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Immunotherapy for Gynecologic Cancer: Current Applications and Future Directions

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Abstract

The role of the immune system in the development of cancer has been a subject of ongoing clinical investigation in recent years. Emerging data demonstrate that tumorigenesis resulting in ovarian, uterine and cervical cancers is a consequence of impaired host immune responses to cancerous cells. Leveraging the immune system through use of immune checkpoint inhibitors, therapeutic vaccine therapy and adoptive cell transfer presents a profound opportunity to revolutionize cancer treatment. This review will encompass the role of the immune system in development of gynecologic cancers and highlight recent data regarding immunotherapy applications in ovarian, uterine and cervical cancers.

Keywords

Immunotherapy; Checkpoint inhibitor; Ovarian Cancer; Endometrial Cancer; Cervical Cancer; Adoptive Cell Transfer

Introduction and Background

Considerable progress has been made over the past two decades regarding understanding the role of the immune system in the development of cancer. Immune-based therapies have revolutionized the treatment of solid malignancies including melanoma and non-small cell lung cancer (NSCLC) with noteworthy efficacy and durable treatment responses. Despite such progress, disease burden from gynecologic cancers remain substantial with a growing need for novel therapeutic approaches including immunotherapy. Interventions targeting anti-tumor immunity through cancer vaccination, checkpoint blockade and adoptive cellular therapy represent a paradigm shift in cancer treatment. This article serves to review emerging data from trials evaluating the impact of immunotherapy in gynecologic malignancies and briefly discuss developing therapeutic interventions with the goal of improving patient outcomes.

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Ongoing advances in the field of tumor immunology demonstrate a complex interplay between immune cells and cancer cells, the tumor microenvironment and the role of the immune system in tumor progression. The concept of immunosurveillance proposed by Burnet and Thomas in 1957 suggested an inherent capacity of tumor cells to develop new antigenic targets that are identified and eradicated by host immune responses (1). Additional study suggests the immune system reflects a balance of selective pressure to protect the host against cancer development while simultaneously influencing tumor evolution and immunogenic phenotype. This process, known as immunoediting, involves tumor stimulation of innate and adaptive immune responses resulting either in successful elimination of tumor or propagation of tumor variants with the capacity to escape or ultimately evade immune attack (2, 3).

Progression from equilibrium between host and tumor-driven immune responses to cancer is a function of intrinsic change within the tumor cell and immunosuppressive transformation in the surrounding tumor microenvironment (TME). These events may include tumor loss of immunogenicity, expression of suppressive factors including interleukin-10 (IL-10) and transforming growth factor- β (TGF- β), or expression of T-cell inhibitory molecules (4). By contrast, effective antitumor immune responses are characterized by recognition of tumor-specific antigens, generation of high avidity effector T cells capable of infiltrating tumor, activation of cytotoxic functions and survival within a suppressive TME. Observations in patients with gynecological malignancies emphasize the favorable impact of tumor-driven immune responses, as the presence of tumor infiltrating lymphocytes (TILs) is associated with improved survival in patients with ovarian, uterine and cervical cancers (5–9).

Immunotherapeutic strategies seek to bolster tumor-directed immune responses through tumor antigen selection in vaccine-based approaches, reinvigorate antitumor responses using immune checkpoint inhibitors, and expand T-cell populations using adoptive cellular therapy (ACT). With promising results in a variety of other disease sites, the implementation and understanding of the role for immunotherapy in gynecologic malignancies is ongoing. We will discuss core concepts for each of these treatment modalities in the context of gynecologic cancers and highlight emerging trials leveraging the immune system to favorably affect disease-related survival.

Overview of Immunotherapy Approaches

Therapeutic Cancer Vaccines

Vaccine-based therapies seek to stimulate immune recognition of cancer cells and enhance activation of tumor-specific effector lymphocytes *in vivo* while simultaneously establishing immunological memory of tumor antigens. In contrast to traditional cytotoxic therapies, vaccine-induced immune responses inhibit disease growth or recurrence using a combination of adaptive and innate immune responses. Vaccines induce specific responses against tumor antigens (TA), classified as one or more of several categories: (i) differentiation antigens (e.g. Melan-A/MART-1, tyrosinase)(10, 11), (ii) mutational antigens (e.g. β -catenin, P53)(12, 13), (iii) amplification antigens (e.g. Her2/neu, P53)(14), (iv) splice variant antigens (e.g. ING1, NY-CO-37/PDZ-45)(13, 15), (v) glycolipid antigens, (vi) viral antigens (e.g.

