THERAPEUTIC ADVANCES in
Medical Oncology

Review

Advances in immunotherapy for cervical cancer

Ther Adv Med Oncol

2023, Vol. 15: 1–18

DOI: 10.1177/17588359231163836

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***Abstract*:** Cervical cancer still represents a major public health problem, being the fourth most common cancer in incidence and mortality in women worldwide. These figures are unacceptable since cervical cancer, an human papillomavirus-related malignancy, is a largely preventable disease by means of well-established screening and vaccination programs. Patients with recurrent, persistent, or metastatic disease unsuitable for curative therapeutic approaches represent a dismal prognosis population. Until recently, these patients were only candidates for cisplatin-based chemotherapy plus bevacizumab. However, the introduction of immune checkpoint inhibitors has revolutionized the treatment landscape of this disease achieving historical overall survival improvements in both the post-platinum and frontline settings. Interestingly, the clinical development of immunotherapy in cervical cancer is currently advancing to earlier stages of the disease, as the locally advanced setting, whose standard of care has not changed in the last decades with still modest outcomes. As more innovative immunotherapy approaches are in clinical early development in advanced cervical cancer, promising efficacy data are emerging that may shape the future of this disease. This review summarizes the main treatment advances carried out in the field of immunotherapy throughout the past years.

Keywords: Cervical cancer, immune checkpoint inhibitor, CAR-T cell therapy, immunotherapy, radiotherapy

Received: 20 November 2022; revised manuscript accepted: 22 February 2023.

Introduction and biological rationale for immunotherapy in cervical cancer

Cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women, with an estimated 606,000 new cases and 342,000 deaths worldwide in 2020. Importantly, more than 70% of deaths from cervical cancer occur in low- to medium-income countries where this tumor places second in both incidence and mortality among women.[1] This striking geographic variation in cervical cancer can be explained not only by the human papillomavirus (HPV) infection prevalence, but also by the unequal access to well-organized screening programs and prophylactic vaccination.[2] Thus, cervical cancer is largely considered as a preventable disease.

HPVs cause the majority of cervical cancers, with HPV types 16 (HPV-16) and 18 (HPV-18) responsible for approximately 70% of the cases.[3] The natural history of cervical cancer is well understood. A multistep carcinogenesis model is widely accepted, starting with HPV infection followed by progression to precancerous lesions, and invasion to cancer, in a long process that may last up to 15 years. Going into greater detail, HPV infects keratinocytes in the basal layers of stratified epithelia, and the integration of the HPV genome into the host chromosome is a key event of HPV-induced carcinogenesis. Expression of the viral E6 and E7 genes is consistently maintained upon integration. The E7 protein targets a number of cell cycle regulatory proteins, including the inhibition of p53 and Rb family proteins,

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thus upregulating genes required for G1/S transition and DNA synthesis. To overcome apoptosis or growth arrest, the E6 oncoprotein targets a variety of cellular proteins involved in regulating terminal differentiation and antiviral defense. When both events occur, viral replication continues, and it can lead to cell transformation.[4,5]

It is important to underscore that carcinogenesis is greatly influenced by the dynamics and composition of the immune microenvironment, in a process known as 'immunoediting'. As a virally driven tumor, cervical cancer shows particularly higher lymphocyte infiltration compared to HPV-negative malignancies. Moreover, the increased presence of CD8+ tumor-infiltrating lymphocytes (TILs) has been linked to improved survival rates,[6–11] and better efficacy outcomes to standard therapy in cervical cancer patients.[12,13] Intriguingly, despite the presence of this T-cell infiltration, tumor growth may persist, since HPV-infected cancer cells are able to modulate the immune microenvironment to create a protumorigenic state of immune suppression and evasion, through multiple mechanisms: (1) E7 oncoprotein has been shown to downregulate the cGAS–STING pathway, an important innate response pathway to viral DNA that induces the expression of type I IFN genes by directly inhibiting STING. (2) HPV E6 can also dampen type I IFN gene expression by inhibiting the IFN regulatory factor IRF3. (3) Downregulation of antigen presentation on major histocompatibility complex (MHC) by HPV E5 or mutations in antigen presentation pathway genes leads to decreased recognition by effector T cells. (4) Overexpression of E7 in a preclinical cervical cancer model has been shown to upregulate the programmed death-ligand 1 (PD-L1) immune checkpoint on infected tumor cells inhibiting cytolytic T-cell activity. (5) HPV modulates HLA expression to engage NK cell inhibitory receptors, for example through the interaction of HLA-E molecules with NKG2A. (6) Evidence of HPV antigen-specific FOXP3+ T regulatory cells (Treg), whose purpose is to suppress both CD8+ and CD4+ cells in the tumor microenvironment.(7) CD4+ T cells are typically skewed toward a TH2 response which potentiates a humoral response.[14]

PD-L1 expression seems to have a major role in creating an 'immune-privileged' site for initiation and persistence of HPV infection by downregulating T-cell activity and generating an adaptive immune resistance. Its expression has not been demonstrated in normal cervical tissue, but it is detectable in 95% of cervical intraepithelial neoplasia, and in cervical cancer T cells, antigen-presenting cells (APCs), and tumor cells. Reports of PD-L1 expression in cervical squamous cell carcinoma (SCC) vary widely from 19% to 88%, and it is less prevalent in cervical adenocarcinoma (14%).[15] The prognostic significance of PD-L1 expression in cervical cancer has been reported in a few studies with contradictory results.[16–20] Interestingly, a study showed that not only the extent but also the pattern of PD-L1 expression is an important prognostic factor, since marginal PD-L1 expression, most likely induced by interferon-gamma (IFNγ) signaling, was associated with a favorable prognosis when compared to diffuse PD-L1 expression or lack of PD-L1.[21]

All these findings mentioned above set a robust biological rationale for the development of immunomodulatory therapies in cervical cancer, such as immune checkpoint inhibitors (ICIs), aiming at restoring an effective antitumor immune response.

The treatment landscape of cervical cancer has not greatly changed over the last decade. The early-stage disease may be cured by radical surgery with tailored adjuvant therapy. However, patients diagnosed with locally advanced disease (FIGO 2018 stages IB3 and IIA2–IVA) despite radical chemoradiation (CRT) plus high-dose-rate brachytherapy experience a 5-year disease-free survival of 40–83% and overall survival (OS) of 41–82.7%.[22] Finally, the management of women with persistent or recurrent disease who are not candidates for radical-intent local therapies and those who present with metastatic (FIGO stage IVB) disease has represented a high unmet clinical need. In the past years, the addition of the anti-vascular endothelial growth factor (VEGF) agent bevacizumab to platinum-based chemotherapy succeeded to extend median OS to nearly 17 months.[23] More recently, the incorporation of immunotherapy, mainly ICI, in the therapeutic armamentarium of cervical cancer has represented a major breakthrough. Two pivotal trials, EMPOWER-Cervical 1 and KEYNOTE-826,[24,25] demonstrated that cemiplimab and pembrolizumab provided a significant OS improvement in both post-platinum failure and frontline persistent, recurrent, or metastatic cervical cancer settings, respectively.

In this review, we will focus on the most relevant published or presented data on clinical trials exploring immunotherapy in cervical cancer in different disease settings, from locally advanced to persistent, recurrent, or metastatic cervical cancer in both frontline and post-platinum progression. We will review each immunotherapy agent and combination following the chronological order of their clinical development.

