Biomolecules and Biomedicine
ISSN: 2831-0896 (Print) | ISSN: 2831-090X (Online)

Journal Impact Factor® (2023): 3.1
CiteScore® (2023): 7.4
www.biomolbiomed.com | www.blog.bjbms.org

REVIEW ARTICLE

Pezer Naletilić et al: Immunotherapy of cervical cancer

The immunotherapy breakthroughs in cervical cancer: Focus on potential biomarkers and further therapy advances

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DOI: https://doi.org/10.17305/bb.2025.12597

ABSTRACT

Despite the well-established role of human papillomavirus (HPV) as the primary cause of cervical cancer (CC) and the existence of an effective HPV vaccine, over half a million women are diagnosed with CC globally each year, with more than half of them dying from the disease. Immunotherapy has rapidly become a cornerstone of cancer treatment, offering substantial improvements in survival rates and reducing treatment-related side effects compared to traditional therapies. For the past 25 years, chemoradiotherapy (CRT) has been the standard treatment for locally advanced CC. However, while adjuvant chemotherapy has failed to improve outcomes in locally advanced CC, the integration of neoadjuvant chemotherapy (NACT) with CRT, as well as chemoimmunoradiotherapy followed by consolidation immunotherapy, has transformed treatment strategies, demonstrating superior efficacy compared to CRT alone. In the first-line treatment of CC, adding pembrolizumab to platinum-based chemotherapy, either with or without bevacizumab, has significantly improved outcomes compared to platinum-based chemotherapy and bevacizumab alone. This review explores the current landscape of immunotherapy and biomarker advancements in CC. Furthermore, we discuss promising future directions, including the potential of personalized immunotherapy approaches and novel combination therapies to further enhance treatment efficacy and improve prognoses for patients with CC.

Keywords: Cervical cancer; CC; immunotherapy, immune checkpoint inhibitors; ICIs; biomarkers

INTRODUCTION

Cervical cancer (CC) is a disease of young women, and even though it is a highly preventable disease, it remains the 4th most common cancer globally in both incidence and mortality (1). The number of new cases was 661,021, and 348,189 deaths were expected worldwide in 2022 (1). More than 70% of mortality from CC occurs in countries of low and medium socioeconomic development, in which CC ranks second in incidence and mortality (1). This can be partially explained by the unequal availability of prophylactic vaccination, inadequate screening programs, consecutive stage shift to the more advanced disease at diagnosis, and the lack of appropriate treatment options through the lines of therapy. In Europe, approximately 61,100 new cases of CC are diagnosed annually, with 25,800 related deaths each year (2). The most critical risk factor for developing CC is infection with high-risk human papillomavirus (HR-HPV) types, mainly HPV-16 and HPV-18 (3). The disease is often diagnosed in developing countries in stages III/IV(4–6). In contrast, in developed countries, it is diagnosed in stage I/II, underscoring the urgent need for better-organized early detection programs (7,8). Evidence from a systematic review and meta-analysis in high-income countries underscores the effectiveness of HPV vaccination programs (9). After 5–8 years, a substantial decline in the prevalence of HPV 16 and 18, the most common causes of cervical cancer, was observed. Specifically, the review demonstrated an 83% reduction in these high-risk HPV types among vaccinated girls aged 13–19 and a 66% decrease among vaccinated women aged 20–24.

CC therapy depends on the stage of the disease, and the main treatment options include surgery, radiotherapy, chemotherapy, and, more recently, immunotherapy and targeted therapy. Until the development of new therapeutic modalities, the success of treatment of recurrent and metastatic disease (r/m CC) was modest, and the median duration of survival with distant metastasis was less than 12 months (10). The recent incorporation of immune checkpoint inhibitors (ICI) in the therapeutic algorithm of CC has revolutionized cancer treatment and has

become one of the most promising treatment approaches in CC. Accordingly, identifying robust biomarkers to guide these novel treatments has become a priority, as discussed next.

BIOMARKERS IN CC

Biomarkers in oncology are biological indicators that reveal the presence, progression, or characteristics of cancer and are crucial for diagnosis, prognosis, treatment decisions, and monitoring therapeutic responses. They can be genetic, epigenetic, proteomic, glycomic, metabolomic, transcriptomic, or image-based. Like most other cancers, biomarkers in cervical lesions, including invasive CC, improve early detection, diagnosis, prognosis, and treatment response. HPV DNA testing is now considered the primary screening test for detection of cervical lesions, rather than visual inspection with acetic acid (VIA) or cytology (Pap smear) (moderate-certainty level of evidence). This applies to all women > 30 years, irrespective of the risk for cervical lesions and subsequent cervical cancer (11).