HPV, EBV)(16, 17), or (vii) cancer-testis antigens (e.g. MAGE, NY-ESO-1, LAGE-1)(18–20).

Vaccines may be dendritic cell (DC)-based using patient-derived tumor, viral, peptide-based or nucleic acid derived. DC-based vaccines require effective tumor antigen exposure as well as successful migration of infused DCs to regional lymph nodes for CD8+ and CD4+ T cell activation to maximize immunogenic capacity. In addition to single-target and cell-based vaccination strategies, developments in next-generation whole exome sequencing and mutanome analysis confer unique opportunities for tumor neoantigen selection. Regardless of vaccination strategy, appropriate antigen selection is critical for effective tumor-specific responses. Favorable tumor antigens are characterized by sufficient immunogenicity and ideally expressed at high frequency within a tumor while sparing normal tissues. For this reason, cancer-testis antigens (CTA) most closely approximate an ideal tumor antigen. CTAs are commonly expressed by gametes and trophoblastic tissue, restricted in adult somatic cells and aberrantly expressed in several cancer types including gynecologic malignancies.

Immune Checkpoint Blockade

Immune checkpoints are co-signaling pathways that modify T-cell receptor (TCR) signaling when an effector T cell binds a specific ligand on APC or tumor, either enhancing or suppressing the immune response. By modulating the effector cell response, immune checkpoints function as a negative feedback mechanism to protect the host against autoimmunity and maintain self-tolerance. These pathways are often co-opted during tumorigenesis as a key mechanism of immune resistance whereby cancer cell expression of the ligands for the receptors dampen antitumor T cell activation. Two major suppressive immune checkpoint receptors have been described: programmed cell death protein (PD-1) via two known ligands PD-L1 and PD-L2, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) via B7–1 and B7–2 ligands (21). CTLA-4 primarily regulates early T-cell activation while PD-1 influences autoimmunity by suppressing activity of T cells in peripheral tissues.

Interference with inhibitory immune checkpoint signaling enhances antitumor responses by restoring T-cell function. Blockade of these pathways are achieved using targeted antibodies directed towards inhibitory T cell receptors or via competitive inhibition of target ligands for these receptors. CTLA4 was the first immune checkpoint receptor to be investigated however early trials demonstrated immune-related toxicities in up to 25–30% of patients (21). Subsequent identification and investigation of PD-1 blockade to reverse tumor-mediated immunosuppression has particularly represented a groundbreaking advance in the field of immuno-oncology. Prolonged treatment responses using pembrolizumab (anti PD-1 immunoglobulin) have been identified in treatment-refractory melanoma, non-small-cell lung cancers, urothelial carcinoma and several other cancers with significantly less toxicity than its predecessors (22–24). These findings led to the first site-agnostic drug approval by the U.S. Food and Drug Administration for treatment-refractory solid tumors with PD-L1 expression, microsatellite instability or DNA mismatch repair deficiencies. Several antibodies targeting PD-1 and CTLA-4 pathways are the subject of ongoing clinical

investigation in women with gynecologic malignancy and will be discussed in further detail (Table 1).

Adoptive Cell Transfer

Adoptive cellular transfer (ACT) is the infusion of lymphocytes either derived from autologous tumor tissue or engineered to target tumor-specific antigens after activation and expansion *ex vivo*. Tumor-reactive effector cells are isolated through leukapheresis, primed in culture using immunomodulatory agents to promote survival and differentiation, expanded and reinfused at a high concentration. Initial investigations into the use of ACT in solid tumors were conducted by Rosenberg and colleagues at the National Cancer Institute utilizing tumor-infiltrating lymphocytes (TILs) and high-dose interleukin-2 for patients with metastatic melanoma, demonstrating objective response in six of 13 patients (25). Further protocol refinement including preinfusion lymphodepletion with cyclophosphamide and fludarabine removes endogenous suppressive regulatory T cells (T_{regs}), improves persistence of infused lymphocytes and enhances anti-tumor responses (26, 27).