Role of ICIs for persistent, recurrent, and metastatic disease following platinum failure

Historically, those patients who progressed to first-line platinum-based therapy had very limited treatment options. Several chemotherapeutic agents were the main therapeutic alternatives in this setting, with a scarce clinical efficacy: An overall response rate (ORR) of less than 20%, and a median progression-free survival (PFS) and OS of 3.3 and 6.7 months, respectively. Thus, there was a high unmet need for novel therapies to improve the dismal prognosis of this particular patient subgroup.[26]

The clinical development of ICI in cervical cancer was initiated in this difficult-to-treat population based on the aforementioned robust biological rationale.

ICI monotherapy approaches

The phase Ib trial KEYNOTE-028 provided the first evidence for clinical activity of an ICI in advanced cervical cancer. This study evaluated the clinical activity and safety of pembrolizumab (anti-PD-1 monoclonal antibody) in 20 cohorts of patients with PD-L1-positive metastatic solid tumors. PD-L1 positivity was defined as membranous staining on ⩾1% modified proportion score or interface pattern as assessed using a laboratory-developed prototype immunohistochemistry assay and the 22C3 antibody. In the cervical cohort, 24 patients were finally enrolled (96% were SCC). The ORR was 17% (95% CI, 5%–37%) with a median duration of response (DOR) of 5.4 months (95% CI, 4.1–7.5 months). The safety profile was consistent with that seen for pembrolizumab in other tumor types.[27]

Following these encouraging results, the phase II basket trial KEYNOTE-158 was launched. This study investigated the efficacy and safety of pembrolizumab at a dose of 200 mg every 3 weeks for up to 2 years in several cohorts of patients with metastatic solid tumors. Patients were enrolled regardless of PD-L1 status. Overall, 98 patients with previously treated advanced cervical cancer received pembrolizumab. Of these patients, 82 were classified as PD-L1-positive tumors according to a combined positive score (CPS) of ⩾1%. CPS is defined as the number of PD-L1 staining cells (tumor and immune cells) divided by the total number of viable tumor cells, multiplied by 100. In the whole population, the ORR was 14.3% (95% CI, 8.0–22.8%) with a DOR not reached (range, 3.7+ to 35.2+ months). It is important to underline that all patients that achieved complete or partial responses had PD-L1-positive tumors, leading to an ORR of 17% in this patient subgroup. Median PFS was 2.1 months (95% CI, 21–2.2 months) and OS was 9.3 months (95% CI, 7.6–11.7 months). Regarding the safety profile, treatment-related adverse events (AEs) occurred in 65.3% of patients and 12.2% of patients had treatment-related grade 3–4 AEs. The most common were hypothyroidism (11.2%) and fatigue (11.2%).[28]

Based on these results, on 12 June 2020, the FDA approved pembrolizumab in patients with persistent, recurrent, or metastatic cervical cancer with disease progression after chemotherapy whose tumors express PD-L1 (CPS ⩾ 1%). To date, this is the only approved drug in this indication.

The clinical activity of the anti-PD1 monoclonal antibody, nivolumab, was evaluated in the phase I/II CheckMate358 in HPV-related recurrent/metastatic cervical, vaginal, or vulvar cancers. In the cervical cancer cohort, 19 patients with squamous cervical cancer were enrolled and treated with nivolumab 240 mg iv every 2 weeks for up to 2 years, prohibitive toxicity or disease progression whichever occurs first. Most of the patients had stage IV disease at enrollment and had received prior systemic therapy for metastatic/recurrent disease. Overall, 62.5% of the tumors were classified as PD-L1 positive. The primary endpoint ORR was 26% (95% CI, 9–51%) and median DOR was not reached. Responses were seen in both PD-L1-positive and PD-L1-negative patients, although responses were greater in the PD-L1-positive tumors: 27% in PD-L1-positive *versus* 14% in PD-L1-negative subgroups. Median PFS achieved in this cohort was 5.1 months (95% CI, 1.9–9.1) and median OS was 21.6 months (95% CI, 8.3–46.9). Sixty-three percent of the patients presented any grade treatment-related

AEs, with diarrhea being the most commonly reported AE.[29,30]

In 2021, the results of the efficacy and safety of balstilimab (monoclonal antibody against PD-1) were published. The phase II trial C-700-01 enrolled 140 patients with previously treated recurrent or metastatic cervical cancer (62.7% squamous, 32.3% adenocarcinoma, and 4.3% adenosquamous) that received balstilimab 3 mg/kg iv every 2 weeks for up to 24 months. Regarding the PD-L1 status, 61.5% of patients were CPS $\geq$ 1%, 26.7% were CPS $<$ 1%, and 11.8% were not evaluable. The ORR was 15% with a median DOR of 15.4 months in the whole population. It is to be noted that in patients with PD-L1-positive tumors, the ORR was 20.0% (95% CI, 12.9–29.7) and 7.9% in patients who were PD-L1 negative. Responses were also observed across all histologic subtypes. Concerning the safety data, asthenia, diarrhea, and pruritis were the most common treatment-related AEs. Immune-mediated enterocolitis (3.1%) was the most common grade 3 treatment-related AEs.[31] After these encouraging results, the BRAVA trial (NCT04943627), a phase III randomized study comparing balstilimab *versus* the investigator's choice of chemotherapy was designed in recurrent, persistent, or metastatic cervical cancer patients who have progressed after receiving platinum-based chemotherapy. Due to the FDA approval of pembrolizumab as a single agent in this disease setting, BRAVA trial was discontinued.

Despite the clinical activity of ICI seeming to be superior to chemotherapy, a head-to-head comparison should be analyzed to determine which might be the standard of care after platinum failure. As a result of this unanswered question, the phase III trial EMPOWER-Cervical-1/GOG-3061/ENGOT-cx9 was launched. This is an open-label, multicentre, phase III randomized trial, comparing cemiplimab, an anti-PD-1 antibody, *versus* the investigator's choice of single-agent chemotherapy in patients with advanced cervical cancer who had progressed after first-line platinum-containing chemotherapy. It is important to underscore that the patients were included regardless of PD-L1 expression status. Among the 608 randomized patients, 77.8% had SCC and 22.2% had adenocarcinoma or adenosquamous carcinoma. Roughly 50% of the patients had received bevacizumab and 40% had received at least two prior systemic therapies for recurrent disease. Following 1:1 randomization, 304 patients were treated with cemiplimab 350 mg every 3 weeks and 304 received pemetrexed, vinorelbine, gemcitabine, irinotecan, or topotecan for up to 96 weeks. The primary endpoint was OS which was analyzed hierarchically in patients with SCC followed by the intention-to-treat (ITT) population, and the secondary endpoints included PFS and ORR. The trial was stopped, after the second planned interim analysis, based on pre-specified criteria for efficacy in the SCC population that demonstrated significantly improved OS in patients receiving cemiplimab monotherapy. Per-protocol final survival analysis was performed after 363 OS events were observed in the SCC patients' cohort, at a median follow-up of 30 months. These outcomes were recently presented at ESMO 2022. In the SCC population, median OS was significantly longer with cemiplimab than with chemotherapy (10.9 months *versus* 8.8 months; HR, 0.69; 95% CI, 0.56–0.85; $p = 0.0023$), as well as in the overall population (11.7 months *versus* 8.5 months; HR, 0.65; 95% CI, 0.54–0.79; $p < 0.001$). The pre-specified exploratory analysis in the population with adenocarcinoma or adenosquamous carcinoma also showed an improvement in OS in favor of cemiplimab whose median OS was 13.5 months, as compared with 7.0 months with chemotherapy (HR, 0.54; 95% CI, 0.36–0.81). Regarding the key secondary endpoint, the ORR in the overall population was 16.4% (95% CI, 12.5–21.1) with cemiplimab and 6.3% (95% CI, 3.8–9.6) with chemotherapy. Note that ORR with cemiplimab was higher than with chemotherapy in both histological subgroups: 12% (95% CI, 6–23) in the adenocarcinoma subgroup and 17.6% (95% CI, 13.0–23.0) in the SCC. Moreover, OS was evaluated according to the status of PD-L1 in an exploratory analysis. In the most recent update, of 608 randomized patients, only 371 (61%) had valid baseline PD-L1 samples (182 in the cemiplimab arm and 189 in the chemotherapy arm). In the PD-L1 tested population, cemiplimab increased OS *versus* chemotherapy in patients with both PD-L1 $\geq$ 1% (HR, 0.61; 95% CI, 0.45–0.83) and PD-L1 $<$ 1% (HR, 0.65; 95% CI, 0.42–0.98), with 38% and 35% lower risk of death, respectively. Besides, responses to cemiplimab were observed in patients with both PD-L1 expression $\geq$1% (21.6%; 95% CI, 14.5–30.1) and $<$1% (13.6%; 95% CI, 6.4–24.3). Concerning safety profile, 45% of patients with cemiplimab presented grade $\geq$3 treatment-related AEs, with anemia being the most frequent.[25,32]

