-001 1 × 10^9 two doses every 21 days DL2: ADXS11-001 3.3 × 10^9 two doses every 21 days DL3: ADXS11-001 1 × 10^10 two doses every 21 days | Stable disease in 7 patients | Pyrexia (100%), vomiting 60%, pain (57%), chills, anemia (53%) Grade 3: 40% (6 pts) |
| Ghamande et al. [19] Phase I | n = 9 Recurrent or metastatic disease | DL1: ADXS11-001 5 × 10^9 thrice weekly during 12 weeks DL2: ADXS11-001 1 × 10^10 thrice weekly during 12 weeks | — | TRAE: 75% AE: 99% Grade 1 and 2 Grade 3: chills, vomit, hypotension, tachycardia, fever, and nausea |
| Basu et al. [20] Phase II | n = 109 Advanced cervical cancer | Arm 1 ADXS11-001 monotherapy Arm 2 ADXS11-001 with cisplatin combination | Median progression-free survival (6.10 vs. 6.08 months) and the overall response rate (17.1% vs. 14.7%) were similar for both groups | More adverse effects in arm 2 |
| Huh et al. [21] (GOG 0265) Phase II | n = 26 Recurrent or metastatic disease | ADXS11-001 1 × 10^9 every 28 days for 3 doses | Mean 12 months survival: 38.5% Median OS: 6.2 months | AE: 91% Grade 1 and 2 TRAE: 38%: nausea, vomiting, chills, fatigue, and fever |

Table 1. Role of vaccination in HPV-associated cervical cancer.
4.1 Peptide-based vaccines in cervical cancer

Refer Table 2.

| Study name        | Patient cohort | Treatment schedule | Response | Toxicity                                                                 |
|-------------------|----------------|--------------------|----------|--------------------------------------------------------------------------|
| Welters et al. [22]| n = 6          | HPV16 E6 E7 SLP vaccine | Vaccine-enhanced number and activity of HPV16-specific CD4+ and CD8+ cells | Grade 1 and Grade 2: local pain, fever, flu-like symptoms, swelling, itching, burning eyes |
| Poelgeest et al. [23]| n = 31         | HPV16 E6-E7 SLP vaccine 300 g for four doses every 21 day | Median OS: 12.6 months no tumor regression or delay of progression | Grade 1 and Grade 2: fever, fatigue, headache, flu-like symptoms, chills, nausea, swelling extremities, rash, vomiting, tingling extremities, and injection site pain |

Table 2. Peptide-based vaccine in cervical cancer.

4.2 Dendritic vaccines in cervical cancer

Refer Table 3.

| Study name        | Patient cohort | Treatment schedule | Response | Toxicity                                                                 |
|-------------------|----------------|--------------------|----------|--------------------------------------------------------------------------|
| Ramanathan et al. [24]| n = 14         | Arm 1: placebo three doses every 14 days Arm 2: unprimed DC three doses 1 × 106 cells every 14 days Arm 3: primed DC three doses 1 × 106 cells every 14 days | SD in Arm 3 | Grade 1 and Grade 2: itching at injection site, fever, chills, abdominal discomfort, vomit, ALP increased |
| Ferrara et al. [25]| n = 15         | Analogous dendritic cells pulsed with HPV E7 protein | Serological response in 3 pts Cellular response in 4 pts No objective clinical response | Mild swelling and erythema at the injection site |
| Santin et al. [26]| n = 10         | DL1: HPV16/18 E7 antigen-pulsed DC5 × 106 for five doses every 21 days DL2: HPV16/18 E7 antigen-pulsed DC10 × 106 for five doses every 21 days DL3: HPV16/18 E7 antigen-pulsed DC15 × 106 for five doses every 21 days | CD4+ T-cell response in all patients | Mild swelling and erythema at the injection site |

Table 3. Dendritic vaccine in cervical cancer.
5. Immune checkpoint inhibitors in cervical cancer

5.1 PD1/PDL1 inhibitors

Programmed cell death protein-1/programmed death ligand-1 immunoregulatory axis is a promising target for cervical cancer treatment [27]. Pembrolizumab is a humanized monoclonal immunoglobulin G4 (IgG4) kappa isotype antibody targeting PD-1 (Table 4).

Other ongoing trials of pembrolizumab include PAPAYA Trial [30] which is a phase I study involving Stage Ib to Stage IV cervical cancer. The treatment schedule includes intravenous pembrolizumab followed by cisplatin-based chemoradiotherapy and brachytherapy and additional pembrolizumab after radiation. Another phase II trial with pembrolizumab followed by chemoradiotherapy and brachytherapy is also open for recruitment [31].

Nivolumab is a human IgG4 monoclonal antibody that causes stimulation of PD1 pathway-mediated immune response inhibition by binding to the PD-1 receptor and blocking its interaction with PD-L1 and PD-L2. [32] Checkmate 358 trial is a phase I/II trial by Hollebecque et al. in 19 patients of cervical cancer which studied nivolumab 240 mg every 2 weeks and showed ORR was 20.8% and disease control rate was 70.8%. Responses were observed regardless of PD-L1 expression, HPV status, and number of prior therapies [33].