The widespread use of adoptive cell transfer is often limited by availability of tumor-specific T cells, driving adoption of genetic engineering techniques to modify peripheral blood lymphocytes into tumor-specific cells. T lymphocytes can be genetically modified to express high affinity tumor antigen-specific TCRs or chimeric antigen receptors (CAR) that incorporate a tumor-antigen binding immunoglobulin domain linked to one or more intracellular costimulatory molecules. The TCR strategy is based on the understanding that binding of major histocompatibility complex (MHC)-antigen complex by TCR is the main determinant of tumor recognition by T cells. Genes that encode α and β chains are cloned from tumor-reactive T cells restricted to a particular HLA allele and introduced into recipient T cells to endow them with the specificity of the donor TCR. Transduced T cells then acquire stable reactivity to the tumor-associated antigens. Several ongoing studies are evaluating the role of TCR-engineered T cells in gynecologic malignancies (Table 2). With response rates as high as 72% in metastatic melanoma using adoptive cell therapy and myeloablative preparation, the goal of sustainable responses in gynecologic cancer using ACT appears within reach (28).

Immunotherapy in Ovarian Cancer

Epithelial ovarian, fallopian tube and peritoneal cancer (EOC) is the deadliest gynecologic malignancy with a projected 22,500 new cases and 14,000 deaths in the United States in 2019 alone (29). Five-year survival remains less than 50% as most new diagnoses occur at advanced stage disease due to a lack of effective screening for ovarian cancer. Furthermore, over 80% of patients will recur despite aggressive primary treatment with cytoreductive surgery and platinum-based chemotherapy. While encouraging data has emerged regarding the use of poly-ADP ribose polymerase inhibitors (PARPi) in patients with BRCA-mutated ovarian cancers, prognosis remains poor for the majority of women diagnosed with EOC (30, 31). The compelling case for immunotherapy in ovarian cancer treatment evidenced by improved survival associated with greater tumoral lymphocyte infiltration underscores the role for therapies targeting immunological responses and antitumor immunity (5, 6).

Vaccine Therapy for Ovarian Cancer

Among the several cancer testis antigens under investigation for vaccine-based therapy in solid tumors, New York esophageal squamous cell carcinoma-1 (NY-ESO-1) has demonstrated durable cellular and humoral immune responses in a majority of patients with NY-ESO-1-positive tumors (32, 33). Expression of NY-ESO-1 in epithelial ovarian cancer (EOC) is associated with phenotypically aggressive disease and significantly reduced overall survival among the 40% of women who express this antigen, suggesting a potential therapeutic benefit of targeting this CTA (34, 35). Several studies evaluating the effect of NY-ESO-1 vaccination in ovarian cancer patients demonstrate vaccine-elicited CD4+ and CD8+ T cell responses, persistence of NY-ESO-1+ lymphocytes and survival benefit among NY-ESO-1 vaccinated patients compared to non-vaccinated patients (35–39). Investigation using demethylation agents in conjunction with NY-ESO-1 vaccination demonstrated meaningful clinical response (partial response or stable disease) in 6 of 10 evaluable patients as well as durable NY-ESO-1+ lymphocyte responses (38). Additional targets for peptide-based vaccines under investigation in EOC include CA125, P53, Her-2/neu and mesothelin (40–44).

Cell-based approaches including dendritic cell vaccines are also a target of ongoing investigation for treatment of ovarian cancer. Preliminary investigation using autologous dendritic cell-based vaccine with whole tumor lysate for 25 patients with recurrent ovarian cancer demonstrated ORR of 8% (n=2;(45). Despite a modest response rate, enhanced CD8+ T cell reactivity was identified against tumor antigens post-vaccination and over half of participants demonstrated stable disease for a median of 14 months (n=13, range 4–96 months). In the CAN-003 phase II study of mucin 1 targeted-dendritic cell treatment for maintenance therapy in recurrent EOC, improved overall survival was noted in patients in remission after second-line therapy with vaccination compared to controls (42 vs. 26 months, $p=.004$)(46). Subsequent trials using DC vaccination techniques in ovarian cancer have demonstrated sustained tumor-specific T cell populations with variable clinical effect, suggesting a benefit to future randomized study (47–49).

While many of these agents have demonstrated effective and prolonged TA-specific immune responses, clinical application has been limited to small pilot studies in ovarian cancer. Additional limitations include surgical resection of adequate tumor samples to synthesize cell-based vaccines, labor-intensive dendritic cell expansion, heterogeneity of antigen expression within a tumor, or recognition of limited epitopes for a given tumor antigen (50, 51). The use of immunostimulatory adjuvants, checkpoint blockade therapy or synthesis of neoantigen-specific engineered T cells may also be combined with these vaccine approaches to enhance therapeutic efficacy and is the subject of several active trials in ovarian cancer.