Following the results of this trial, cemiplimab was granted priority review by the FDA for patients with previously treated metastatic cervical cancer in September 2021. Nevertheless, the manufacturing company, Regeneron/Sanofi, finally decided to withdraw the biologics license application for cemiplimab following discussion with the FDA in January 2022. On 25th March 2022, cemiplimab was approved in Canada for patients with advanced cervical cancer who had progressed after first-line platinum-containing chemotherapy. Recently, on 22nd November 2022, the European Commission has approved cemiplimab monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer who have progressed on or after platinum-based chemotherapy regardless of PD-L1 status.

ICIs combination approaches

ICIs targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) axis have also been studied in the setting of recurrent or metastatic cervical cancer. Previous studies have demonstrated an increase in antigen presentation to the immune system after the blockade of the CTLA-4 antigen, resulting in an expanded cytotoxic T-cell response.[33]

A phase I/II dose-escalation trial evaluated ipilimumab monotherapy in patients with recurrent or metastatic cervical cancer whose disease had progressed on platinum chemotherapy. Ipilimumab was administered 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 of 34 evaluable patients displaying a partial response while the remainder had stable or progressive disease.[34] These efficacy data seem to suggest that anti-CTLA-4 agents are probably ineffective as monotherapy for metastatic disease but could potentially be used as part of a combined regimen. It was hypothesized that the combination of PD-1 and CTLA-4 blockers could have a synergist effect on the activation of the antitumor immune response, increasing the response rates in patients. Several phase II trials that investigated anti-PD-(L)1 in combination with anti-CTLA-4 in advanced cervical cancer have been carried out.

The phase I/II CheckMate-358 also included two treatment arms in which nivolumab was tested in combination with ipilimumab (anti-CTLA-4) in patients with recurrent/metastatic squamous cervical cancer who had received two or fewer prior therapies. Patients were randomized to two different dosage regimens: (A) nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks or (B) nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab maintenance 240 mg every 2 weeks, for up to 24 months. The positivity of PD-L1 was similar in both cohorts (62.2% in arm A and 67.7% in arm B). Regarding the trial's primary endpoint, ORR was 31% (95% CI, 18–47%) in arm A and 38% (95% CI, 29–48) in arm B. It is important to underline that responses were observed regardless of PD-L1 expression status, although ORR was slightly superior in the PD-L1-positive subgroup. Interestingly, this trial also enrolled patients with no prior systemic therapy for recurrent or metastatic disease (40% of patients in arm A and 64% in arm B). It is to be noted that chemo-naïve patients showed better efficacy outcomes across both treatment regimens, as compared with those previously treated (arm A: ORR in first line was 39% *versus* 26% in $\geqslant$ second line; arm B: 41% in first line *versus* 35% in $\geqslant$ second line). Concerning the key secondary endpoints, the median OS was 15.2 months (95% CI, 9.0–36.2 months) in arm A and 20.9 months (95% CI, 14.4–32.8 months) in arm B. The median PFS was found to be 3.8 (95% CI, 1.9–9.1) in arm A and 5.8 months (95% CI, 3.8–9.3) in arm B. Regarding the toxicity profile, it should be noted that there was a higher incidence of grade $\geqslant$3 hepatitis and diarrhea/colitis in arm B compared with arm A (16% *versus* 5%, respectively). In addition, the discontinuation rate due to treatment-related EAs was higher in arm B compared with arm A (24% *versus* 18%).[30]

The phase II trial C-550-01 evaluated the safety and efficacy of the combination of balstilimab (anti-PD-1 antibody) and zalifrelimab (anti-CTLA-4 antibody) in patients with advanced cervical cancer who had relapsed after prior platinum-based therapy regardless of PD-L1 status. The primary endpoint was ORR, and the secondary endpoints included DOR and safety. Overall, 155 patients were finally enrolled and treated with balstilimab 3 mg/kg every 2 weeks plus zalifrelimab 1 mg/kg every 6 weeks, up to 24 months. Concerning PD-L1 status, 56.8% of tumors were classified as positive (CPS $\geqslant$ 1%), 25.2% as negative (CPS $\leqslant$ 1%), and 18.1% were not evaluable. The ORR of the combined therapy was 25.6% (95% CI, 18.8–33.9), 32.8% in

PD-L1-positive tumors, and 9.1% in PD-L1-negative tumors. Besides, ORR was observed across all histological subtypes (32.6% in SCC and 8.8% in adenocarcinoma/adenosquamous carcinoma). The overall disease control rate was 52% (95% CI, 43.3–60.6). Regarding the toxicity profile, the most common immune-mediated AEs were hypothyroidism (14.2%) and hyperthyroidism (7.1%).[31] Following the promising efficacy results of this combination, the RaPiDS study (NCT03894215), a phase II randomized clinical trial evaluating balstilimab monotherapy and combined with zalifrelimab in women with recurrent or metastatic cervical cancer with relapse or progression after first-line platinum-based chemotherapy was launched. Patients' enrollment has been completed and results are still pending.