Other trials of nivolumab include NRG-GY002, a phase II trial in recurrent or metastatic breast cancer [34]. A trial of nivolumab with HPV 16 SLp vaccine in HPV 16 positive cervical cancer is also underway [35].

Other checkpoint inhibitors under investigation include atezolizumab which is a fully humanized monoclonal antibody IgG1 isotype PD-L1. It is being studied to assess the safety and efficacy in combination with cyclophosphamide/carboplatin in gynecological cancer including cervical cancer in phase Ib PRO-LOG study [36]. Another phase II study is ongoing to study the synergistic action of antiangiogenic therapy with immunotherapy by combining bevacizumab with atezolizumab in women with recurrent or metastatic cervical cancer [37, 38].

Durvalumab is a human IgG1 monoclonal antibody that blocks the action of PD-L1 with PD1 and CD 80. It is being studied along with tremelimumab, which is an antibody against CTLA4 in patients who have failed to respond or relapsed to standard treatment [39].

5.2 CTLA-4 inhibitors

Ipilimumab is a fully human monoclonal IgG1κ antibody which acts against the cytotoxic T lymphocyte antigen-4 (CTLA-4). CTLA4 is an immune-inhibitory

| Study name     | Patient cohort | Treatment schedule | Response          | Toxicity                        |
|----------------|----------------|--------------------|-------------------|--------------------------------|
| Keynote 028    | n = 24 Patients having metastatic disease in PD L1 > 1% | Pembrolizumab 10 mg/kg every 2 weeks up to 2 years | ORR = 12.5% 6 months PFS 13% OS 66.7% (preliminary results) | 75% pts with treatment-related adverse effects 20.8% with Grade 3 toxicity |
| Frenel et al. [28] Phase Ib |                |                    |                   |                                |
| Schellens et al. [29] Phase II | n = 47 Metastatic disease | Pembrolizumab 200 mg thrice weekly to 2 years | ORR 17% (independent of tumor PD L1 status) | Not reported                   |

Table 4. PD1/PDL1 inhibitors in cervical cancer.
molecule which is expressed in activated T cells and in suppressor T regulatory cells \[40\] (Table 5).

## 5.3 Adoptive cell transfer therapy

Adoptive cell transfer therapy using autologous tumor-infiltrating lymphocytes is emerging as a promising treatment modality in immunotherapy for various cancers. There are two types of adoptive cell therapy which includes chimeric antigen receptor T-cell (CAR T-cell) therapy and tumor-infiltrating lymphocyte (TIL) therapy.

Chimeric antigen receptor (CAR) T-cell therapy involves genetically engineered patient’s autologous T cells that causes them to express a CAR specific for a tumor antigen. These cells are extracted, further divided, and reinfused back into the patient \[43\].

A trial was conducted by Lu et al. which evaluated adoptive CD4+ T-cell therapy in solid metastatic cancer. It had two patients of metastatic cervical cancer, out of which one patient had objective complete response \[44\].

There is a trial ongoing to test the safety, feasibility, and efficacy of CAR T-cell immunotherapy in patients who have GD@, PSMA, Muc1, mesothelin, or positive cervical cancer markers by Chang et al. \[45\].

TIL therapy predates the CAR T-cell therapy, and the basic principle involves the ex vivo culture of tumor specimens which have been resected and expansion of tumor-infiltrating lymphocytes (TILs) with interleukin-2. Selected T cells of a preferred antigen specificity and phenotype can be identified in vitro and divided. The number of antigen-specific T cells in peripheral blood after this method usually exceeds by far that possible by current vaccine treatment strategies alone. In addition, adoptive T cells appear more effective in inducing tumor regression than lymphocytes generated by vaccines, suggesting greater ability to overcome tumor-mediated immune evasion mechanisms \[46\].
Stevanovic et al. [47] conducted a trial on 17 patients of metastatic cervical cancer who received high-dose lymphocyte-depleting chemotherapy followed by aldesleukin. Patients were treated with a single infusion of human papillomavirus (HPV) E6 and E7 reactivity (HPV-TILs). Three of nine patients experienced objective tumor responses (two complete responses and one partial response).

### 6. Endometrial cancer

Endometrial cancer is the 4th most commonly occurring cancer in women and the 15th most commonly occurring cancer overall. There were over 380,000 new cases in 2018 [48]. In women with advanced and recurrent cancer, the prognosis is considered very poor. Unfortunately, there are limited treatment options for advanced or recurrent endometrioid endometrial cancer. However, with the advent of immunotherapy, immune checkpoint inhibitors have shown promising results in these cases.

