Advances in immunotherapy for cervical cancer: recent developments and future directions

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ABSTRACT

There is an unmet need for novel therapies to improve clinical outcomes for patients with locally advanced, recurrent, or metastatic cervical cancer. Most cases of cervical cancer are driven by infection with human papillomavirus (HPV), which uses multiple mechanisms to avoid immune surveillance. Several classes of agents have been developed that seek to activate the immune system in order to overcome this resistance and improve treatment outcomes. These include immune checkpoint inhibitors, therapeutic vaccines, engineered T cells, and antibody-drug conjugates. Here, we review the immune landscape of cervical cancer and the growing clinical data regarding the use of immunotherapy. Checkpoint inhibitors are the best studied treatments, with encouraging phase II studies available in the definitive setting and recently published phase III data defining a new standard of care for patients with recurrent or metastatic disease. Vaccines and engineered T cells are generally in earlier phases of development but use unique mechanisms of immune activation. It is possible that combination of immunotherapy, with either conventional systemic therapy or multiple immunomodulatory agents, may provide further benefit. We also discuss possible synergies between immunotherapy and radiation therapy, which is frequently used in the management of cervical cancer. Ultimately, immunotherapy represents an emerging treatment option for patients with cervical cancer. It is an appropriate component of first-line treatment in the recurrent or metastatic setting and may soon be incorporated into definitive management of locally advanced disease.

INTRODUCTION

Cervical cancer is the most common gynecologic malignancy, with over 500 000 estimated cases annually worldwide, resulting in 311 000 deaths.[1] The burden is highest in developing countries with limited access to appropriate screening and treatment resources. However, even with optimal treatment, there are significant opportunities to improve outcomes. Patients with locally advanced disease are typically treated with a combination of chemoradiation and brachytherapy, both of which have been demonstrated to improve survival compared with external beam radiation treatment alone.[2–4] However, long-term survival rates remain approximately 50% for those with FIGO stage IIIA–C1 disease[4–6] and are even worse for patients with para-aortic lymph node involvement (stage IIIC2).[6 7] For those with recurrent or metastatic disease, treatment with combination chemotherapy and bevacizumab results in a median overall survival of 17 months.[8]

The pathogenesis of cervical cancer is typically driven by infection with high-risk strains of human papillomavirus (HPV).[9] The role of the immune system in clearing HPV infection[10] and increased incidence of cervical cancer in patients with HIV[11] provide a strong rationale for the use of immunomodulatory therapies in cervical cancer. The recent success of immunotherapy across many cancer types, including in other HPV-driven malignancies,[12] also offers hope. Here, we review the mechanisms underlying the immunogenicity of cervical cancer, the available clinical data regarding immunotherapy use, and postulated synergies with existing treatment strategies.

IMMUNOMODULATION OF CERVICAL CANCER

Infection with oncogenic strains of HPV results in the production of E6 and E7 proteins, which inhibit critical tumor suppressor genes p53 and Rb, respectively.[13] In addition to oncogenesis, these proteins may also contribute to the ability of infected cells to escape detection and elimination by the immune system. For example, E7 is known to be 'tolerogenic'—it will be taken up by local dendritic cells and presented to the immune system in a manner similar to a non-inflammatory self-antigen, resulting in tolerance rather than an adaptive immune response.[14] Pre-cancerous and malignant cells may also affect cytokine balance in the tumor microenvironment, resulting in immune suppression.[15 16] Finally, the majority of cervical cancers express the programed cell death ligand 1 (PD-L1),[17] which helps to downregulate the host immune response as seen in Figure 1.

These mechanisms play an important role in the development of cervical cancer, but probably also influence the response to treatment. Analysis of the tumor microenvironment from patients who responded well (n=11) or poorly (n=10) to standard therapy demonstrated that adequate responders had higher pre-treatment levels of CD8 + tumor-infiltrating lymphocytes and higher expression of PD-L1.[18]