Cadonilimab is a first-in-class anti-PD-1/CTLA-4 bispecific monoclonal antibody being evaluated as monotherapy for patients with recurrent or metastatic cervical cancer after failure with platinum-based chemotherapy. It has received FDA fast-track and orphan drug designation as well as China's National Medical Products Administration breakthrough therapy designation. The pivotal trial was a phase II, multicenter, open-label, single-arm study that enrolled 100 patients with previously treated recurrent or metastatic cervical cancer (92.8% were SCC) and was treated with cadonilimab at a dose of 6 mg/kg every 2 weeks. The ORR (primary endpoint) was 33% (95% CI, 23.9–43.1%). In the subgroup analysis, among the 64 patients with PD-L1 positive (CPS $\geqslant$ 1%), the ORR was 43.8%. Results also showed a median DOR that was not reached (range: 0.95+ to 13.14+ months), a median PFS of 3.75 months (95% CI, 2.00–6.41), and a median OS of 17.51 months (95% CI, 11.37–NR). Up to 96.4% of patients experimented with treatment-related AEs of any grade, 28.8% were grade 3 to 4, and the most common were anemia (7.2%) and decreased appetite (2.7%).[35] In light of these results, a phase III trial, assessing cadonilimab in the frontline setting, has been launched in China, as mentioned below.

Another ICI combination that is currently under investigation is the anti-TIGIT (T-cell immunoreceptor with Ig and ITIM domains) and anti-PD-(L)1 antibodies. TIGIT is an inhibitory molecule that is expressed on a variety of immune cells such as T cells, Tregs, and natural killer cells. A suppressive phenotype is associated with elevated TIGIT expression on CD8+ T cells and Tregs, correlating with reduced cytokine production and poor survival in multiple cancer models. Preclinical mouse models suggested that TIGIT/PD-(L)1 dual blockade could increase the efficacy of these treatments *via* modulation of the T cell.[36]

The efficacy and safety of vibostalimab (anti-TIGIT antibody) in combination with pembrolizumab were assessed in the phase I KEYVIBE-001 trial. Patients with advanced or recurrent cervical cancer naïve to PD-(L)1 inhibitor were enrolled. Two dose levels of vibostalimab were evaluated: vibostalimab 200 mg + pembrolizumab 200 mg (arm A) or vibostalimab 700 mg + pembrolizumab 200 mg (arm B) every 3 weeks for up to 35 cycles. The primary endpoints were safety and tolerability and the secondary endpoints included ORR, DOR, and PFS. The patients were enrolled regardless of the status of PD-L1 but it was subsequently evaluated in all the patients: arm A: 49% were CPS $\geqslant$ 1%, 32% were CPS $<$ 1% and 20% were unknown; arm B: 74% were CPS $\geqslant$ 1%, 21% were CPS $<$ 1%, and 5% were unknown. At the moment of cutoff, 41 and 39 patients were enrolled in arms A and B, respectively. The ORR was 15% in arm A and 23% in arm B. It should be noted that ORR was higher in CPS $\geqslant$ 1% than in CPS $<$ 1% tumors (20% *versus* 14%), although responses were seen irrespective of PD-L1 status. These results are encouraging since pembrolizumab monotherapy showed no objective responses in PD-L1 negative disease in the same setting. Concerning the safety profile, rash, pruritus, and pyrexia were the treatment-related AEs in both arms.[37] Following these efficacy outcomes, the phase II basket trial KEYVIBE-005 (NCT05007106) is currently evaluating the safety, tolerability, and preliminary efficacy of pembrolizumab/vibostolimab co-formulation in patients with cervical cancer naïve to PD-1/PD-L1 inhibitors.

Besides, the SKYSCRAPER-04 (NCT04300647) is a randomized, open-label phase II trial, assessing the efficacy and safety of tiragolumab (anti-TIGIT) plus atezolizumab (anti-PD-L1 antibody) and atezolizumab monotherapy in patients with metastatic or recurrent PD-L1-positive (per SP263) cervical cancer, and its results are still awaited.

ICIs for persistent, recurrent, and metastatic disease in the frontline setting

The introduction of the antiangiogenic agent bevacizumab to the frontline platinum-based chemotherapy has extended median OS from about 12 to 17 months, since becoming the standard of care for this population, based on the GOG-240 trial's results.[23] Beyond this historical approval back in 2014, no further targeted therapy has demonstrated a survival benefit in the frontline setting, until the recent advent of immunotherapy.

The solid biological rationale for the introduction of ICIs and the encouraging results in previously treated advanced cervical cancer patients led the investigators to assess immunotherapy early on in the disease course when the host immune system is more robust. Interestingly, chemo-naïve patients seemed to show better efficacy outcomes when treated with ICIs according to the Checkmate-358 trial's results, shown above. Besides, new combination approaches with ICIs and other agents have been proposed to enlarge the population benefiting from immunotherapy. In this sense, both platinum agents and bevacizumab can modulate the immune tumor microenvironment favoring the synergism with anti-PD-1/PD-L1 monoclonal antibodies. Chemotherapy increases immunogenic cell death leading to the release of tumor-associated neoantigens and cellular danger-associated molecular patterns, resulting in increased activity of APCs and downstream T-cell activation. Concerning the anti-VEGF agents, they may exert an immunostimulatory action upon the tumor microenvironment through multiple mechanisms: (1) stimulation of dendritic cell maturation enabling efficient priming and activation of T-cell response; (2) normalization of tumor vasculature, resulting in increased trafficking of T cell into the tumor; (3) decreasing the activity of myeloid-derived suppressor cells, regulatory T cells, and tumor-associated macrophages; and (4) restoring T-cell-mediated cancer cell killing (decreased expression of T-cell exhaustion markers, such as PD-1 and TIM-3).[38,39]

Three phase III trials are currently exploring the synergistic combination of ICIs and first-line standard of care therapy based on platinum doublet (platinum and paclitaxel) with or without bevacizumab, for recurrent, persistent, or metastatic cervical cancer patients: KEYNOTE-826 (NCT03635567), BEATcc (NCT03556839), and FERMATA (NCT03912415) trials. Un until now, the KEYNOTE-826 is the only of these trials to have published its results.

MK-3475-826/KEYNOTE-826 is a phase III randomized, double-blind, placebo-controlled study, designed to assess the benefit of adding pembrolizumab to chemotherapy with or without bevacizumab, in persistent, recurrent, or metastatic cervical cancer patients, in the frontline setting. A total of 617 eligible patients (72% SCC and 28% adenocarcinoma/adenosquamous) were randomly assigned in a 1:1 ratio to receive pembrolizumab at a flat dose of 200 mg or placebo every 3 weeks for up to 35 cycles plus platinum-based chemotherapy for up to 6 cycles and bevacizumab at the investigators' discretion. Stratification factors included metastatic status at diagnosis (yes/no), bevacizumab use (yes/no), and PD-L1 expression status at baseline either in an archival tumor tissue sample or fresh biopsy. PD-L1 expression was assessed during screening at a central laboratory with the use of the PD-L1 IHC 22C3 pharmDx assay and measured according to the CPS. The dual primary endpoints were PFS and OS, each tested sequentially in patients with a PD-L1 CPS $\geq$ 1%, in the ITT population, and finally, in patients with a PD-L1 CPS $\geq$ 10%. After a median follow-up of 22.0 months, 548 patients with a PD-L1 CPS $\geq$ 1% (89% of the overall population) showed a median PFS of 10.4 months in the pembrolizumab group and 8.2 months in the placebo group (HR, 0.62; 95% CI, 0.50–0.77; $p < 0.001$). In 617 patients of the ITT population, median PFS was 10.4 months and 8.2 months, respectively (HR, 0.65; 95% CI, 0.53–0.79; $p < 0.001$). Finally, in 317 patients with a PD-L1 CPS $\geq$ 10%, median PFS was 10.4 months and 8.1 months, respectively (HR, 0.58; 95% CI, 0.44–0.77; $p < 0.001$). OS at 24 months was 53.0% in the pembrolizumab group and 41.7% in the placebo group (HR, 0.64; 95% CI, 0.50–0.81; $p < 0.001$), 50.4% and 40.4% (HR, 0.67; 95% CI, 0.54–0.84; $p < 0.001$), and 54.4% and 44.6% (HR, 0.61; 95% CI, 0.44–0.84; $p = 0.001$), in the PD-L1 CPS $\geq$ 1%, ITT, and PD-L1 CPS $\geq$ 10% populations, respectively. Regarding the protocol-specified subgroup analysis, the OS benefit provided by the addition of pembrolizumab was generally consistent across all patient subgroups. However, PD-L1 CPS $<$ 1% subgroup did not seem to obtain survival benefit (HR, 1.00; 95% CI, 0.53–1.89). A post-hoc subgroup analysis showed that the concomitant use of bevacizumab (63%) may have a positive impact