| Study name | Patient cohort | Treatment schedule | Response | Toxicity |
|------------|----------------|--------------------|----------|----------|
| Ott et al. [53] | n = 24 Locally advanced or metastatic PD-L1-positive endometrial cancer | Pembrolizumab 10 mg/kg every 2 weeks for up to 24 months or until progression or unacceptable toxicity | Three (13%) patients achieved confirmed partial response. Three additional patients achieved stable disease, with a median duration of 24.6 weeks | Grade 3 treatment-related AEs were reported in four patients |
| Makker et al. [54] | n = 53 Metastatic endometrial cancer unselected for microsatellite instability or PD-L1 | 20 mg oral lenvatinib daily plus 200 mg intravenous pembrolizumab every 3 weeks, until progression or unacceptable toxicity | Patients had an objective response at week 24 | Serious treatment-related adverse events occurred in 16 (30%) patients, and one treatment-related death was reported (intracranial hemorrhage) |
| Santin et al. [55] | n = 2 Pretreated polymerase ε (POLE) ultramutated and MSH6 hypermutated recurrent endometrial tumors refractory to surgery, radiation, and chemotherapy | Anti-PD1 immune checkpoint inhibitor nivolumab 3 mg/kg biweekly | Both patients demonstrated a remarkable clinical response to the anti-PD1 immune checkpoint inhibitor nivolumab | No Grade 3 or higher side effects reported |
| Fleming et al. [56] | n = 15 Previously treated recurrent endometrial cancer | Atezolizumab 1200 mg or 15 mg/kg IV q3w was administered until toxicity or loss of clinical benefit | ORR was 13% (2/15) Of the remaining pts, two had SD, nine had PD, and two were non-evaluable | Seven (47%) pts had any related AE, mainly G1-2 (5 pts). No G4-5-related AEs occurred |

Table 6. Immunotherapy in endometrial cancer.
Microsatellite instability-high (MSI-H) status, tumor mutation burden, and high PD-L1 expression have been associated with higher response rates to this therapy [49]. Approximately 25% of endometrial cancer show microsatellite instability which is caused by defects in mismatch repair genes. These defective MMR genes lead to high somatic mutation rates, thereby increasing the number of neoantigens in MMR-deficient tumors [50].

Endometrial cancer has been subdivided into four prognostically distinct molecular subgroups based on the findings of the cancer genome atlas, namely, polymerase epsilon (POLE) ultramutated, MSI hypermutated, copy-number (CN) low, and CN high [51].

The ultramutated POLE subgroup and MSI hypermutated subgroup have immune-rich microenvironment and high mutation load. Evidence has supported over-expression of the PD-1/PD-L1 pathway in these molecular subtypes, and therefore, PD1/PD L1-targeted immunotherapy has a role in these tumors [52] (Table 6).

An ongoing phase II, two group trials are studying the role of avelumab in POLE-mutated endometrial cancer and MSS-mutated endometrial cancer. Avelumab is administered at 10 mg/kg as 1-hour IV infusion every 2 weeks until disease progression or unacceptable toxicity. Sixteen patients are enrolled in each cohort in the first stage. The preliminary results are yet to be published [57].

6.1 Anticancer vaccines in endometrial cancer

The following studies have been conducted (Table 7).

7. Ovarian cancer

Ovarian cancer accounts for 2.5% of all malignancies among females but 5% of female cancer deaths because of low survival rates, largely driven by late-stage diagnoses [60]. There were nearly 300,000 new cases in 2018. Ovarian cancer is considered to be an ideal type of tumor which can be dealt with immunomodulatory

| Study name         | Patient cohort                                                                 | Treatment schedule                                                                 | Response                                         | Toxicity                              |
|--------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------|---------------------------------------|
| Ohno et al. [58],  | $n = 12$ WT1/human leukocyte antigen (HLA)-A*2402-positive gynecological cancer | Intradermal injections of a HLA-A*2402-restricted, modified 9-mer WT1 peptide every week for 12 weeks | Stable disease in three patients and progressive disease in nine patients. The disease control rate was 25.0% | Local erythema occurred at the WT1 vaccine injection site |
| [phase II]         |                                                                                 |                                                                                   |                                                 |                                       |
| Coosemans et al. [59] | $n = 6$ Pretreated patients with uterine cancer | Four times weekly vaccines of autologous dendritic cells (DCs) electroporated with WT1 mRNA | Three out of four human leukocyte antigen-A2 (HLA-A2)-positive patients showed an oncological response. Two HLA-A2-negative patients did not show an oncological or an immunological response | One patient had a local allergic reaction |

Table 7.
Anticancer vaccines in endometrial cancer.
Gynaecological Malignancies - Updates and Advances

approach as the disease does not negatively affect the immunoregulatory cells in the bone marrow or other locations of the body, and the patients suffering from ovarian cancer maintain a relatively good performance status even in later stages, so immunotherapy can be used as a potential treatment option in these patients. Cytotoxic chemotherapy given in ovarian cancer can negatively impact the immunoregulatory cells, but the effect is short lasting. Further the patients who are in advanced stages, if they respond to standard treatment of ovarian cancer, have a relatively long disease-free period which is substantial for the activation of immune defense mechanism either by cancer vaccines or by immunomodulator drugs [61].