Immune Checkpoint Blockade in Ovarian Cancer

Given the favorable response rates seen with immune checkpoint blockade in historically treatment-refractory diseases, the expansion of this approach to management of ovarian cancer has been the subject of many reported and ongoing trials (Table 1). Early investigation of immune checkpoints in EOC demonstrated increased PD-L1 was associated with poor prognosis and suggests a central role of the PD-1 pathway in interruption of host-

tumor immune responses (52). Further evaluation confirmed an inverse correlation between PD-1 and PD-L1 mRNA expression and survival, supporting a role for checkpoint blockade in ovarian cancer patients (53). The earliest use of immune checkpoint blockade in ovarian cancer was a phase II study of nivolumab in patients with platinum-resistant epithelial ovarian cancer with a response rate of 15% among 21 patients (54). No significant correlation between clinical response to nivolumab and PD-L1 expression was noted in this study, suggesting limited predictive value in PD-L1 expression as an independent biomarker for treatment response.

Pembrolizumab, another anti-PD1 inhibitor, is the only agent approved at present for use in microsatellite instability-high (MSI-H) ovarian cancer and has been the subject of several recent trials. In the KEYNOTE-028 phase Ib basket study of pembrolizumab for PD-L1+ solid tumors, 26 patients with PD-L1 positive recurrent ovarian cancer demonstrated a disease control rate of 34.6% including one complete response (55). These results prompted a phase II expansion (KEYNOTE-100) of 376 patients categorized by platinum sensitivity as well as level of PD-L1 expression using a combined positive score (CPS), defined as the ratio of PD-L1 positive cells compared to total viable cells $\times 100$ (56). Findings show an overall response rate (ORR) of 8% for all patients, 10.2% for patients with CPS ≥ 1 and 17.1% with CPS ≥ 10 . Median duration of response was 8.2 months. No correlation between response to pembrolizumab and sensitivity to platinum-based therapy or number of prior therapies was demonstrated. Unlike prior analyses, this study suggests a subset of ovarian cancer patients may derive greater clinical benefit to PD-1 therapy based on level of PD-L1 expression.

PD-L1 inhibition has also been a target of interest in clinical trials including the recently reported JAVELIN studies. In a heavily pretreated advanced ovarian cancer population with a median of three prior lines of chemotherapy, Disis and colleagues demonstrated an ORR of 9.6% with disease control rate of 52.0% using single-agent avelumab, an anti-PDL1 antibody (57). Median duration of treatment response was of 10.4 months in this population. It is important to highlight that responses occurred in regardless of tumor PD-L1 status and no significant patterns could be identified between clinical response and PD-L1 expression. A second study evaluating avelumab in the primary treatment setting for advanced EOC in combination with platinum-based chemotherapy with or without maintenance therapy was closed for futility after interim analysis. Evaluation of additional anti-PD-L1 agents including durvalumab in primary and recurrent ovarian cancer are ongoing ([NCT02726997](#), [NCT03405454](#), [NCT03026062](#)).

Overall, data regarding use of immune checkpoint blockade in ovarian cancer demonstrate relatively low response rates compared to other disease sites (6–22%; Table 1). While it is clear some patients demonstrate significant clinical benefit with the use of single-agent checkpoint blockade, our ability to predict clinical responses to this treatment approach using PD-L1 expression alone is lacking. It is likely that a combination of PD-L1 expression, BRCA mutation status and presence of mismatch repair deficiency will better define candidates for immune checkpoint blockade (58, 59). In addition to single-agent therapy, several ongoing trials are evaluating combination therapy using anti-PD1 with angiogenesis inhibitors or PARPi as multistep interference with antitumor responses. This

approach is of particular interest in patients with BRCA mutations, as combination treatment with niraparib (a PARPi) and pembrolizumab has demonstrated ORR as high as 45% (60). Exploration of predictive biomarkers, mechanisms of resistance and use of combination therapies using immune checkpoint will provide even greater opportunity to improve patient outcomes in ovarian cancer using immunotherapy.