on OS (HR, 0.63; 95% CI, 0.47–0.87), as well as the use of cisplatin *versus* carboplatin as chemotherapy backbone (HR, 0.59 *versus* 0.69). Despite that the trial met its primary endpoint in the intent to treat population, based on the aforementioned subgroup analysis, both FDA and EMA have recently approved the use of pembrolizumab added to platinum-based chemotherapy plus or minus bevacizumab only for those patients whose tumors are CPS $\geqslant$ 1%. Anyhow, further studies are required to better understand the performance of pembrolizumab in the subgroup of CPS $<$ 1%, which constituted only 11% of KEYNOTE-826 trial's population. Regarding the safety profile, the toxicity of this combination approach was manageable. The most common grade 3 to 5 AEs were anemia (30.3% in the pembrolizumab group and 26.9% in the placebo group) and neutropenia (12.4% and 9.7%, respectively). The most common any-grade immune-related AEs were hypo- and hyperthyroidism (18.2% and 7.5%, respectively), colitis (5.2%), and skin reactions (4.6%). It is important to note that 5.2% of patients treated with Pembrolizumab discontinued any treatment due to AEs *versus* 0.3% of patients on the placebo arm.[24,40]

Other clinical trial worth mentioning is the BEATcc trial (ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030). The BEATcc trial is a randomized, open-label phase III trial designed to assess the efficacy and safety of adding the anti-PD-L1, atezolizumab to platinum chemotherapy plus paclitaxel with bevacizumab in metastatic, persistent, or recurrent cervical cancer patients, regardless of PD-L1 expression status. Both OS and PFS will be evaluated as co-primary endpoints of the study. The BEATcc enrolled patients with a confirmed diagnosis of squamous cell, adenocarcinoma, or adenosquamous metastatic, recurrent or persistent cervical cancer not amenable to any curative treatment. It is important to highlight that the number of patients with adenocarcinoma was capped by 20% of the overall population, enriching the enrolled population with squamous histology. Women were not eligible if they have received prior systemic anticancer therapy in the advanced setting or they have a disease involving the bladder or rectum at the baseline pelvic MRI or any other condition that may contraindicate the use of bevacizumab which is mandatory for all enrolled patients. Available archival or fresh tumor samples for PD-L1 expression assessment will be mandatory. Patients were randomized in a 1:1 ratio to receive chemotherapy (cisplatin 50 mg/m^2 or carboplatin AUC 5 + paclitaxel 175 mg/m^2) and bevacizumab 15 mg/kg or atezolizumab 1200 mg flat dose in combination with the same chemotherapy regimen and bevacizumab, in a 21-day cycle until disease progression, unacceptable toxicity, death, withdrawal of consent or study termination by the Sponsor, whichever occurs first. In those cases, developing prohibitive toxicity or achieving complete response after $\geqslant$6 cycles, chemotherapy can be dropped out, continuing only on biologics therapy, namely bevacizumab and/or atezolizumab after discussion with the principal investigator. Randomization will be stratified by three factors: (1) prior concomitant chemo-radiation; (2) histology (SCC *versus* adenocarcinoma and adenosquamous); and (3) chemotherapy backbone (cisplatin *versus* carboplatin). It is of note that PD-L1 expression status was not included as a stratification factor; however, its analysis and association with clinical outcomes will be studied as part of a translational exploratory endpoint. The BEATcc trial has been run under the ENGOT umbrella alongside GOG-F and J-GOG, being GEICO the lead group on behalf of ENGOT. The trial was launched in Q3-2018 and met its recruitment target of 404 patients in August 2021. It is expected to be able to report the first read-out data by 2023.[41]

The FERMATA trial is an international randomized, double-blind, placebo-controlled, designed to test the efficacy and safety of the addition of BCD-100, an anti-PD-1 monoclonal antibody, to platinum-based chemotherapy with or without bevacizumab, in advanced (FIGO IVB) squamous cervical cancer patients, irrespective of PD-L1 expression status. The primary endpoint of the study is OS exclusively. A total of 316 subjects are expected to be recruited for the study. The planned duration of the trial is approximately 60 months (Q4 2019–Q4 2024).

Beyond the CheckMate-358 trial, the dual blockade anti-CTLA-4/PD-L1 has been investigated in the frontline setting, in combination with the standard therapy. Following the promising efficacy results of cadonilimab monotherapy as second or third line, a phase II clinical trial conducted in China (NCT04868708), reported an ORR of 79.3% regardless of PD-L1 expression in a cohort of 45 patients with persistent, recurrent, or metastatic cervical cancer treated with cadonilimab in combination with platinum-based chemotherapy $\pm$ bevacizumab.[42] Thus, a phase III trial of

cadonilimab *versus* placebo combined with platinum-based chemotherapy ± bevacizumab for first-line persistent, recurrent, or metastatic cervical cancer was launched in July 2021 (NCT04982237).

Role of ICIs in the locally advanced cervical cancer setting

Locally advanced cervical cancer (LACC) accounts for approximately 50% of newly diagnosed cases of cervical cancer (FIGO 2018 stages IB3 and IIA2-IVA). Weekly cisplatin concurrent to external beam radiotherapy (average dose of 45 Gy) followed by brachytherapy continues to be the standard treatment for LACC and has remained unchanged over the last two decades.[43,44] The 5-year OS is approximately 70% after completion of concurrent CRT,[45,46] but it is particularly poor in high-risk subgroups, namely those with stage III and IVA (FIGO staging 2018). Indeed, patients with pelvic and para-aortic nodal involvement showed a 5-year OS rate of 34% and 12%, respectively.[47–51]

Over the last decades, several strategies have been investigated to improve the poor prognosis of LACC patients, especially those at higher risk of progression and death.

Based on the provocative results shown by Peters *et al.* in the GOG 109 study,[52] the role of adjuvant treatment has been explored in several important trials. A phase III randomized trial, published by Dueñas-González *et al.*, enrolling LACC patients with FIGO 1997 stage IIB to IVA assessed a double approach, adding gemcitabine to cisplatin as concurrent with radiotherapy followed by gemcitabine monotherapy as maintenance .This approach showed to improve OS (HR 0.68; 95% CI, 0.49–0.95, $p = 0.0224$) compared with experimental arm but at the expense of increased toxicity[53]; a rate of grade 2–4 adverse effects of 86.5% *versus*. 46.3%, $p < 0.00$ in the experimental and standard arms, respectively. Despite being a positive trial, it remains difficult interpreting whether the survival benefit was attributable to either the concomitant administration of a platinum-doublet with radiotherapy, adjuvant chemotherapy, or both. This fact alongside a greater toxicity has contributed to its lack of acceptance among the scientific community[54] (Cochrane review 2014).