The most common histologic subtype of CC is squamous cell carcinoma (SCC). Almost all (> 95%) cervical SCCs are HPV-associated (positive). However, HPV-independent SCC, although rare, has been described in the literature (12). Therefore, all cervical squamous lesions, including SCC, are classified into HPV-associated and HPV-independent subtypes (13). The second most common histologic subtype of CC is adenocarcinoma. Similar to SCC, a new WHO classification of CC also recognizes HPV-associated and HPV-independent cervical adenocarcinomas (14). In contrast to SCC, cervical adenocarcinomas appear to be less associated with HPV infections (15,16). A subset of cervical adenocarcinomas may also be associated with an autosomal-dominant syndrome called Peutz-Jeghers syndrome (#OMIM 175200). The syndrome is caused by germline mutations of the *STK11* gene and is associated with various benign conditions (e.g., hamartomatous gastrointestinal polyps and mucocutaneous pigmentations) and increased risk of various cancers (17).

HPV-associated and HPV-independent CC cannot be reliably distinguished based on morphologic criteria alone. Therefore, biomarkers are required for this subclassification. The most common biomarker is p16INK4a (p16), a surrogate marker for high-risk HPV infections (e.g., HPV-16, HPV-18). p16 expression in cervical lesions, including cancer, is tested by immunohistochemistry (IHC). Almost all HPV-associated CC exhibit a strong and diffuse nuclear and cytoplasmic p16 overexpression by IHC (18). A strong and diffuse p16 positivity in cervical lesions indicates a transcriptionally active HPV infection, but cases of p16 and HPV-negative cervical lesions, including CC, have been increasingly recognized and reported in the literature (19–21).

The clinical use of p16 IHC is frequently accompanied by the Ki-67 IHC staining (MIB1 antibody), which indicates cellular proliferation. Combined (dual) p16/Ki-67 staining may be particularly useful in assessing the degree of cervical dysplasia, but Ki-67 expression alone is not enough, as it does not correlate with HPV infections. The combined use of p16/Ki-67 IHC is also useful in diagnosing and grading cervical glandular intraepithelial disease (precursors of cervical adenocarcinoma) (22). In addition, HPV DNA testing and E6/E7 mRNA detection have become essential for identifying persistent high-risk HPV infections associated with CC development and progression (cervical intraepithelial lesions, CIN1-3) (23). HPV DNA testing also exhibits superior sensitivity compared with cervical cytology alone.

Commonly observed genomic alterations in SCCs are those within the PI3K/MAPK and/or TGF-β signaling pathways (24). The most frequently mutated genes in SCC are *ERBB3 (HER3)*, *SHKBP1*, *CASP8*, *HLA-A*, and *TGFBR2* (24). None of these genomic biomarkers has been approved as predictive for precision oncology purposes in CC patients, underscoring the need for new predictive biomarkers in the era of immunotherapy.

IMMUNOTHERAPY IN CC

ICI in CC

Immunotherapy with ICI is an anti-cancer treatment directed against the immune suppression in the tumor microenvironment, which could lead the immune system to target and eliminate cancer cells. Specifically, T-cell activation requires two signals: antigen presentation via major histocompatibility complex (MHC) on antigen-presenting cells (APC) to the T-cell receptor, and co-stimulation by B7 on APC binding CD28 on T-cells, to fully activate T-lymphocytes against a specific target. Conversely, when the programmed death receptor-1 ligand (PD-L1), an inhibitory transmembrane protein, is present on the surface of APC or cancer cells, it binds to programmed death receptor-1 (PD-1) on T-lymphocytes, suppressing the T-cell activity and dampening the immune response. PD-L1 expression on cancer or immune cells has emerged as a predictive biomarker for ICI in many but not all tumor sites. In CC, PD-L1 expression assessed by IHC has been described as positive in ~30-70% of CC (25). The introduction of ICI has marked a significant advancement in the treatment of cancers such as melanoma and lung cancer, revolutionizing the therapeutic landscape for these malignancies (26). By targeting immune regulatory pathways like PD-1/PD-L1, ICIs have demonstrated notable efficacy across various cancer types, leading to their approval for multiple indications and transforming patient outcomes. The development of companion diagnostic tests (CDx) to identify individuals most likely to benefit from these therapies has further personalized and optimized their use in clinical practice. In CC, immunotherapy with ICI has gained approval for second-line treatment, first-line treatment of recurrent or metastatic disease, and locally advanced CC (Figure 1).