Adoptive Cellular Therapy

Early clinical trials using adoptive cell transfer in ovarian cancer evaluated the efficacy of tumor-infiltrating lymphocytes for advanced stage disease and demonstrated substantial duration of response compared to conventional chemotherapy (61, 62). Investigation of 13 women receiving TIL infusion after completion of primary surgery and cisplatin-based treatment demonstrated an impressive 3 year disease-free survival rate of 82.1% among women receiving TIL therapy versus 54.5% in control group (62). Intraperitoneal TIL infusion has also been a target of investigation but with less promising results. In a pilot study conducted by Freedman and colleagues for recurrent ovarian cancer, no significant clinical responses were identified in the treatment group, however 50% demonstrated clinical effect of TIL and low-dose IL-2 therapy with reduction in ascites or stabilization in CA-125 (63). Similar response patterns were seen with 4 cycles of intraperitoneal infusion of MUC1 stimulated peripheral blood leukocytes with only one of seven patients demonstrating prolonged disease remission (64). A common limitation among these early trials include the lack of pretreatment lymphodepletion therapy, which may have negatively impacted results.

Several studies evaluating ACT with TILs, CAR and TCR-engineered T cells in ovarian cancer are ongoing (Table 2). With the advent of newer technologies including transduction of chimeric antigen receptors and TCRs, the repertoire of potential targets for ACT in ovarian cancer has grown exponentially. Targets for CAR T cells include MUC16, mesothelin and folate receptor. Murine models of ovarian cancer treated with CAR T cells specific to an activating lymphocyte receptor (NKG2D) demonstrated long-term survival, development of durable tumor-specific memory responses and tumor rejection upon re-exposure (65). Despite such favorable results, early translational study of folate receptor α -targeted CAR T cells demonstrated no reduction in tumor burden due to lack of extended T cell persistence after treatment (66).

Several studies are ongoing or completed testing CD8TCR redirected T cells targeting NY-ESO-1 in ovarian cancer patients ([NCT01567891](#), [NCT002650986](#), [NCT03017131](#)). Although spectacular responses have been observed, most responses are short-lived with ultimate tumor relapse. This suboptimal outcome is likely a result of the relatively limited long-term survival and effector function due to suppression or exhaustion of infused engineered T cells. Therefore, additional strategies in on-going clinical trials in ovarian cancer include combination with DNA methyltransferase inhibitor to enhance antigen expression and viral mimicry ([NCT03017131](#)), incorporation of a decoy dominant negative receptor for TGF β R2 ([NCT02650986](#)), and the use of CD4TCR to generate CD4+ T cells for promoting CD8+ T-cell persistence.

Uterine Cancer

In contrast to the relatively rare diagnosis of ovarian cancer, uterine cancer represents the most common gynecologic malignancy in the United States with approximately 3.1% of women affected by this disease in their lifetime (29). Historically classified as type I or type II disease based on histology and grade, genomic data from The Cancer Genome Atlas has revealed 4 distinct molecular subtypes of endometrial cancer that may influence adjuvant therapy decisions (67, 68). These categories include ultra-mutated, hypermutated, copy number high and copy number low endometrial carcinomas. Similar to ovarian cancer, the presence of tumor infiltrating lymphocytes is associated with a favorable prognosis, reduced recurrence risk and is an independent risk factor for improved overall survival (7). Although the application of immunotherapy to uterine cancers is relatively recent, evidence supports the potential benefits of this approach in an increasingly prevalent disease.

Immune Checkpoint Blockade in Uterine Cancer

The use of immune checkpoint inhibitors in uterine cancer have been a growing area of interest as 20–30% of endometrial cancers are characterized by defects in the DNA mismatch repair pathway (MMR). Aberrant MMR pathway function as a result of genetic deficiencies or somatic mutation leads to accumulation of single-strand breaks and DNA replication errors resulting in accumulation of neoantigens (69). Frequent DNA transcription errors in trinucleotide repeat sequences of tumor cells, known as high microsatellite instability (MSI-H), further characterize this phenotype. MMR-deficient tumors including ultramutated and hypermutated endometrial cancers further exhibit higher TIL infiltration and PD-L1 expression compared to microsatellite-stable tumors, suggesting therapeutic benefit to immune checkpoint blockade in this subpopulation.

Preliminary study of seven patients with metastatic MMR-deficient tumors treated with pembrolizumab revealed a 71% immune-related objective response rate, prompting further study of immune checkpoint blockade in endometrial cancer (58). Among 9 women with MMR-deficient recurrent or metastatic endometrial cancer in a phase II trial of PD-1 blockade, overall response rate is 56% with a disease control rate of 88.9% (n=8), including one complete response (70). In contrast to MMR status, expression of PD-L1 appears less predictive of response to immune checkpoint blockade in endometrial cancer. The endometrial cancer cohort of KEYNOTE-028 evaluating pembrolizumab in solid tumors with PD-L1 positivity demonstrated 13% objective response rate with a median duration of 24.6 weeks, comparable with traditional chemotherapy regimens (71).