Recently, the OUTBACK trial was specifically designed to assess whether the addition of adjuvant carboplatin–paclitaxel after CRT would improve OS or PFS compares with the standard of care.[55] This phase III clinical trial included 926 patients with FIGO 2009 stage IB1 and node positive, IB2, II, IIIB or IVA, and were randomized in a 1:1 ratio to standard arm (CRT alone) or experimental arm (four cycles of paclitaxel plus carboplatin post-CRT). Both arms were well balanced regarding baseline characteristics. While CRT compliance was equal between arms, in the experimental arm, only 285 (62% of the total) completed the four planned cycles of adjuvant chemotherapy. The trial did not meet its primary endpoint, OS and PFS outcomes were similar in both arms: A 5-year-OS rate of 71% *versus* 72% (HR, 0.91; 95% CI, 0.70–1.18) and a 5-year-PFS rate of 61% *versus* 63% (HR, 0.87; 95% CI, 0.70–1.08); therefore, the LACC therapeutic approach remains the same as the last past decades.

In this scenario, immunotherapy has begun to gain importance as a potential strategy to improve clinical outcomes of LACC patients, based on a robust biological rationale and the fast-growing evidence for its use in both advanced/recurrent and frontline setting. Indeed, incorporating immunotherapy during and/or after concomitant CRT seems to be one of the best scenarios since it takes advantage of a more favourable immune tumor microenvironment induced by radiation and cytotoxic agents. Radiation therapy has shown not only to increase the cancer cell surface expression of MHC class I molecules, but may also increase the release of tumor-associated antigens, helping the immune system to recognize tumor cells increasing the immune cell infiltration.[56–58] Moreover, cisplatin demonstrates immunomodulatory properties, as it increases MHC class I expression, promotes proliferation and recruitment of effector cells and blocks immunosuppressive factors in the tumor microenvironment. Therefore, new strategies of combining cisplatin with immunotherapy such as ICIs may favor a synergistic effect.[59]

Based on to this scientific rationale, in the lung cancer disease, the PACIFIC trial showed that durvalumab (anti-PD-L1) maintenance in patients with unresectable stage III NSCLC without progressive disease after CRT improved significantly OS compared to placebo: median OS 47.5 months (95% CI, 38.1–52.9) and 29.1 months (95% CI, 22.1–35.1), respectively (HR, 0.72; 95% CI, 0.59–0.89).[60,61] Pembrolizumab has also

Table 1. Clinical trials evaluating ICIs in LACC.

Clinical trial	CALLA	KEYNOTE-A18	ATOMICC	ATEZOLACC	NiCOL
ClinicalTrials.gov	NCT03830866	NCT04221945	NCT03833479	NCT03612791	NCT03298893
Study design	Randomized, double-blind, global, placebo-controlled, phase III	Randomized, double-blind, placebo-controlled, phase III	Randomized, open-label, phase II	Randomized, open-label, phase II	Phase I
Estimated *N*	770	980	132	189	21
Population	Stages IB2–IIB with N+ or IIIA–IVA any node (FIGO 2009)	Stages IB2–IIB with N+ or III–IVA (FIGO 2014)	Stages IB2–IIB with pelvic N+, any stage with para-aortic N+ or III–IVA (FIGO 2009)	Stages IB1–IIA with pelvic N+, stages IIB–IVA, any stage with para-aortic N+ (FIGO 2009)	Stages IB2 to IVA with or without nodal involvement (FIGO 2009)
ICI	Anti-PD-L1 durvalumab	Anti-PD-1 pembrolizumab	Anti-PD-1 dostarlimab	Anti-PD-L1 atezolizumab	Anti-PD-1 nivolumab
ICI intervention and maximum duration of adjuvant therapy	Concurrent to CRT followed by maintenance up to 24 months	Concurrent to CRT during 5 cycles Q3W and maintenance Q6W for 15 cycles (20 months approx.)	Maintenance after response to concurrent CRT for up to 24 months	Concurrent to CRT followed by maintenance for 20 cycles (12 months approx.).	Concurrent to CRT Q2W and maintenance for 5 months
Primary endpoint	PFS	PFS and OS	PFS	PFS	Rate of DLT, secondary: ORR and PFS

CRT, chemoradiation; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

been explored in the locally advanced setting of head and neck SCC in combination with and following concurrent CRT. The addition of pembrolizumab was associated with a favorable trend toward improved event-free survival *versus* placebo plus CRT, but the difference did not reach statistical significance in the ITT population (the 24-month event-free survival rate was 63.2% for the pembrolizumab arm *versus* 56.2% in the placebo arm).[62]

Currently, several clinical trials are exploring the role of different ICIs in LACC setting (Table 1).

To date, CALLA study is the only clinical trial evaluating immunotherapy in the LACC setting with reported results. CALLA is a phase III, double-blind, placebo-controlled clinical trial, exploring the role of durvalumab with and following concurrent CRT. Randomized patients with LACC received (in a 1:1 fashion) durvalumab 1500 mg IV or placebo every 4 weeks for 24 cycles (Bradley J. Monk, presented at IGCS 2022). This study was run in a population of newly diagnosed high-risk LACC, namely FIGO 2009 stages IB2–IIB with positive lymph nodes and stages IIIA–IVA regardless node status. For concurrent chemotherapy, both cisplatin 40 mg/m^2 or carboplatin AUC 2 once a week per 5–6 weeks were allowed. Stratification factors were disease stage (FIGO IB2–IIB and positive lymph nodes, FIGO $\geq$ III and negative lymph nodes and FIGO $\geq$ III and positive lymph nodes) and world region. The primary endpoint was PFS assessed by the investigator according to RECIST 1.1. or histopathological confirmation of local tumor progression or death.

A total of 385 patients were assigned to each treatment arm. Demographics and baseline clinicopathological characteristics were globally well balanced. Most patients had squamous histology (83% in each arm) and PD-L1-positive tumors (>90% in each arm) according to the tumor area positivity score (SP263). Pelvic lymph node involvement rate (patients with at least

one positive lymph node were enrolled) was numerically lower in durvalumab arm (63.9%) compared to placebo arm (69.6%). Conversely, stage IVA and para-aortic lymph node involvement was slightly greater in the experimental arm (6.5% *versus* 4.9% and 12.2% *versus* 9.9%, respectively). Regarding CRT compliance, placebo arm seemed to have a lower concurrent chemotherapy compliance, 87% *versus* 90.1%. Pelvic external radiotherapy and brachytherapy delivery and biological total dose (Gy) did not differ substantially between arms, and 72% of patients in each arm completed radiotherapy in less than 60 days.