7.1 Immune checkpoint inhibitors in ovarian cancer

The first published data supporting checkpoint inhibitors as a potentially valuable therapeutic option in ovarian cancer were observed in the trials of the anti-PD-1 antibody nivolumab and the anti-PD-L1 antibody BMS-93655 [62]. Other studies are as follows (Table 8).

| Study name | Patient cohort | Treatment schedule | Response | Toxicity |
|------------|----------------|--------------------|----------|----------|
| Hamanishi et al. [63] | Platinum-resistant ovarian cancer | IV nivolumab every 2 weeks at a dose of 1 or 3 mg/kg | Overall response rate was 15%, and the disease control rate was 45% | Grade 3 or 4 TRAEs in 40% patients |
| Disis et al. [64] | Recurrent/refractory ovarian cancer | Avelumab 10 mg/kg IV every 2 weeks | ORR was 9.7% based on 12 partial responses; 6 were ongoing. Stable disease was observed in 55 pts (44.4%); disease control rate was 54.0% | Grade 3 or 4 TRAEs reported in 6.5% |
| Varga et al. [65] | Advanced ovarian cancer | Pembrolizumab 10 mg/kg was given every 2 weeks for up to 2 years or until confirmed progression or unacceptable toxicity | The best overall (confirmed) response was 11.5%. 6/26 (23.1%) had evidence of tumor reduction; 3 had a tumor reduction of at least 30% | Drug-related AEs occurred in 69.2% of pts |
| Lee et al. [66] | BRCA positive with ovarian cancer | Durvalumab at 1500 mg every 4 weeks plus olaparib at 300 mg twice daily and durvalumab at 1500 mg every 4 weeks plus cediranib at 20 mg 5 days on/2 days off per week | ORR of 17% and disease control rate of 83% | Grade 3 or 4 TRAEs were reported in 75% patients |

Table 8. Immune checkpoint inhibitors in ovarian cancer.
Ongoing trials include JAVELIN Ovarian 200 is the first phase III trial, which is a three-arm trial, comparing avelumab administered alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory recurrent ovarian cancer [67].

NCT02839707 is undergoing trial which is comparing pegylated liposomal doxorubicin with atezolizumab and/or bevacizumab in refractory ovarian cancer [68].

A phase II study by Wenham et al. [69] is studying combination of weekly paclitaxel and an anti-PD-1 (pembrolizumab). The primary endpoint of this study is a 6-month progression-free survival rate.

ATALANTE trial is an ongoing phase III study to assess the efficacy of atezolizumab in combination with platinum-based chemotherapy plus bevacizumab administered concurrent to chemotherapy and in maintenance [70].

CheckMate 032 study trial to study the safety and efficacy of nivolumab as a single agent or in combination with ipilimumab is currently underway [71].

Similar trial in which nivolumab with or without ipilimumab in treating patients with persistent or recurrent epithelial ovarian is being studied by the National Cancer Institute [72].

A phase II trial to determine the median immune-related progression-free survival (irPFS) in combination of an anti-CTLA-4 antibody (tremelimumab) with an anti-PD-L1 antibody (durvalumab) versus their sequential use in platinum-resistant epithelial ovarian cancer is also currently ongoing [73].

Multiple other trial are using immune checkpoint inhibitors in initial therapy to improve progression-free survival like durvalumab or pembrolizumab with standard paclitaxel and carboplatin therapy, where pembrolizumab is used as adjuvant therapy after surgery [74]. The role of immune checkpoint inhibitors as maintenance therapy is also under investigation with JAVELIN Ovarian 100 phase II study of avelumab (anti-PD-L1) as maintenance after standard therapy or in combination with standard therapy and then continued as maintenance treatment [75].

7.2 Cancer vaccines in ovarian cancer

Various types of cancer vaccines are studied for the treatment of ovarian cancer. The cancer testis antigen, NY ESO1, is most frequently expressed in epithelial ovarian cancer, and vaccine against it has shown induced T-cell-specific immunogenicity [76]. Since NY-ESO-1 is regulated by DNA methylation, it was hypothesized that DNA methyltransferase (DNMT) inhibitors may augment NY-ESO-1 vaccine therapy. Decitabine is a hypomethylating agent that inhibits DNA methyltransferase. A phase I trial was conducted to study dose escalation of decitabine in addition to NY-ESO-1 vaccine and doxorubicin liposome in 12 patients with relapsed epithelial ovarian carcinoma. The results showed stable disease or partial response in six patients [77].

Sabbatini et al. conducted a phase I trial in 28 patients which showed that in order to enhance the immunogenic response to NY-ESO1, 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 (polynosinic-polycytidylic acid—stabilized by lysine and carboxymethylcellulose) can be considered [78].

Other antigen under investigation is Her/neu2, which is expressed in 90% of epithelial ovarian cancers. A phase I/II study conducted BY Chu et al. demonstrated a 90% 3-year overall survival response in patients with advanced ovarian cancer who were remission for vaccination with monocyte-derived dendritic cells (DC) loaded with Her2/neu, hTERT, and PADRE peptides, with or without low-dose intravenous cyclophosphamide [79].
In a phase I/II study by Baek et al., 10 ovarian cancer patients with minimal residual disease were treated with dendritic cell vaccination with IL2. Three out of 10 patients showed maintenance of complete response, and one patient showed stable disease [80].