Expression of PD-1 and PD-L1 are more frequently identified in endometrial cancer compared to other gynecologic malignancies, however a combination of molecular phenotyping and MMR deficiency status may best predict response to immune checkpoint blockade in uterine cancer (72–74). Both single-agent checkpoint inhibition and combination treatment with cytotoxic and targeted therapies in endometrial cancer are subject of ongoing investigation in clinical trials. A promising interim analysis of combined lenvatinib (a multiple kinase inhibitor) and pembrolizumab therapy in recurrent endometrial cancer demonstrated an objective response rate of 39.6%, leading to FDA approval of this treatment regimen regardless of MMR status or PD-L1 expression (75). These novel

combinations suggest the potential for synergistic anti-tumor activity using multiple agents and improved disease response in a population with few treatment options.

Adoptive Cell Transfer

The role of ACT in endometrial cancer has largely remained uninvestigated. A pilot analysis by Santin and colleagues evaluated the role of adoptively transferred T cells primed with tumor lysate-pulsed dendritic cells in a patient with metastatic endometrial cancer (76). Tumor infiltration and accumulation of labeled lymphocytes was demonstrated with clinically stable disease; however duration of response was limited. There is currently one ACT-based clinical trial recruiting patients with metastatic endometrial cancer ([NCT01174121](#)), however no preliminary findings have been published to date.

Cervical Cancer

Cervical cancer is the third most common gynecologic malignancy in the United States with declining incidence largely attributed to modern screening practices and prophylactic human papillomavirus (HPV) vaccination. Unfortunately, despite these advances, cervical cancer remains a leading cause of cancer mortality worldwide due to lack of available resources. Persistent HPV infection is associated with 99.7% of invasive cervical cancers, accounting for the single greatest attributable factor of any major cancer (77). Prophylactic HPV vaccination presents a profound opportunity for disease prevention but harbors little benefit for treatment of established malignancies. The addition of chemotherapy and bevacizumab to radiation treatment has improved outcomes in cervical cancer, however patients with advanced stage disease have limited 4-year overall survival of 55% (29, 78, 79). The use of chemotherapy has largely been reserved for palliative purposes in advanced stage and lymph-node positive disease.

Vaccines in Cervical Cancer

In contrast to the widespread use of prophylactic HPV vaccines, therapeutic HPV vaccines seek to enhance antigen-specific immune responses, targeting constitutively expressed E6 and E7 antigens resulting from HPV infection. Several strategies have been evaluated including vaccinia and adenovirus vectors, peptide with adjuvants, DNA, and dendritic cell-based vaccines (80–83). Although many of these approaches were well tolerated and demonstrated HPV-specific immune responses, treatment effect has been modest for invasive disease. It is possible that such an approach may be more beneficial for management of preinvasive lesions. Evaluation of therapeutic vaccination of preinvasive cervical lesions using a DNA vaccine, pNGVL4a-CRT/E7(detox) demonstrated regression in 30% of patients with increased CD8+ T cell infiltration among women who received intralesional administration (82). Similarly encouraging results including viral clearance, disease regression and intralesional HPV-specific T cell responses have been demonstrated in high grade cervical dysplasia using other vaccine strategies (84, 85).

Immune Checkpoint Blockade in Cervical Cancer

A high frequency of PD-L1 expression has been reported in up to 80% of patients with squamous cell carcinoma of the cervix, making this disease a prime candidate for PD-1/PD-

L1 inhibition (86). Pathologic expression of PD-L1 due to HPV infection generates a relatively immune-privileged tumor environment whereby lymphocyte infiltration and function is reduced, driving progression of dysplasia to invasive disease (87). As a result, several investigations leverage the PD-1 pathway in cervical cancer but demonstrate a variable prognostic influence of PD-L1 expression. Data from a phase II expansion analyzing patients with PD-L1 positive advanced squamous cell carcinoma treated with pembrolizumab (KEYNOTE-158) showed 12.2% ORR with 3 complete responses and 9 partial responses among 98 patients (88). Median duration of response had not been reached after 11 months of follow up, with 91% of participants responding to treatment for at least 6 months. These findings led to expedited approval of pembrolizumab for the treatment of PD-L1 positive advanced cervical cancer given the paucity of available treatments for this disease. Additional PD-1-directed therapy with nivolumab in the phase I/II CheckMate 358 study had an ORR of 26.3% among 19 cervical cancer patients regardless of PD-L1 or HPV positivity (89).