The role of immunotherapy in previously treated recurrent, metastatic CC

Before immunotherapy, the standard treatment for recurrent, persistent, or metastatic CC after first-line failure was chemotherapy (27). There was little benefit with second-line or further systemic therapies, with modest clinical efficacy: an overall response rate (ORR) of less

than 20%, median progression-free survival (PFS), and overall survival (OS) of 3.3 and 6.7 months, respectively (27, 28).

The first evidence for the clinical activity of ICIs in this setting was based on the phase Ib KEYNOTE-028 trial. This study examined the efficacy and safety of pembrolizumab (anti-PD-1 monoclonal antibody) in patients with PD-L1-positive (≥ 1% by modified positive score) metastatic solid tumors, of which there were 24 patients in the cervical cancer cohort (96% were SCC). The ORR was 17% (95% CI, 5-37%) and the median duration of response (DOR) was 5.4 months (95% CI, 4.1–7.5 months) (29). KEYNOTE-158 revealed similar results (30). The study investigated the safety and efficacy of pembrolizumab in patients with different metastatic tumors regardless of PD-L1 status. Ninety-eight patients were in the cohort, 82 samples were PD-L1 positive, defined as combined positive score (CPS) ≥1% with previously treated advanced CC. The ORR was 12.2% (95% CI, 8.0–22.8%) in the whole cohort, and 14.6% in the patient subgroup with PD-L1-positive tumors. The median PFS was 2.1 months (95% CI, 2.1–2.2 months), and the OS was 9.3 months (95% CI, 7.6–11.7 months). The safety profile was consistent with that seen for pembrolizumab in other tumor types (30). Based on these results, the FDA approved pembrolizumab for patients with persistent, r/m CC whose tumors express PD-L1 ≥1%. ICI and ADC regimens approved to date by the FDA and EMA for the treatment of cervical cancer are summarized in Table 1.

Beyond pembrolizumab, another ICI, cemiplimab, demonstrated improved survival in second-line treatment. Cemiplimab, a programmed cell death-1 receptor monoclonal antibody, significantly improved PFS and OS compared to chemotherapy in a phase III randomized study EMPOWER-Cervical 1/GOG-3016/ENGOTcx9 (27). In this study were enrolled patients with r/m CC, SCC, or adenocarcinoma who had progressed after first-line platinum-based chemotherapy, regardless of PD-L1 status. In the overall trial population, the mOS was longer in the cemiplimab group (12.0 months vs. 8.5 months, hazard ratio (HR) 0.69; 95% CI, 0.56 to

0.84; $P < 0.001$), with consistent benefits in both histologic subgroups. PFS was also longer in the cemiplimab group in the overall patient population (HR 0.75; 95% CI, 0.63 to 0.89; $P < 0.001$). Grade ≥3 adverse events were less frequent in the cemiplimab group compared to the chemotherapy group. Cemiplimab was approved by the EMA for r/m CC, regardless of PD-L1 status, in patients who have progressed on platinum-based chemotherapy.

These trials established single-agent anti-PD-1 therapy as a new standard after chemotherapy failure, setting the stage for exploring combination immunotherapies.

Is dual immunotherapy better?

Several phase I/II trials investigated anti-PD-(L)1 in combination with anti-CTLA-4 blocking cytotoxic T-lymphocyte antigen-4 (CTLA-4) or anti-TIGIT blocking T-cell immunoreceptor with Ig and ITIM domains (TIGIT) in advanced CC. TIGIT is an inhibitory target molecule expressed in T cells and natural killer cells (31).