A phase II study was conducted to study the efficacy of personalized peptide vaccine (PPV) for recurrent ovarian cancer patients by Kawano et al. [81]. The patients enrolled in this study showed an overall survival (OS) of 39.3 months in platinum-sensitive cases and 16.2 months in platinum-resistant cases. This was attributed to be secondary to the stabilization of disease and the prolongation of tumor progression rather than disease regression.

7.3 Adoptive cell transfer in ovarian cancer

Adoptive cell transfer therapy is not widely studied in ovarian cancers. In a Japanese study by Fujita et al., 13 patients with epithelial ovarian cancer were treated with tumor-infiltrating lymphocyte therapy. Eleven patients served as control group who received only chemotherapy following primary operation. The estimated 3-year overall survival rate of disease-free patients in the TIL group and in the control group was 100 and 67.5%, respectively [82].

Vulvar and vaginal cancer: Immunotherapy has shown promising results in advanced gynecological cancer. Checkmate 358 trial has shown that nivolumab has encouraging clinical activity in cases of HPV-positive vulvar and vaginal malignancies. A lot of research is warranted to establish immunotherapy as emerging treatment option in these cancers.

8. Conclusion

Immunotherapy is emerging as a viable treatment modality in multiple cancers, and its safety and efficacy are under investigation in advanced gynecological malignancies. Immune checkpoint inhibitors have shown promising preliminary results in advanced ovarian, cervical, and endometrial cancer.

Author details

Neha Sharma¹ and Deepti Sharma²*

1 Department of Radiation Oncology, Lady Hardinge Medical College and Associated SSK and KSC Hospital, New Delhi, India

2 Department of Radiation Oncology, Institute of Liver and Biliary Science, New Delhi, India

*Address all correspondence to: drdeeptisharma16@gmail.com

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Borghaei H, Smith MR, Campbell KS. Immunotherapy of cancer. European Journal of Pharmacology. 2009;625:41-54

[2] Jazaeri A, Coleman RL, Sood AK, Frumovitz MM, Soliman PT, Shafer A, et al. A practical guide for the safe implementation of early phase drug development and immunotherapy program in gynecologic oncology practice. Gynecologic Oncology. 2018;151:374-380

[3] Ito F, Chang AE. Cancer immunotherapy. Surgical Oncology Clinics of North America. 2013;22:765-783

[4] Woo S-R, Corrales L, Gajewski TF. Innate immune recognition of cancer. Annual Review of Immunology. 2015;33:445-474

[5] Binder RJ. Functions of heat shock proteins in pathways of the innate and adaptive immune system. The Journal of Immunology. 2014;193:5765-5771

[6] Zhang H, Chen J. Current status and future directions of cancer immunotherapy. Journal of Cancer. 2018;9:1773-1781

[7] Vesely MD, Schreiber RD. Cancer immunoediting: Antigens, mechanisms, and implications to cancer immunotherapy. Annals of the New York Academy of Sciences. 2013;1284:1-5

[8] Shore ND. Advances in the understanding of cancer immunotherapy. BJU International. 2015;116:321-329

[9] Maheshwari A, Kumar N, Mahantshetty U. Gynecological cancers: A summary of published Indian data. South Asian Journal of Cancer. 2016;5:112

[10] Vu M, Yu J, Awolude OA, Chuang L. Cervical cancer worldwide.

[11] Cervical Cancer—Statistics [Internet]. Cancer.Net. 2019. Available from: https://www.cancer.net/cancer-types/cervical-cancer/statistics

[12] Friedlander M, Grogan M, US Preventative Services Task Force. Guidelines for the treatment of recurrent and metastatic cervical cancer. The Oncologist. 2002;7(4):342-347

[13] Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human papillomavirus testing in the prevention of cervical cancer. Journal of the National Cancer Institute. 2011;103:368-383

[14] Pinto LA, Dillner J, Beddows S, Unger ER. Immunogenicity of HPV prophylactic vaccines: Serology assays and their use in HPV vaccine evaluation and development. Vaccine. 2018;36(32):4792-4799. DOI: 10.1016/j.vaccine.2017.11.089

[15] Miles B, Safran HP, Monk BJ. Therapeutic options for treatment of human papillomavirus-associated cancers—Novel immunologic vaccines: ADXS11-001. Gynecologic Oncology Research and Practice. 2017;4:10

[16] Silva AJD, Zangirolami TC, Novo-Mansur MTM, Giordano RDC, Martins EAL. Live bacterial vaccine vectors: An overview. Brazilian Journal of Microbiology. 2014;45:1117-1129

[17] Pan Z-K, Ikonomidis G, Lazenby A, Pardoll D, Paterson Y. A recombinant Listeria monocytogenes vaccine expressing a model tumour antigen protects mice against lethal tumour cell challenge and causes regression of established tumours. Nature Medicine. 1995;1:471-477
[18] Maciag PC, Radulovic S, Rothman J. The first clinical use of a live-attenuated *Listeria monocytogenes* vaccine: A phase I safety study of Lm-LLO-E7 in patients with advanced carcinoma of the cervix. Vaccine. 2009;27(30):3975-3983