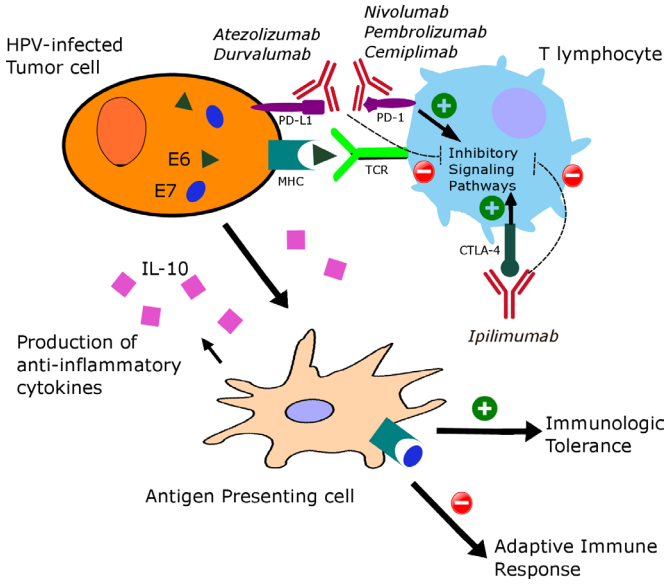

Figure 1 Mechanisms of immune escape in cervical cancer. Cervical cancer cells avoid immune surveillance via several mechanisms, including induction of immune tolerance, changes in the tumor microenvironment, and expression of PD-L1. the mechanisms of checkpoint inhibitors targeting the PD-1 and CTLA-4 axes are shown. CTLA-4, cytotoxic T-cell lymphocyte-associated antigen-4; HPV, human papillomavirus; IL-10, interleukin-10; MHC, major histocompatibility comples; PD-1, programed cell death protein; PD-L1, programed cell death ligand 1; TCR, T-cell receptor.

Treatment also results in activation of the immune system, with changes in T-cell subsets within the tumor detectable as soon as 1 week after the initiation of chemoradiation.[19] These data suggest that further augmentation of the immune response with checkpoint blockade immunotherapy targeting the PD-1 or cytotoxic T-lymphocyte antigen-4 (CTLA-4) pathways, or other immune activators, may be beneficial for improving outcomes.

CLINICAL TRIALS: DEFINITIVE TREATMENT

The Gynecologic Oncology Group conducted a phase I trial (GOG-9929) testing the sequential addition of the anti-CTLA-4 checkpoint inhibitor ipilimumab after standard definitive chemoradiation for patients with node-positive cervical cancer.[20] Ipilimumab was administered for four cycles every 21 days at two different dose levels: 3 mg/kg and 10 mg/kg. Twenty-one patients were enrolled and completed at least two cycles of ipilimumab. Only two dose-limiting toxicities were observed across the entire study (both at the 10 mg/kg dose), consisting of grade 3 dermatitis and grade 3 lipase elevation, both of which self-resolved. There were no noted grade 4 or 5 toxicities. Thus, the maximum tolerated dose was established at 10 mg/kg.

Initial oncologic outcomes from the study were also promising, with a 1-year progression-free survival of 81% and overall survival of 90%. These results compared favorably with historical studies of patients with lymph node involvement. Biomarkers of immune activation were also monitored during and after treatment.[21] Expression of T-cell activation markers ICOS ('inducible co-stimulator') and programed cell death protein (PD-1) increased following chemoradiation and was sustained or further increased during the subsequent ipilimumab therapy.

In addition to sequential treatment, there is interest in using immunotherapy concurrently with standard chemoradiation to take advantage of potential synergies between radiation and immune therapy as discussed below. However, this approach may carry a higher risk of toxicity, such as colitis. These risks were evaluated in a phase II randomized trial from the University of Virginia, where patients were randomized to receive the PD-1 inhibitor pembrolizumab either sequentially after chemoradiation or concurrently.[22] Pembrolizumab was given at 200 mg every 3 weeks for three cycles. Eligible patients had biopsy-proven FIGO 2009 stage IB–IVA disease with positive pelvic and/or para-aortic lymph nodes. Initial acute toxicity data have been published from 52 patients (24 treated sequentially, 28 concurrently).[22] The overall rate of grade 2+ toxicity was 88%, grade 3+ 44%, and grade 4 21%. There was no grade 5 toxicity. No significant differences were found in side effect rates or profiles between the concurrent and sequential immunotherapy arms. The most common toxicities in both arms were nausea/vomiting and cytopenias. The authors were particularly concerned about diarrhea as this can be a common side effect of both pelvic radiation treatment and pembrolizumab; however, only two cases of grade 3 diarrhea were noted, one in each arm of the trial. These data suggest that concurrent immunotherapy with chemoradiation is well tolerated without excessive synergistic toxicity. Oncologic outcomes from the trial are not yet available.