Anti-CTLA-4 therapy has also been evaluated in advanced cervical cancer. Single-agent therapy using ipilimumab appears tolerable among patients with advanced disease however objective response rates are less than 5% (90). While the role of ipilimumab monotherapy appears limited, combination therapy using ipilimumab with nivolumab has demonstrated significant promise with dramatically increased response rates as high as 31.6% in advanced disease (91). Additional approaches include combinations of anti-CTLA4 or anti-PD1 agents with radiation therapy for cervical cancer, which may demonstrate a synergistic abscopal effect. A phase I investigation of ipilimumab following standard chemoradiation for locally advanced cervical cancer among 19 evaluable patients was 74%, representing an estimated 20% increase compared to historical data (92). These preliminary findings support the rationale for several active trials evaluating immune checkpoint inhibition with concurrent chemotherapy and radiation for locally advanced or persistent cervical cancer ([NCT03277482](#), [NCT02635360](#), [NCT03738228](#)).

Adoptive Cell Transfer in Cervical Cancer

ACT is the newest immunotherapy approach adapted to cervical cancer treatment. The first clinical trial using ACT were published by Stevanovic and colleagues using a single infusion of HPV E6 and E7 reactive tumor infiltrating lymphocytes after lymphodepletion. Five of 18 patients experienced objective response, two of which were complete responses ongoing at time of most recent publication lasting 53 and 67 months respectively (93, 94). Although pretreatment lymphocyte depletion increased the toxicity of this study protocol, T cell infusion was well tolerated without autoimmune or cytokine-related adverse effects. Similar studies using tumor-derived lymphocytes, tumor protein specific TCRs for MAGE-A3, or HPV-reactive peripheral blood lymphocytes are being evaluated in patients with cervical cancer (Table 2).

Conclusions and Future Directions

Cancer immunotherapy is evolving quickly. Understanding the biomarkers of response to this therapy and identifying mechanisms to overcome immune suppression and counter-

regulation will lead to development of effective personalized targeted approaches. Immunotherapy is expected to mediate tumor destruction and drive local inflammation in the tumor microenvironment, but also trigger coordinated induction of multiple counter-regulatory and suppressive pathways e.g. IDO, TGF β , PD-L1, and Tregs. Concomitant blockade of these suppressive pathways at the time of vaccination, immune checkpoint or T cell transfer allow inflammation-induced transformation of the tumor milieu from a tolerogenic to an immunogenic signature.

Application of vaccine therapy, checkpoint inhibition and adoptive cell therapy is encouraging but not without limitations. Single-agent checkpoint blockade in murine models of ovarian cancer is associated with upregulation of alternative checkpoint blockade pathways, however simultaneous blockade of PD-1 and LAG-3 has a synergistic effect on CD8 cell function (95). Administration of ACT is furthermore limited to specialized centers, as TIL, CAR or TCR transgenic T cell manufacturing is a complex and labor-intensive process requiring specialized laboratory facilities. In addition, focused clinical expertise is required to manage the auto-immune and cytokine-related toxicities associated with this treatment.

Based on the limited efficacy of immunotherapy in most gynecologic cancer patients, it is crucial to consider opportunities for combination therapies including dual checkpoint blockade (e.g. the combination of CTLA-4 and PD-1 blockade). CTLA-4 blockade removes a physiological brake on T cells during activation, whereas anti-PD-1 removes a brake on activation during T-cell effector function. This combination may overcome resistance to CTLA-4 blockade mediated by tumor PD-L1 expression or resistance to PD-1 blockade mediated by T-cell downregulation through the co-expression of CTLA-4. Investigation using combination of conventional and immune-based treatment modalities is ongoing as well as development of effective biomarker strategies to identify patients most likely to benefit from use of immunotherapy. As scientific research continues to elucidate the role of the immune system in tumorigenesis, understanding of immunosuppressive pathways including regulatory T cells, indolamine 2,3 dioxygenase (IDO) and alternative checkpoint pathways will continue to progress. These techniques in combination with traditional chemotherapy, radiation and targeted therapeutics offer renewed hope to women diagnosed with gynecologic cancers.