With a median follow-up of 18.5 months and 31% of data maturity, durvalumab in combination with and following CRT did not improve significantly PFS *versus* placebo (HR, 0.84; 95% CI, 0.65–1.08; $p = 0.174$). No benefit in terms of OS was observed either; however, it is important to stress that data maturity at data cutoff was only 17% . While PFS outcome was consistent across all analyzed subgroups, higher-risk patients, such as those with para-aortic lymph node involvement and stage III–IVA with positive lymph node, seemed to draw a greater benefit from the addition of durvalumab (HR, 0.60; 95% CI, 0.30–1.17) for para-aortic node positive and (HR, 0.71; 95% CI, 0.49–1.03) for stage III–IVA node positive. Regarding the safety profile, AEs of grade 3–4 occurred in 51.7% and 51% of patients in the durvalumab and placebo arms, respectively, so, it does not seem that durvalumab endangers the radiotherapy deliver.[63]

Despite a strong rationale, the CALLA trial did not meet its primary endpoint. Several factors may have influenced these disappointing results, such as the short follow-up with a low maturity of the survival data, patient selection and their risk of progression, or the adequacy of PFS as a primary endpoint. Indeed, immunotherapy may impact more likely on OS than PFS, as observed in other tumor types. Anyhow, the role of ICI in this disease setting is still to be determined in the upcoming years and the ongoing clinical trials exploring similar or identical approaches to CALLA trial will further corroborate or overcome these discouraging efficacy outcomes.

MK-3475-A18/KEYNOTE-A18/ENGOT-cx11/GOG-3047 is a randomized, double-blinded, phase III trial assessing the role of adding pembrolizumab to CRT in high-risk LACC. This study planned to enroll around 980 patients with stages IB2 to IIB with node-positive disease or stages III–IVA regardless of lymph node status (FIGO 2014). Patients are randomized to receive 3-weekly pembrolizumab or placebo concurrent to CRT for five cycles followed by 6-weekly pembrolizumab for up to 15 cycles (maintenance phase). This trial set two co-primary endpoints, PFS and OS. Recruitment is planned to end by Q42022.

The ATOMICC trial has a different approach. This is a randomized, open-label, phase II trial evaluating the efficacy of dostarlimab solely as maintenance *versus* no further treatment (standard of care) after complete or partial response to concurrent CRT in patients with high-risk LACC, namely FIGO 2009 stages IB2, IIA2, and IIB with at least two positives pelvic nodes, stages IIIA, IIIB, IVA or any stage with at least one positive para-aortic lymph node. Eligible patients must have received at least four doses of weekly cisplatin concomitant to radiotherapy. PFS was set as the primary endpoint. The trial is estimated to be closed for recruitment in Q1-2023. Results are expected to be released in Q1-2025.[64]

The ATEZOLACC is another randomized, open-label, phase II trial assessing the use of the anti-PD-L1 atezolizumab concurrently and after CRT. As the ATOMICC, this trial is being run in a high-risk LACC population, although patients with stage IB1 with pelvic nodal involvement and stage IVB with metastasis limited to the para-aortic lymph nodes are also eligible. Its primary endpoint is PFS as well.

Besides, nivolumab is being explored in a phase I clinical trial (NiCOL) that recruited 21 patients with LACC with stages IB2 to IVA regardless lymph node status. Nivolumab is administered concurrent and following to CRT for 6 months. Its primary endpoint is safety and secondary endpoints are ORR and PFS among others.

Novel immunotherapy approaches in cervical cancer

Beyond ICIs, there are several other immunotherapy approaches under investigation in the setting of advanced cervical cancer. Cancer therapeutic vaccines and cell-based therapy are among the most promising strategies.[14]

Prophylactic vaccines against HPV utilize capsid proteins from multiple high-risk HPV strains aiming at generating to a neutralizing antibody response to prevent subsequent HPV infection. Antibody-generating HPV vaccination has proved to be successful to prevent HPV-related cervical cancer in healthy individuals. Moreover, the well-established pathogenic implication of HPV in cervical cancer makes HPV E6 and E7 oncoproteins attractive target antigens for vaccine-based therapies in the setting of preinvasive or invasive disease. These cancer vaccines can facilitate T-cell priming generating both new antigen-specific T-cell responses and amplifying existing responses against tumor cells. Therapeutic HPV vaccines utilized in the clinic have used different technologies to deliver HPV-related antigens as well as various adjuvants to stimulate an immune response. Below, we discuss the vaccination strategies for the platforms most frequently tested in the clinic, namely peptide based, vector based (bacterial or viral), and DNA based. For the purpose of this review, we will focus on those clinical trials exploring this strategy, alone or combined with ICI in invasive disease.

Vector-based vaccines are genetically engineered live attenuated or inactive, either viral or bacterial vectors modified to express an antigen of interest. Their main interest in vaccine technology arises from the ease of their generation, scalability, and their ability to produce large amounts of antigens *in vivo*, eliciting a strong immune response. The risk of producing the original disease of the vector, especially in live attenuated vectors, does exist.

The phase III AIM2CERV trial was launched to evaluate the efficacy of ADXS11-001 (live attenuated *Listeria monocytogenes* immunotherapy bioengineered to secrete an HPV16-E7 fusion protein) administered in the adjuvant setting after completion of CRT in patients with high-risk LACC. Unfortunately, the study was put on hold by the FDA due to an inquiry into manufacturing procedures and it was finally closed in 2019 based on the funding company priorities and before full accrual was reached.

Peptide-based vaccines directly deliver short or long peptides encoding HPV oncoproteins. These have been shown, however, to be weakly immunogenic and need to be delivered with adjuvants to improve the potency of both cellular and humoral immune responses. It is important to underline that short peptides are HLA-restricted, while longer peptides avoid this need for HLA restriction, as they are processed intracellularly before being presented on MHC molecules.

ISA101 consists of 12 synthetic long peptides from the E6/E7 HPV16 capable of inducing HPV-specific T cells. A single-arm phase II trial (NCT02426892) explored the combination of ISA101 and nivolumab in patients with recurrent or metastatic HPV-16-positive cancer. Of the 24 patients enrolled in this study (among the enrolled patients, only one had advanced cervical cancer), the ORR was 33%, with a median DOR of 11.2 months. Interestingly, 3 out of 8 (38%) patients with objective response were without progression at 3 years. The median OS and PFS were 15.3 months and 2.66 months, respectively.[65] Following these preliminary results, two trials exploring ISA101 in different settings and combinations have been launched: A phase II, single-arm, open-label study (NCT04646005) assessing ISA101b in combination with cemiplimab in recurrent/metastatic HPV16-positive cervical cancer patients who have experienced disease progression after the first-line chemotherapy, and a phase I/II (NCT02128126) investigating the safety, tolerability and the HPV-specific immune responses of different doses of ISA101 vaccine with or without pegylated IFNα as combination therapy with carboplatin and paclitaxel ± bevacizumab.

PDS0101 is another HPV therapeutic peptide vaccine consisting of the immune-activating cationic lipid R-DOTAP and HLA-unrestricted HPV16 E6 and E7 peptides that have shown *in vivo* CD8+ T-cell induction and tolerable safety profile in a phase I study.[66] The IMMUNOCERV (NCT04580771) study is a single-arm phase II trial currently evaluating the safety and efficacy of CRT combined with the PDS0101 vaccine in treating LACC patients (stages IB3-IVA FIGO 2018). Moreover, an ongoing phase I/II trial (NCT04287868) is evaluating PDS0101 in combination with anti-PD-L1/TGFb trap (M7824), interleukin-12 in recurrent or metastatic HPV-positive tumors, including cervical cancer.