These results have led to the activation of larger trials, which are currently accruing. These include two large multicenter phase III randomized trials, the CALLA study[23] (NCT03830866) and GOG-3047 (NCT04221945). Complete study titles, primary endpoints, and planned enrollment for these and other studies investigating immunotherapy in the definitive management of cervical cancer are shown in Table 1. These two placebo-controlled studies test concurrent and adjuvant durvalumab and pembrolizumab, respectively, in addition to standard chemoradiation. Inclusion criteria for both trials are similar, with patients eligible if they have FIGO 2014 stage IB2–IIB disease with positive lymph nodes or FIGO 2014 stage III–IVA disease regardless of lymph node status.

Other ongoing studies include a randomized French phase II trial studying chemoradiation ± the PD-L1 inhibitor atezolizumab for locally advanced disease (NCT03612791). Lastly, NRG-GY017 (NCT03738228) uses concurrent atezolizumab and chemoradiation in both arms, with a randomization to with or without a 'priming' dose of immunotherapy 3 weeks before the start of chemoradioimmunotherapy. The results of these and the other pending studies in Table 1 will help to refine the role of immunotherapy in the definitive management of cervical cancer. If checkpoint inhibitors are successful at improving long-term clinical outcomes, they will probably represent a new standard of care for patients with locally advanced disease.

CLINICAL TRIALS: METASTATIC DISEASE

Immune checkpoint inhibitors targeting both the PD-L1 and CTLA-4 axes have also been studied in the setting of recurrent or metastatic cervical cancer. A phase I/II dose escalation study of ipilimumab

Table 1 Selected ongoing studies using checkpoint blockade immunotherapy in definitive treatment of locally advanced cervical cancer

NCT identifier	Title	Phase	Planned enrollment	Primary endpoint(s)
NCT03830866	Study of Durvalumab With Chemoradiotherapy for Women With Locally Advanced Cervical Cancer (CALLA)	III	770	Progression-free survival
NCT04221945	Study of Chemoradiotherapy With or Without Pembrolizumab (MK-3475) For The Treatment of Locally Advanced Cervical Cancer (MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047)	III	980	Progression-free and overall survival
NCT03612791	Trial Assessing the Inhibitor of Programmed Cell Death Ligand 1 (PD-L1) Immune Checkpoint Atezolizumab (ATEZOLACC)	II	189	Progression-free survival
NCT02635360	Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer	II	88	Change in immunologic markers
NCT03833479	TSR-042 as Maintenance Therapy for Patients With High-risk Locally Advanced Cervical Cancer After Chemoradiation (ATOMICC)	II	132	Progression-free survival
NCT03738228	Atezolizumab Before and/or With Chemoradiotherapy in Immune System Activation in Patients With Node-Positive Stage IB2, II, IIIB, or IVA Cervical Cancer	I	40	Clonal expansion of T-cell receptors
NCT03298893	Nivolumab in Association With Radiotherapy and Cisplatin in Locally Advanced Cervical Cancers Followed by Adjuvant Nivolumab for up to 6 Months (NiCOL)	I	21	Dose-limiting toxicity

monotherapy for patients with recurrent or metastatic disease whose disease had progressed on platinum chemotherapy found that treatment was well tolerated with mild toxicity.[24] Ipilimumab was delivered at 10 mg/kg every 3 weeks for four cycles, followed by four cycles of maintenance therapy every 12 weeks. Unfortunately, clinical responses were disappointing, with only 1 out 34 evaluable patients displaying a partial response while the remainder had stable or progressive disease. Median progression-free survival was 2.5 months. These data suggest that anti-CTLA-4 agents are probably ineffective as monotherapy for metastatic disease but could potentially be useful as part of a combined regimen.

More encouraging data in the metastatic setting is available for pembrolizumab, nivolumab, and cemiplimab, which all target the PD-1 receptor on immune cells. In the phase II KEYNOTE-158 study, pembrolizumab 200 mg every 3 weeks was given for up to 2 years to 98 heavily pre-treated patients, most of whom had PD-L1 positive tumors.[25] While the objective response rate was only 12%, responses were durable, with 75% lasting for longer than 9 months. All responders had PD-L1 positive tumors. In the phase I/II Checkmate-358 study, patients were treated with nivolumab 240 mg every 2 weeks and an even higher overall response rate of 26% was found among 19 patients with cervical cancer.[26] The median duration of response was not reached at 19 months of follow-up. Unfortunately, these findings were not replicated in the multicenter NRG-GY002 study of nivolumab monotherapy, where the response rate was only 4%.[27] The reason for the discrepancy is unclear, although the authors note that response rate as defined by Response Evaluation Criteria In Solid Tumors (RECIST) may not be ideal in the setting of immunotherapy.