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Table 1:

Response Rates with Single-Agent Checkpoint Blockade in Gynecologic Malignancies

Target	Antibody	Sample Size	Objective response rate (ORR)	Disease control rate (including CR, PR, SD)
Recurrent Ovarian Cancer				
CTLA-4	Ipilimumab ⁽⁹⁶⁾	n=39	10.3%	--
PD-1	Nivolumab ⁽⁵⁴⁾	n=20	15%	45%
	Pembrolizumab	n=26 ⁽⁵⁵⁾	11.3%	38.4%
		n=376 ⁽⁵⁶⁾ (100 evaluable)	8% - CPS 1: 10.2% - CPS 10: 17.1%	37.2% - CPS 1: 38.1% - CPS 10: 41.5%
PD-L1	BMS 936559 ⁽⁹⁷⁾	n=17	6%	18%
	Atezolizumab ⁽⁹⁸⁾	n=9	22%	22%
	Avelumab ⁽⁵⁷⁾	n=125	9.6%	52%
Uterine Cancer				
PD-1	Pembrolizumab	n=9, (MMR-deficient) ⁽⁷⁰⁾	56%	88.9%
		n=23 ⁽⁷¹⁾	13%	26.1%
	Nivolumab	n=22 ⁽⁹⁹⁾	23%	--
PD-L1	Avelumab ⁽⁷³⁾	n=15 (MMR-deficient)	26.7%	53.3%
		n=16 (MMR-proficient)	6.25%	31.3%
Cervical Cancer				
CTLA-4	Ipilimumab ⁽⁹⁰⁾	n=34	2.9%	32.4%
PD-1	Nivolumab ⁽⁸⁹⁾	n=19	26.3%	68.4%
	Pembrolizumab ⁽⁸⁸⁾	n=98	12.2%	30.6%

CR: complete response, PR: partial response, SD: stable disease, CPS: combined positive score

Table 2:**Adoptive Cellular Therapy Clinical Trials in Gynecologic Malignancy**

	Trial Number	Category	Target	Pretreatment Conditioning	Immunomodulators
Ovarian Cancer					
	03412526	TIL	broad	Fludarabine, Total body radiation (2 Gy)	IL-2
	03158935	TIL	broad	Cyclophosphamide, Fludarabine	IL-2 Pembrolizumab
	00101257	PBL - CD4 NY-ESO-1 reactive	NY-ESO-1	Cyclophosphamide	–
	03318900	PBL - CD8 tetramer	PRAME	Cyclophosphamide	IL-2, Anti-CD137 (utomilumab)
	03585764	CAR	Folate receptor	Cyclophosphamide, Fludarabine	–
	03017131	TCR - CD8	NY-ESO-1	Cyclophosphamide	IL-2, Decitabine
	02096614	TCR - CD8	MAGE-A4	Cyclophosphamide, Fludarabine	–
	03691376	TCR - CD8 TCR - CD4	NY-ESO-1	Melphalan	IL-2, Decitabine, Hematopoietic stem cells (HSC)
Cervical Cancer					
	03108495	TIL	broad	Cyclophosphamide, Fludarabine	IL-2
	02111850	TCR - CD4	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2
	02379520	PBL – HPV-16/18 E6, E7 reactive	HPV-16, 18	Cyclophosphamide, Fludarabine	Nivolumab
Solid Tumors – including Ovary					
	01174121	TIL	broad	Cyclophosphamide, Fludarabine	IL-2, Pembrolizumab
	02876510	PBL - CD8 tetramer	8 targets 12 HLA	Cyclophosphamide	IL-2, Atezolizumab
	03054298	CAR	Mesothelin	Cyclophosphamide, Fludarabine	IL-2
	02713984	CAR	HER2	Cyclophosphamide, Fludarabine	IL-2
	02830724	CAR	CD70	Cyclophosphamide, Fludarabine	IL-2
	02650986	TCR - CD8	NY-ESO-1	Cyclophosphamide	IL-2
	03132922	TCR - CD8	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2
	03139370	TCR - CD4	MAGE-A3/A6	Cyclophosphamide, Fludarabine	IL-2
	03412877	TCR - neoantigens	Neoantigens	Cyclophosphamide, Fludarabine	IL-2
Solid Tumors – including Uterine					
	01174121	TIL	broad	Cyclophosphamide, Fludarabine	IL-2, Pembrolizumab
Solid Tumors – including Cervix					
	02111850	TCR - CD4	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2

TIL: tumor infiltrating lymphocytes, PBL: peripheral blood lymphocytes, CAR: chimeric antigen receptor, TCR: T cell receptor, IL-2: interleukin-2. Reference: <https://clinicaltrials.gov>, Accessed Oct 1 2019.