CheckMate 358 is an open-label, multicohort phase I/II trial that evaluated the efficacy of nivolumab, alone or in combination with ipilimumab, in patients with virus-related tumors (32). Patients with HPV-negative tumors were excluded from the study. The CC cohort enrolled patients with r/m SCC of the cervix and up to two previous systemic therapies. Patients were randomized into three groups: nivolumab monotherapy 240 mg, nivolumab plus ipilimumab every six weeks (Nivo 3 mg/kg + Ipi 1 mg/kg), and nivolumab plus ipilimumab every three weeks for four cycles, followed by nivolumab every two weeks (Nivo 1 mg/kg + Ipi 3 mg/kg). According to preliminary findings, nivolumab showed durable anti-tumor responses, and the combination of nivolumab and ipilimumab showed promising clinical activity as well. Nivolumab monotherapy yielded an ORR of 26%, mPFS of 5.1 months, and mOS of 21.6 months. The two combination arms showed ORRs of 31% (Nivo3 + Ipi1) and 40% (Nivo1 + Ipi3), with the Nivo1 + Ipi3 arm achieving the longest mPFS of 7.2 months and mOS of 24.7 months, but also more pronounced toxicity.

Cadonilimab is a novel, bispecific immune checkpoint inhibitor that targets PD-1 and CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4). By targeting both pathways, cadonilimab may provide synergistic effects while minimizing side effects compared with combining two separate monoclonal antibodies. Cadonilimab was approved in China in 2022 for second-line treatment of r/m CC. The approval is based on the positive results of the phase II clinical study, which assessed the efficacy and safety of cadonilimab in patients with r/m CC who had progressed on or after two or fewer previous chemotherapy regimens, with or without bevacizumab, regardless of PD-L1 status (33). The primary endpoint was ORR, which was 33%; the mPFS and mOS were 3.75 months and 17.51 months, respectively. Subgroup analysis showed that in PD-L1-positive patients, the ORR was 43.8%, with a mPFS of 6.34 months. The mOS was not reached. The incidence rate of grade ≥3 adverse events was 27%, which indicates that cadonilimab may have a more favorable safety profile than dual therapies combining separate PD-1 and CTLA-4 inhibitors. A phase III trial is ongoing and explores the combination of cadonilimab plus concurrent chemoradiotherapy (CCRT) for treating locally advanced CC (LACC) (34).

Balstilimab (PD-1 inhibitor) and zalifrelimab (CTLA-4 inhibitor) have been investigated in patients with r/m CC who had progressed on first-line therapy (35). The ORR was 25.6% in the whole cohort, and 32.8% in the patient subgroup whose tumors expressed PD-L1 ≥1%. In patients with squamous cell histology, the ORR was 32.6%. Further investigation of the balstilimab and zalifrelimab combination in this setting is ongoing.

Tiragolumab, an anti-TIGIT antibody in combination with atezolizumab was investigated in the SKYSCRAPER-04, phase II trial (NCT04300647). The results of the study did not improve ORR compared to those patients treated with atezolizumab alone (36). The combination of pembrolizumab and vibostolimab (anti-TIGIT antibody) was evaluated in the phase 1 KEYVIBE-001 trial (NCT02964013) and the phase 2 KEYVIBE-005 trial

(NCT50007106), but it did not improve ORR, PFS, or OS compared to pembrolizumab alone in metastatic CC with PD-L1 CPS ≥1 (37,38). Given these results, the combination has no future in treating patients with PD-L1–positive recurrent CC. Tislelizumab (anti-PD-1) and ociperlimab (anti-TIGIT) are being investigated in combination for r/m CC as part of the phase 2 AdvanTIG-202 trial. The study has begun enrollment, and recruitment is ongoing (39).

Bintrafusp alfa is an innovative immunotherapy agent representing a bifunctional fusion protein. It combines two mechanisms: it acts as a "trap" for TGF-β, a key cytokine that promotes tumor growth, and simultaneously blocks the PD-L1 protein. In the phase II trial of 146 patients with r/m CC who had disease progression during or after platinum-based chemotherapy, the confirmed ORR was 21.9% with manageable toxicity (40).

The lack of superiority of any investigated immunotherapy combinations over the mono-immunotherapy approach and their combinations with existing treatment modalities highlight the complexity of the tumor microenvironment. This suggests that further research is needed to determine the optimal timing and which combined approaches may offer benefits. This also highlights the importance of further evaluation of biomarkers to identify subgroups that may benefit from combined approaches to immunotherapy, and additional studies are needed to determine the safety and efficacy of these combinations in patients who have already been exposed to immunotherapy, as previous research has been conducted in immunotherapy-naive patients.