[19] Ghamande SA, Platt D, Wheatley D, Rungruang BJ, Janik JE, Khleif S. Phase I study evaluating high-dose treatment with ADXS11-001, a *Listeria monocytogenes*-listeriolysin O (Lm-LLO) immunotherapy, in women with cervical cancer. Journal of Clinical Oncology. 2016;34(15 Suppl.):e14580

[20] Basu P, Mehta A, Jain M, Gupta S, Nagarkar RV, John S, et al. A randomized phase 2 study of ADXS11-001 *Listeria monocytogenes*-Listeriolysin O immunotherapy with or without cisplatin in treatment of advanced cervical cancer. International Journal of Gynecologic Cancer. 2018;28:764-772

[21] Huh WK, Brady WE, Moore KN, Lankes HA, Monk BJ, Aghajanian C, et al. A phase 2 study of live-attenuated *Listeria monocytogenes* cancer immunotherapy (ADXS11-001) in the treatment of persistent or recurrent cancer of the cervix (GOG-0265). Journal of Clinical Oncology. 2014;32(15 suppl.):TPS5617

[22] Welters MJ, Kenter GG, Piersma SJ, Vloon AP, Lowik MJ, DMB-VD M, et al. Induction of tumor-specific CD4 and CD8 T-cell immunity in cervical cancer patients by a human papillomavirus type 16 E6 and E7 long peptides vaccine. Clinical Cancer Research. 2008;14:178-187

[23] Poelgeest MIEV, Welters MJP, Esch EMGV, Stynenbosch LFM, Kerpershoek G, Van Meerten ELVP, et al. HPV16 synthetic long peptide (HPV16-SLP) vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carcinoma, a phase II trial. Journal of Translational Medicine. 2013;11:88

[24] Ramanathan P, Ganeshrajah S, Raghanvan RK, Singh SS, Thangarajan R. Development and clinical evaluation of dendritic cell vaccines for HPV related cervical cancer—A feasibility study. Asian Pacific Journal of Cancer Prevention. 2014;15:5909-5916

[25] Ferrara A, Nonn M, Sehr P, Schreckenberger C, Pawlita M, Dürst M, et al. Dendritic cell-based tumor vaccine for cervical cancer II: Results of a clinical pilot study in 15 individual patients. Journal of Cancer Research and Clinical Oncology. 2003;129:521-530

[26] Santin AD, Bellone S, Palmieri M, Zanolini A, Ravaggi A, Siegel ER, et al. Human papillomavirus type 16 and 18 E7-pulsed dendritic cell vaccination of stage IB or IIA cervical cancer patients: A phase I escalating-dose trial. Journal of Virology. 2007;82:1968-1979

[27] Reddy OL, Shintaku PI, Moatamed NA. Programmed death-ligand 1 (PD-L1) is expressed in a significant number of the uterine cervical carcinomas. Diagnostic Pathology. 2017;12:45

[28] Frenel J-S, Tourneau CL, O’neil BH, Ott PA, Piha-Paul SA, Gomez-Roca CA, et al. Pembrolizumab in patients with advanced cervical squamous cell cancer: Preliminary results from the phase Ib KEYNOTE-028 study. Journal of Clinical Oncology. 2016;34:5515

[29] Schellens JH, Marabelle A, Zeigenfuss S, Ding J, Pruit S, Chung H. Pembrolizumab for previously treated advanced squamous cell cancer: preliminary results from the phase 2 KEYNOTE-158 study. Journal of Clinical Oncology. 2017;35(15 Suppl):5514

[30] A Study of Pembrolizumab and Platinum with Radiotherapy in Cervix Cancer - Full Text View - ClinicalTrials.gov, clinicaltrials.gov/ct2/show/NCT03144466
Immunotherapy in Gynecological Malignancies

[31] Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02635360

Rosenberg SA. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Research. 2010;70:6171-6180

[32] Guo L, Zhang H, Chen B. Nivolumab as programmed death-1 (PD-1) inhibitor for targeted immunotherapy in tumor. Journal of Cancer. 2017;8:410-416

[33] Hollebecque A, Meyer T, Moore KN, Machiels J-PH, De Greve J, López-Picazo J. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. Journal of Clinical Oncology 2017;35(15 Suppl.):5504

[34] Nivolumab in Treating Patients With Persistent, Recurrent, or Metastatic Cervical Cancer—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02257528

[35] Nivolumab and HPV-16 Vaccination in Patients With HPV-16 Positive Incurable Solid Tumors—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02426892

[36] Carboplatin-cyclophosphamide Combined With Atezolizumab—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02914470

[37] Atezolizumab and Bevacizumab in Treating Patients With Recurrent, Persistent, or Metastatic Cervical Cancer—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02921269

[38] Shrimali RK, Yu Z, Theoret MR, Chinnasamy D, Restifo NP, Rosenberg SA. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Research. 2010;70:6171-6180

[39] A Phase 1 Study to Evaluate MEDI4736 in Combination With Tremelimumab—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT01975831