Building on these studies, the first phase III data for checkpoint immunotherapy in patients with recurrent or metastatic disease is beginning to emerge. In the second-line setting, the recently presented EMPOWER-Cervical 1 trial enrolled patients whose disease had progressed on a platinum-based regimen and randomized them to cemiplimab versus investigator's choice chemotherapy.[28] The trial was discontinued early after an interim analysis demonstrated that cemiplimab met the primary endpoint of the study and improved overall survival (median 12 months vs 8.5 months with chemotherapy, p<0.001). The KEYNOTE-826 trial studied the addition of pembrolizumab 200 mg q3 weeks to chemotherapy (±bevacizumab) as first-line therapy for 617 patients with recurrent or metastatic disease. The addition of pembrolizumab significantly improved the 2-year overall survival in the intention-to-treat population from 40.4% to 50.4%.[29]. Improved outcomes were seen among nearly all subgroups except perhaps those with PD-L1 combined positive scores of <1, although this was a small subset of patients. Similar to the studies discussed above for localized disease, there was no evidence of excess synergistic toxicity between checkpoint blockade and other systemic agents. These compelling results suggest that upfront treatment with chemoimmunotherapy is an appropriate standard of care for patients with recurrent or metastatic disease.

Other studies have also attempted to combine immunotherapy with traditional systemic agents, particularly angiogenesis inhibitors such as bevacizumab, which was shown to be effective in the GOG-240 trial.[8] A small study of 10 patients testing the combination of atezolizumab 1200 mg every 3 weeks and bevacizumab failed to show any responses.[30] However, a larger recent Chinese phase

II study tested the combination of camrelizumab (an anti-PD-1 antibody) and apatinib (a tyrosine kinase inhibitor of the vascular endothelial growth factor-2 receptor.[31] Forty-five patients were enrolled, including 10 who had previously received bevacizumab. Camrelizumab was given at a dose of 200 mg every 2 weeks and apatinib 250 mg orally once per day. The overall response rate was 56%, including two complete responses and 23 partial responses. However, the toxicity of combined therapy was significant as more than two-thirds of patients experienced grade 3+ toxicity. The most common side effects included high blood pressure, anemia, and fatigue. Similar to KEYNOTE-158, median progression-free survival was significantly higher in patients with PD-L1 positive tumors.

Another possible avenue for combination therapy involves using two separate checkpoint inhibitors. Data presented in abstract form at European Society of Medical Oncology (ESMO) 2020 found that the combination of balstilimab (anti-PD-1) and zalifrelimab (anti-CTLA-4) for patients with recurrent or metastatic disease resulted in an overall response rate of 22%, better than the 14% with single agent balstilimab.[32] Responses were again more likely in PD-L1 positive patients but were also seen in approximately 10% of PD-L1 negative patients.

In summary, there is an increasing role for immunotherapy in the treatment of metastatic cervical cancer, particularly for patients with PD-L1 positive tumors. Response rates with immune monotherapy as second-line therapy are low but show promising durability. In the upfront setting, recently published randomized phase III data support the addition of pembrolizumab to chemotherapy as first-line treatment. Further research will continue to define appropriate patient selection and determine if combination immunotherapy may further improve outcomes. Ongoing trials using checkpoint blockade immunotherapy in the metastatic setting are summarized in Table 2.

BEYOND CHECKPOINT BLOCKADE: EMERGING IMMUNOTHERAPEUTIC APPROACHES

Checkpoint inhibitors are the best studied class of immunotherapy for cervical cancer, but numerous other strategies to activate the immune system have been proposed. Some of the most promising solutions include immunologic vaccines, infusion of tumor infiltrating lymphocytes, infusion of genetically engineered T cells targeting HPV-associated proteins, and antibody-drug conjugates. Ongoing trials using these approaches are summarized in Table 3.