Finally, DNA vaccination is an approach that incorporates an antigen-encoding gene into a backbone of a bacterial plasmid. Its main advantage is the ability to activate both innate and adaptive immune responses. Upon its injection, the bacterial plasmid transfects myocytes and

triggers the expression of the antigen. The bacterial plasmid contains unmethylated CpG motifs, which act as adjuvant and trigger a robust dendritic cell-mediated TLR9-dependent innate immune response. Besides, these dendritic cells subsequently act as APCs and activate the adaptive immune response. The variability of the immune response to DNA vaccine is partially attributable to the expression of TLR9 on immune cells.

GX-188E is a DNA vaccine encoding the E6/E7 fusion protein of HPV subtypes 16 and 18, plus the immune-enhancer, Fms-like tyrosine kinase-3 ligand (FLT3L), with potential immunostimulating and antineoplastic activities. A phase Ib/II, open-label trial has been launched to evaluate the combination of GX-188E and pembrolizumab (NCT03444376) in previously treated patients with HPV-16/18-positive recurrent/advanced cervical cancer. A total of 60 patients were analyzed in the phase II treatment group. Results showed an ORR of 31.7% (19 of 60 patients) with 10.0% and 21.7% of complete and partial response rates, respectively. The median DOR was 12.3 months and OS was 17.2 months. Interestingly, responses were observed regardless of PD-L1 status (PD-L1 expression was evaluated using the PD-L1 IHC 22C3 pharmDx assay), with an ORR of 36.1% and 25% in the PD-L1-positive and -negative subgroups, respectively. Regarding the safety data, the combination therapy was found to be safe and tolerable with a similar safety profile to that of pembrolizumab monotherapy.[67]

VB10.16 is a therapeutic DNA vaccine composed of three parts, one encodes the E6/E7 fusion protein of HPV type 16, the second is a dimerization entity, and the third part encodes a protein that specifically binds to APCs, with potential immunostimulating and antineoplastic effects. A multicenter, open-label, phase IIa trial (NCT04405349) evaluated the safety and efficacy of VB10.16 in combination with atezolizumab in patients with advanced or recurrent non-resectable HPV16-positive cervical cancer. In an interim analysis, with a median follow-up of 6 months, the combination therapy yielded an ORR of 21% in the heavily pretreated population (minimum 2 prior lines of therapy), including two complete responses and six partial responses, and a disease control rate of 64%. Responses were observed in both PD-L1-positive and PD-L1-negative patients, with an ORR of 27% and 17%, respectively. Updated efficacy data from the trial are expected to read out during the first half of 2023.[68]

One of the main advances in the immunotherapy field is the adoptive cell transfer based on autologous T cells which showed encouraging responses in patients with advanced/recurrent cervical cancer. C-145-04 (NCT03108495) is an open-label, multicenter phase II trial assessing the safety and efficacy of LN-145 TIL therapy in patients with recurrent, metastatic, or persistent cervical carcinoma. This study contains five arms as follows: arm 1: LN-145 monotherapy in cervical cancer patients who had undergone at least one prior line of chemotherapy for advanced disease; arm 2: LN-145 monotherapy in patients that had also received treatment with an ICI in the setting of recurrent, metastatic, or persistent disease either as monotherapy or in combination; arm 3 (the United States only): LN-145 plus pembrolizumab in a cervical population who had not received prior lines of therapy in the advanced setting; arm 4: LN-145 monotherapy in a patient population not meeting the inclusion criteria of arms 1 and 2; and arm 5: patients who have been previously treated with LN-145 may be given a second treatment with TIL.

To obtain the TILs, tumors surgically harvested at local institutions were shipped to central facilities for TIL generation in a 22-day manufacturing process. The final LN-145 TIL product was then cryopreserved and shipped to sites. Patients receive 1 week of preconditioning lymphodepletion (cyclophosphamide and fludarabine) and a single LN-145 infusion, followed by up to six doses of IL-2 (600,000 IU/kg). For arm 3, patients were administered pembrolizumab, followed by lymphodepletion chemotherapy, then infused with their autologous TIL (LN-145) followed by pembrolizumab every 3 or 6 weeks post-IL-2 administration up to 24 months.

In arm 1, a total of 27 evaluable patients were finally included in the efficacy analysis. Preliminary efficacy results of this cohort were impressive, with an ORR of 44% (12/27) and a disease control rate of 89%, with 11/12 patients maintaining their response at a median follow-up of 3.5 months.[69] Following these promising results, in 2019, FDA granted LN-145 breakthrough therapy designation for the treatment of pre-treated advanced cervical cancer patients. Besides, 14 treatment-naïve recurrent, metastatic or persistent cervical cancer patients were enrolled

in arm 3, receiving the combination of LN-145 and pembrolizumab, as previously indicated. The reported ORR was 57.1% with a disease control rate of 92.9% (median study follow-up of 7.6 months), and a manageable toxicity profile.[70]

Genetically engineered T cell therapy, namely T-cell receptor-modified T cells (TCR-Ts) and chimeric antigen receptors T cells (CAR-T) has represented a therapeutic breakthrough for hematologic malignancies and is now being investigated for the treatment of HPV-associated carcinomas.

TCR-engineered T cells are generated by transduction of T cells with a single TCR demonstrated to recognize a specific tumor antigen in an HLA-dependent manner. Given the reliance of this technology on TCR–MHC pairing, HLA matching of patients is required for this approach and also an important limitation. Several early-phase trials showed preliminary data of TCR-Ts targeting different tumor-specific antigens such as proteins E6 (NCT02280811, NCT03578406), and E7 (NCT02858310) of high-risk HPV and MAGE-A3 (NCT02153905, NCT02111850).

CAR-T-cell therapy in HPV-mediated cancers is a promising strategy, as it targets surface antigens directly and thus avoids the need to target MHC-bound antigens, overcoming defects in the antigen presentation pathway seen in HPV-related malignancies. Nevertheless, the identification of recurrent and unique cell-surface antigens outside of MHC-bound viral antigens in HPV-related malignancies presents a major challenge to this approach. CAR-T therapies targeting antigens such as mesothelin (NCT01583686), CD22 (NCT04556669), or others (NCT03356795) are still underway in the cervical cancer population.[71]

Conclusions

The introduction of immunotherapy in the treatment landscape of recurrent, persistent, and metastatic cervical cancer has represented a major breakthrough for this poor prognosis population. Two well-designed randomized phase III trials have demonstrated a clinically and statistically significant survival benefit of adding ICIs in both post-platinum progression and frontline settings, respectively. Beyond this, several ongoing clinical trials will define the role of immunotherapy in the high-risk locally advanced setting in the next future, although preliminary results from CALLA trial resulted disappointing. Promising clinical efficacy data are now emerging from early-phase clinical trials investigating novel approaches of immunotherapy in cervical cancer, such as therapeutic HPV vaccination and adoptive cell transfer.

It is important to underscore that a significant proportion of patients do not draw a significant clinical benefit from ICIs, revealing the presence of primary mechanisms of resistance, which have not been well identified yet. Indeed, patient selection for immunotherapy approaches remains challenging, and further research on predictive biomarkers beyond PD-L1 status appears to be critical in the upcoming years. Translational research aiming at analyzing the immune tumor microenvironment and its dynamics may be essential to uncover potential resistance, better stratify our patients, and develop novel therapeutic strategies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Acknowledgements

Not applicable.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Research articles selected for this review were obtained from scientific journals and congress abstracts and presentations, including ASCO, ESMO, and IGCS.

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