[40] Graziani G, Tentori L, Navarra P. Ipilimumab: A novel immunostimulatory monoclonal antibody for the treatment of cancer. Pharmacological Research. 2012;65:9-22

[41] Lheureux S, Butler M, Fleming G, Hirte H, Cristea M, Ghatage P, et al. 938 TiPA phase 1/2 study of ipilimumab in women with metastatic or recurrent hpv-related cervical carcinoma: A study of the princess margaret and Chicago N01 Consortia. Annals of Oncology. 2014;25:iv324

[42] Mayadev J, Brady WE, Lin YG, Silva DMD, Lankes HA, Fracasso PM, et al. A phase I study of sequential ipilimumab in the definitive treatment of node positive cervical cancer: GOG 9929. Journal of Clinical Oncology. 2017;35:5526

[43] Miliotou AN, Papadopoulou LC. CAR T-cell therapy: A new era in cancer immunotherapy. Current Pharmaceutical Biotechnology. 2018;19:5-18

[44] Lu Y-C, Parker LL, Lu T, Zheng Z, Toomey MA, White DE, et al. Treatment of patients with metastatic cancer using a major histocompatibility complex class II–restricted T-cell receptor targeting the cancer germline antigen MAGE-A3. Journal of Clinical Oncology. 2017;35:3322-3329

[45] Intervention of CAR-T Against Cervical Cancer—Full Text View
Adoptive T-cell therapy is a promising salvage approach for advanced or recurrent metastatic cervical cancer. Journal of Clinical Oncology. 2015;33:1521-1522

Stevanović S, Draper LM, Langhan MM, Campbell TE, Kwong ML, Wunderlich JR, et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus–targeted tumor-infiltrating T cells. Journal of Clinical Oncology. 2015;33(14):1543-1550

Endometrial cancer statistics [Internet]. World Cancer Research Fund. 2018. Available from: https://www.wcrf.org/dietandcancer/cancer-trends/endometrial-cancer-statistics

Zhao P, Li L, Jiang X, Li Q. Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. Journal of Hematology & Oncology. 2019;12

Alexandrov LB, Nik-Zainal S, Wedge DC, Campbell PJ, Stratton MR. Deciphering signatures of mutational processes operative in human cancer. Cell Reports. 2013;3:246-259

Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73. DOI: 10.1038/nature12113

Gargiulo P et al. Tumor genotype and immune microenvironment in POLE-ultramutated and MSI-hypermethylated endometrial cancers: New candidates for checkpoint blockade immunotherapy? Cancer Treatment Reviews. 2016;48:61-68. DOI: 10.1016/j.ctrv.2016.06.008

Ott PA, Bang Y-J, Berton-Rigaud D, Elez E, Pishvaian MJ, Rugo HS, et al. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1–positive endometrial cancer: Results from the KEYNOTE-028 study. Journal of Clinical Oncology. 2017;35:2535-2541

Makker V, Rasco D, Vogelzang NJ, Brose MS, Cohn AL, Mier J, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: An interim analysis of a multicentre, open-label, single-arm, phase 2 trial. The Lancet Oncology. 2019;20:711-718

Santin AD, Bellone S, Buza N, Choi J, Schwartz PE, Schlessinger J, et al. Regression of chemotherapy-resistant polymerase (POLE) ultra-mutated and MSH6 hyper-mutated endometrial tumors with nivolumab. Clinical Cancer Research. 2016;22:5682-5687. DOI: 10.1158/1078-0432.ccr-16-1031

Fleming GF, Emens LA, Eder JP, Hamilton EP, Liu JF, Liu B, et al. Clinical activity, safety and biomarker results from a phase Ia study of atezolizumab (atezo) in advanced/recurrent endometrial cancer (rEC). Journal of Clinical Oncology. 2017;35:5585. DOI: 10.1200/jco.2017.35.15_suppl.5585

Konstantinopoulos P, Liu J, Barry W, Krasner C, Buss M, Birrer M, et al. Phase II, two-stage study of avelumab in patients with microsatellite stable (MSS), microsatellite instable (MSI) and polymerase epsilon (POLE) mutated recurrent or persistent endometrial cancer. Gynecologic Oncology. 2018;149:24-25. DOI: 10.1016/j.jygyno.2018.04.060

Ohno S, Kyo S, Myojo S, Dohi S, Ishizaki J, Miyamoto K, et al. Wilms' tumor 1 (WT1) peptide immunotherapy for gynecological malignancy. Anticancer Research. 2009;29:4779-4784
[59] Coosemans A, Vanderstraeten A, Tuyaerts S, Verschueren T, Moerman P, Berneman ZN, et al. Wilms’ tumor gene 1 (WT1)-loaded dendritic cell immunotherapy in patients with uterine tumors: A phase I/II clinical trial. Anticancer Research. 2013;33:5495-5500

[60] Howlader N, Noone AM, Krapcho M, et al., editors. SEER Cancer Statistics Review, 1975-2014. Bethesda, MD: National Cancer Institute; 2017. Available from: seer.cancer.gov/csr/1975_2014/. [Accessed: 01 March 2018]