One of the leading vaccine strategies for treatment of cervical cancer uses a bacterial vector (attenuated *Listeria monocytogenes*), which infects host antigen-presenting cells and secretes a fusion HPV E7 protein.[33] Known as AXAL, the virus thus stimulates a CD4- and CD8-mediated adaptive immune response targeting HPV-infected cells. Initial phase I data showed that the vaccine was well tolerated, although all patients were noted to have a flu-like syndrome, which ultimately did not require prescription treatment.[34] Two phase II trials have since been completed. The GOG phase II study enrolled 50 patients with metastatic disease whose disease had progressed on at least one prior systemic therapy and administered three doses of the vaccine. The 12-month overall survival was 38%, which represented an improvement compared with historical controls.[35] In India, 110 patients with recurrent disease were randomized to three to four doses of AXAL with or without weekly cisplatin 40 mg/m^2. More than a third of patients had stable disease or responses (including five complete responses) and 2- year overall

Table 2 Selected ongoing studies using checkpoint blockade immunotherapy in treatment of recurrent or metastatic cervical cancer

NCT identifier	Title	Phase	Planned enrollment	Primary endpoint(s)
NCT03257267	Study of Cemiplimab in Adults With Cervical Cancer	III	590	Overall survival
NCT03912415	Efficacy and Safety of BCD-100 (Anti-PD-1) in Combination With Platinum-Based Chemotherapy With and Without Bevacizumab as First-Line Treatment of Subjects With Advanced Cervical Cancer (FERMATA)	III	316	Overall survival
NCT03556839	Platinum Chemotherapy Plus Paclitaxel With Bevacizumab and Atezolizumab in Metastatic Carcinoma of the Cervix (BEATcc)	III	404	Overall survival
NCT03192059	Study of Pembrolizumab, Radiation and Immune Modulatory Cocktail in Cervical/Uterine Cancer (PRIMMO)	II	43	Objective response rate
NCT03614949	SBRT and Atezolizumab in the Management of Recurrent, Persistent, or Metastatic Cervical Cancer	II	26	Overall response rate
NCT01693783	Ipilimumab in Treating Patients With Metastatic or Recurrent Human Papilloma Virus-Related Cervical Cancer	II	44	Adverse events, objective response rate
NCT03277482	Durvalumab, Tremelimumab+Radiotherapy in Gynecologic Cancer	I	32	Maximum tolerated dose
NCT03452332	Stereotactic Body Radiation Therapy, Tremelimumab and Durvalumab in Treating Participants With Recurrent or Metastatic Cervical, Vaginal, or Vulvar Cancers	I	20	Adverse events

Table 3 Selected ongoing studies using vaccines, antibody-drug conjugates, or engineered T-cell therapies in the treatment of cervical cancer

NCT identifier	Title	Phase	Planned enrollment	Primary endpoint(s)
NCT04697628	Tisotumab Vedotin vs Chemotherapy in Recurrent or Metastatic Cervical Cancer (innovaTV 301)	III	482	Overall survival
NCT04646005	Cemiplimab and ISA101b Vaccine in Adult Participants With Recurrent/Metastatic Human Papillomavirus (HPV)16 Cervical Cancer Who Have Experienced Disease Progression After First-Line Chemotherapy	II	103	Objective response rate
NCT04580771	A Vaccine (PDS0101) and Chemoradiation for the Treatment of Stage IB3–IVA Cervical Cancer, the IMMUNOCERV Trial	II	35	Grade 3+ acute toxicity
NCT04405349	Investigating the Combination of VB10.16 and Atezolizumab in Patients With HPV 16-positive Cervical Cancer	II	50	Adverse events, overall response rate
NCT03444376	The Combination of GX-188E Vaccination and Pembrolizumab in Patients With HPV 16 and/or 18+ Advanced Cervical Cancer	I/II	60	Overall response rate
NCT02858310	E7 TCR T Cells for Human Papillomavirus-Associated Cancers	I/II	180	Overall response rate
NCT03260023	Phase Ib/II of TG4001 and Avelumab in HPV16 Positive R/M Cancers	I/II	150	Overall response rate and progression-free survival
NCT02379520	HPV-16/18 E6/E7-Specific T Lymphocytes, Relapsed HPV-Associated Cancers, HESTIA (HESTIA)	I	32	Dose-limiting toxicity
NCT02172911	A Study of INO-3112 DNA Vaccine With Electroporation in Participants With Cervical Cancer	I	10	Adverse effects
NCT03578406	HPV-E6-Specific Anti-PD1 TCR-T Cells in the Treatment of HPV-Positive NHSCC or Cervical Cancer	I	20	Maximum tolerated dose

survival was 18% across both treatment arms.[36] The addition of cisplatin did not appear to improve outcomes compared with AXAL alone. Based on these encouraging data, a larger phase III trial was initiated in the definitive setting (NCT02853604). Unfortunately, the trial was closed prematurely in 2019,[37] and no results have been presented or published to date.