Immunotherapy as a first-line treatment for recurrent, metastatic CC

In 2021, the FDA approved pembrolizumab in conjunction with chemotherapy, either with or without bevacizumab, for patients with r/m CC with PD-L1 expression (CPS ≥1), based on the KEYNOTE-826 research results (Table 1). The KEYNOTE-826 trial was created to assess the effectiveness of pembrolizumab as a first-line treatment for patients with r/m CC, regardless of PD-L1 expression, when combined with chemotherapy, either with or without

bevacizumab. In advanced CC, PD-L1 positivity (CPS ≥1) was reported at 83.7% in the KEYNOTE-158 trial and 88.8% in the KEYNOTE-826 trial (30,41). The mPFS for patients with PD-L1 >1% (CPS ≥1) was 8.2 months for the placebo group and 10.4 months for the pembrolizumab group (HR 0.62; 95% CI, 0.50 to 0.77; $P < 0.001$). PFS in the intent to treat (ITT) group was 10.4 and 8.2 months, respectively (HR 0.65; 95% CI, 0.53 to 0.79; P<0.001). Pembrolizumab demonstrated a statistically significant and clinically meaningful survival benefit. At 24 months of follow-up, the OS rate in the PD-L1 >1 group was 53% with pembrolizumab compared to 41.7% with placebo (HR 0.64; 95% CI, 0.50 to 0.81; $P < 0.001$). In ITT population, the OS rates were 50.4% and 40.4% for pembrolizumab and placebo, respectively (HR 0.67; 95% CI, 0.54 to 0.84; $P < 0.001$). The safety profile showed slightly higher rates of anemia and neutropenia in the pembrolizumab group (41). After a median follow-up of over three years, the pembrolizumab extended OS and PFS in the CPS ≥1 and ITT populations in all subgroups (determined by histologic type, previous use of bevacizumab, and chemoradiotherapy treatment). The mOS in the PD-L1 CPS ≥1 population was the same for both bevacizumab-treated (HR 0.62; 95% CI 0.45-0.87) and bevacizumab-untreated (HR 0.67; 95% CI 0.47-0.96) subgroups. Pembrolizumab resulted in a mOS of 24.4 months for squamous histology compared to 14.2 months with placebo (HR 0.60; 95% CI 0.46-0.79); for non-squamous histology, mOS was not reached (NR) in pembrolizumab group compared to 23.5 months in placebo group (HR 0.70; 95% CI 0.41-1.20); HR 0.56 (95% CI 0.39-0.81) and HR 0.72 (95% CI 0.52-1.00) with and without previous CRT. Additionally, HR for OS favored the pembrolizumab group across all ITT population subgroups. Over three years of follow-up revealed no additional safety findings (42).

In line with the benefits observed with bevacizumab in KEYNOTE-826, the BEATcc trial, a phase III study, evaluated the addition of atezolizumab, an anti-PD-L1 ICI, to a standard regimen of chemotherapy and bevacizumab in patients with r/m CC irrespective of PD-L1

status. Atezolizumab and standard therapy had mPFS of 13.7 and 10.4 months, respectively (HR 0.62; 95% CI 0.49–0.78); $p < 0.0001$); mOS were 32.1 and 22.8 months (HR 0.68; 95% CI 0.52–0.88; $p = 0.0046$). In the atezolizumab group, 79% of patients experienced adverse events of grade >3, whereas, in the control group, 75% did (43).

Cadonilimab has shown promising results in the first-line treatment of r/m CC in trials conducted in China. The effectiveness of using cadonilimab in combination with standard chemotherapy, either with or without bevacizumab, as a first-line treatment for r/m CC was evaluated in the phase II trial COMPASSION-13 (44). With an ORR of 92.3% in patients who received cadonilimab, chemotherapy, and bevacizumab, this trial showed encouraging findings. Another study reported an ORR of 71.4% with cadonilimab in PD-L1-negative patients, showing an even higher response rate of 80% (45). In real-world settings, cadonilimab demonstrated an ORR of 43% and a disease control rate (DCR) of 77.4% (46). The COMPASSION-16, phase III trial further evaluated cadonilimab in combination with first-line chemotherapy, with or without bevacizumab, in patients with persistent, recurrent, or metastatic CC (47). The addition of cadonilimab significantly improved PFS and OS compared to the placebo group. Median PFS was 12.7 months in the cadonilimab group versus 8.1 months in the placebo group (HR 0.62; 95% CI 0.49–0.80; $p < 0.0001$). Median OS was not reached in the cadonilimab group (27.0 months to not estimable) compared to 22.8 months in the placebo group (HR 0.64; 95% CI 0.48–0.86; $p = 0.0011$). Together, these data suggest that adding PD-1/CTLA-4 bispecific immunotherapy to first-line chemotherapy (± bevacizumab) can substantially improve outcomes, offering a potential new treatment option pending broader regulatory review.