[61] Markman M. Immunotherapy in ovarian cancer—where are we going? American Journal of Hematology/Oncology. 2016. Available from: https://www.gotoper.com/publications/ajho/2016/2016feb/immunotherapy-in-ovarian-cancer-where-are-we-going

[62] Taneja SS. Re: safety and activity of anti-PD-L1 antibody in patients with advanced cancer. Journal of Urology. 2012;188:2148-2149

[63] Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, et al. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. Journal of Clinical Oncology. 2015;33:4015-4022

[64] Disis ML, Patel MR, Pant S, Hamilton EP, Lockhart AC, Kelly K, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the JAVELIN solid tumor phase Ib trial: Safety and clinical activity. Journal of Clinical Oncology. 2016;34:5533

[65] Varga A, Piha-Paul SA, Ott PA, Mehnert JM, Berton-Rigaud D, Johnson EA, et al. Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study. Journal of Clinical Oncology. 2015;33:5510

[66] Lee JM et al. Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women’s cancers: A dose-escalation, phase I study. Journal of Clinical Oncology. 2017;35(19):2193-2202

[67] Pujade-Lourraine E, Colombo N, Disis ML, Fujiiwara K, Ledermann JA, Mirza MR, et al. Avelumab (MSB0010718C; anti-PD-L1) ± pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone in patients with platinum-resistant/refractory ovarian cancer: The phase III JAVELIN Ovarian 200 trial. Journal of Clinical Oncology. 2016;34(15 suppl.):TPS5600

[68] Pegylated Liposomal Doxorubicin Hydrochloride With Atezolizumab and/or Bevacizumab in Treating Patients With Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02839707

[69] Wenham RM, Apte SM, Shahzad MM, Lee JK, Dorman D, Chon HS. Phase II trial of dose dense (weekly) paclitaxel with pembrolizumab (MK-3475) in platinum-resistant recurrent ovarian cancer. Journal of Clinical Oncology. 2016;34(15 suppl.):TPS5612

[70] ATALANTE: Atezolizumab vs Placebo Phase III Study in Late Relapse Ovarian Cancer Treated With Chemotherapy Bevacizumab—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02891824

[71] A Study of Nivolumab by Itself or Nivolumab Combined With Ipilimumab in Patients With Advanced or Metastatic Solid Tumors—Full Text View
[72] Nivolumab With or Without Ipilimumab in Treating Patients With Persistent or Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02498600

[73] Durvalumab and Tremelimumab in Treating Participants With Recurrent or Refractory Ovarian, Primary Peritoneal, or Fallopian Tube Cancer—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT03026062

[74] Pembrolizumab, Carboplatin, and Paclitaxel in Treating Patients With Stage III-IV Ovarian, Primary Peritoneal, or Fallopian Tube Cancer—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02520154

[75] Avelumab in Previously Untreated Patients With Epithelial Ovarian Cancer (JAVELIN OVARIAN 100)—Full Text View [Internet]. ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT02718417

[76] Diefenbach CS, Gnjatic S, Sabbatini P, Aghajanian C, Hensley ML, Spriggs DR, et al. Safety and immunogenicity study of NY-ESO-1b peptide and montanide ISA-51 vaccination of patients with epithelial ovarian cancer in high-risk first remission. Clinical Cancer Research. 2008;14:2740-2748

[77] Odunsi K, Matsuzaki J, James SR, Mhawech-Fauceglia P, Tsuji T, Miller A, et al. Epigenetic potentiation of NY-ESO-1 vaccine therapy in human ovarian cancer. Cancer Immunology Research. 2014. Available from:

https://www.ncbi.nlm.nih.gov/pubmed/24535937

[78] Sabbatini P, Tsuji T, Ferran L, Ritter E, Sedrak C, Tuballes K, et al. Phase I trial of overlapping long peptides from a tumor self-antigen and poly-ICLC shows rapid induction of integrated immune response in ovarian cancer patients. Clinical Cancer Research. 2012. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23032745

[79] Chu CS, Boyer J, Schullery DS, Gimotty PA, Gamerman V, Bender J, et al. Phase I/II randomized trial of dendritic cell vaccination with or without cyclophosphamide for consolidation therapy of advanced ovarian cancer in first or second remission. Cancer Immunology, Immunotherapy. 2012. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22021066

[80] Baek S, Kim Y-M, Kim S-B, Kim C-S, Kwon S-W, Kim YM, et al. Therapeutic DC vaccination with IL-2 as a consolidation therapy for ovarian cancer patients: A phase I/II trial [Internet]. Cellular & Molecular Immunology. 2015. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24976269

[81] Kawano K, Tsuda N, Matsueda S, Sasada T, Watanabe N, Ushijima K, et al. Feasibility study of personalized peptide vaccination for recurrent ovarian cancer patients. Immunopharmacology and Immunotoxicology. 2014. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24773550

[82] Fujita K, Ikarashi H, Takakuwa K, Kodama S, Tokunaga A, Takahashi T, et al. Prolonged disease-free period in patients with advanced epithelial ovarian cancer after adoptive transfer of tumor-infiltrating lymphocytes. Clinical Cancer Research. 1995. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9816009