Another novel immunotherapeutic approach uses a patient's own tumor-reactive T cells. These are cultured from samples of a metastatic tumor or draining lymph node[38] and tested for activity against E6 and E7 proteins. Cultures that show high T-cell content and purity with good reactivity are further propagated and then administered to the patient in a single-dose IV infusion after preparatory lymphocyte depleting chemotherapy.[39] Initial data from nine patients with metastatic disease showed three responses, including two complete responses. The cohort was expanded to 18 patients and longer-term follow-up data were recently published.[40] The two patients with a complete response remained free of disease at 53 and 67 months after treatment. Factors predictive of treatment response included the HPV reactivity of the cultured T cells prior to infusion as well as the number of HPV reactive T cells in the peripheral blood post-infusion, as quantified by flow cytometry.

Genetically engineered T-cell therapy has resulted in several breakthroughs for treatment of hematologic malignancies and is now being investigated for the treatment of HPV-associated epithelial cancers.[41] This technique isolates a patient's peripheral mononuclear blood cells and then uses a retrovirus encoding HPV-related genes to engineer the T cells to target infected cells. These cells are engineered and propagated over several weeks[42] and then infused back into the patient after preparative chemotherapy. Phase I data are now available for engineered T cells targeting both the E6[41] and E7 proteins.[43] In the latter study, which included 12 patients with metastatic HPV-associated cancer from multiple primary sites (including five with cervical primaries), 50% of patients demonstrated tumor response, including several who had previously been given anti-PD-1 immunotherapy.

Lastly, a recently published phase II study showed an encouraging objective response rate of 24% after treatment of patients with recurrent or metastatic disease with an antibody drug conjugate.[44] The antibody targets a protein known as tissue factor, which is highly prevalent in cervical cancers, ultimately resulting in the intracellular delivery of a microtubule disrupting agent. In addition to direct cytotoxicity, multiple mechanisms of immune activation are also thought to contribute to the effectiveness of the treatment.[44]. Toxicity was grade 3 or higher in more than a quarter of patients, and there was one treatment-related fatality due to septic shock. These encouraging results overall have led to the initiation of a randomized phase III study (NCT04697628).

RADIATION AND IMMUNOTHERAPY

Since radiation therapy is frequently used as a component of cervical cancer management, potential synergies between radiation

treatment and immunotherapy are another exciting area of ongoing investigation. Pre-clinical data show an improved response to treatment with combination therapy including both anti-CTLA-4 and PD-1 agents as well as radiation.[45] The improved response with all three therapies suggests complementary mechanisms, with the CTLA-4 inhibition reducing immunosuppressive Treg cells, anti PD-1 therapy preventing immune exhaustion of CD8 positive cells, and radiation treatment enhancing the diversity of T-cell receptors present on tumor-infiltrating lymphocytes. Similar data suggest that the release of tumor-associated antigens with radiation treatment may also be beneficial for enhancing the efficacy of infused T cell therapies.[46]

A clinical phenomenon known as the abscopal effect (regression of tumors outside the radiation field after treatment) is thought to be immune mediated, and may be promoted in the setting of immunotherapy.[47] For example, anti-CD40 treatment and single-fraction radiation significantly improved tumor control and survival in a mouse model of cervical cancer.[48] Radiation also changes the tumor microenvironment, even in non-irradiated distant tumors.[49] However, the abscopal effect is controversial and is a rare phenomenon, with clinical data largely limited to case reports.[50 51] Further research is ongoing to understand the treatments and patients for whom this is most likely to occur (eg, NCT03614949). Another important question still under investigation is the optimal sequencing of immune therapy with radiation to achieve the optimal therapeutic ratio.[52]

CONCLUSION

Immunotherapy represents an emerging treatment option for patients with cervical cancer. Checkpoint blockade therapy is now an appropriate component of first-line treatment in the metastatic setting and is under investigation in several phase III trials that may change the standard of care for definitive management of locally advanced disease. Other immunotherapies, including vaccines and engineered T cells, are in earlier phases of development, with promising initial results. All these treatments may synergize with radiation therapy to provide an optimal immune response.

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