The role of immunotherapy for locally advanced CC

Over the last twenty years, the mainstay of care for LACC has been concurrent chemoradiotherapy followed by brachytherapy. Concurrent chemoradiotherapy had a

substantial 5-year survival advantage of about 6% (HR 0.81, p<001) when compared to radiotherapy alone, according to five major, randomized trials that investigated the addition of chemotherapy to pelvic radiation. Also, chemoradiotherapy enhanced disease-free survival and decreased both local and distant recurrence (48–52). Recurrence rates remain high, about 40% of patients experience a recurrence of the disease within five years, and 5-year OS remains around 65-70% (53). Using methods like image-guided radiation therapy (IGRT) and intensity-modulated radiation therapy (IMRT)/volumetric arc therapy (VMAT), significant progress has been made in the treatment of locally progressed CC. With these improvements, survival has potentially increased, and treatment-related morbidity has decreased, but without significant impact on outcomes on the global scene (54).

New strategy trials are ongoing in locoregional disease, like studies using PD-L1 ICI (atezolizumab and durvalumab) or PD-1 ICI (nivolumab, pembrolizumab) in the context of LACC. Pembrolizumab in conjunction with chemoradiotherapy is being investigated in the ENGOT-cx11/GOG-3047/KEYNOTE-A18 study, a phase III clinical trial, to treat high-risk, LACC, stage IB2–IIB with node-positive disease or stage III–IVA irrespective of the nodal state, histologically proven carcinoma (FIGO 2014). The results showed that as compared to chemoradiotherapy alone, pembrolizumab significantly increased PFS and OS. The median follow-up period was 17.9 months, and the PFS was 67.8% in the pembrolizumab–chemoradiotherapy group and 57.3% in the placebo–chemoradiotherapy group (HR = 0.70; 95% CI, 0.55-0.89; *P* = 0.0020). Neither group reached the mOS; the 36-month OS was 74.8% in the placebo–chemoradiotherapy group and 82.6% in the pembrolizumab–chemoradiotherapy group (HR 0.67; 95% CI 0.50–0.90; *p* = 0.0040). Hematological toxicity was the most common adverse event, with no noticeable difference between the two groups (49). According to the findings of the ENGOT-cx11/GOG-3047/KEYNOTE-A18 study, the first positive randomized phase III study in this patient population since 1999, pembrolizumab in combination with

chemoradiotherapy could be the new standard of care for patients with LACC. In 2024, the FDA approved pembrolizumab combined with chemoradiotherapy for patients with LACC (stages III and IV, FIGO 2014) (Table 1). The CALLA trial is a phase III, multicenter trial that examines the efficacy of combining durvalumab with chemoradiotherapy as a treatment for patients with LACC (adenocarcinoma, squamous, or adenosquamous), stage IB2-IIB lymph node-positive, or stage ≥ III irrespective of the nodal state. However, the trial results did not indicate a substantial improvement in PFS, which was the study's primary goal. Durvalumab had a 12-month PFS of 76%, compared to 73.3% for placebo (HR 0.84; 95% CI 0.65-1.08; p = 0.17). There was no significant difference in toxicity between the two investigated groups (55). Possible reasons for the negative results of the CALLA study are the small follow-up period, PFS as the primary objective of the trial, a broader population of patients with locally advanced stage disease was included, the patients in KEYNOTE-A18 were a higher-risk population, and there were no selected subgroups that would potentially have more significant benefit (e.g., those with a high level of PD-L1 expression). The results of the CALLA study emphasize the need for a better definition of biomarkers and a more exact selection of patients who may benefit from immunotherapy in combination with regular treatment options. Nevertheless, we are eagerly awaiting the most important outcome of this trial, the OS results.

The NiCOL phase 1 trial aims to assess the safety and recommended trial dose of concurrent nivolumab with definitive CRT, followed by nivolumab, as maintenance treatment in 16 patients with LACC. Initial results were positive: ORR was 93.8% (95% CI: 69.8%-99.8%), and 2-year PFS was 75% (95% CI: 64.2%-100%) (56). The promising results and safety of nivolumab in this study indicate the need for further studies aimed at investigating the role of nivolumab in the treatment of LACC.

The ATEZOLACC trial is a phase II, open-label study examining the effectiveness of atezolizumab concurrently and after CCRT in high-risk patients (IB1-IIA with positive nodes,

stages IIB-IVA, and any stage with para-aortic positive lymph nodes). The primary endpoint is PFS, and the first results are awaited (57).

Another approach being tested is consolidation immunotherapy after completing chemoradiation. The ATOMICC trial is a double-blind, phase II trial that has a slightly different goal, investigating the efficacy of dostarlimab as a consolidation treatment for those with locally advanced, high-risk CC who responded partially or completely to chemoradiation. Its goal is to evaluate whether dostarlimab can reduce recurrence and improve survival compared to follow-up without additional treatment after response to CRT. Recruitment is closed, and results are awaited (58).

Is it time for neoadjuvant immunotherapy in CC?

According to the INTERLACE trial, patients with LACC who received induction chemotherapy followed by standard chemoradiation against standard chemoradiation alone had impressive outcomes. Following a median follow-up of 67 months, the 5-year PFS between the groups receiving induction chemotherapy and chemoradiotherapy was 72% and 64%, respectively (HR 0.65, 95% CI 0.46–0.91, p = 0.013). The group receiving induction chemotherapy and chemoradiotherapy had an 80% 5-year OS, while the group receiving chemoradiotherapy alone had a 72% 5-year OS (HR 0.60, 95% CI 0.40–0.91, p = 0.015).(59).

Neoadjuvant immunotherapy is a developing strategy in the treatment of many cancers, and this approach could also lead to similar breakthroughs in CC (60).

Neoadjuvant camrelizumab plus chemotherapy is being investigated in patients with LACC (IB3 to IIB/IIIC1, PD-L1 positive, with a tumor diameter ≥4 cm) in the NACI study (NCT04516616), a single-arm, phase II clinical trial. Patients who had a complete or partial response underwent major surgery, whereas those with progressing or stable disease received concomitant chemoradiotherapy. At the data cutoff, the median follow-up was 11 months, and

the ORR was 98% (95% CI 92–100). No serious adverse events occurred (61). The immune-based neoadjuvant therapy is currently being studied in two further trials. The first is the NCT04799639 trial, which recruited patients with stage IB3 and IIA2 CC on neoadjuvant chemotherapy consisting of paclitaxel, cisplatin, and sintilimab (PD-1 inhibitor), for three cycles before undergoing radical surgery. The ORR was 95%, and by the data cutoff in February 2024, 33% of patients had achieved the pathological complete response. The anticipated date of study completion is March 2026 (62). Notably, all these neoadjuvant immunotherapy trials are reporting high response rates (≈95% or higher), hinting at the potential of this strategy to shrink tumors pre-surgery. Longer follow-up is needed to see if this translates to better survival.

The MITO CERV 3 trial (NCT04238988), a phase II, single-arm, multicenter study, is the second one investigating the use of pembrolizumab in combination with carboplatin and paclitaxel as neoadjuvant therapy for LACC (stages IB2-IIB, PD-L1-positive tumors). Maintenance therapy with pembrolizumab was given to patients after the surgery if there was no disease progression. The study is ongoing, and results are awaited (63).

Neoadjuvant immunotherapy in combination with chemotherapy shows promising antitumor activity with manageable safety profiles, and this approach may improve rates of complete pathological responses and event-free survival in patients with LACC. Future research should focus on identifying which patients are most likely to benefit based on predictive biomarkers, as well as establishing the optimal timing, sequencing, and integration of these therapies with current neoadjuvant or concomitant treatment regimens.

New treatment approaches

Although treatment with ICI has been most extensively studied in CC with very promising results, numerous alternative approaches and therapeutic strategies are under investigation. The two most promising approaches are cell-based treatment and therapeutic vaccinations (64).

Therapeutic vaccines

Therapeutic vaccines for HPV represent an innovative approach to treating HPV infections and related diseases, such as CC and other malignancies. Therapeutic vaccinations aim to cure HPV-caused lesions or infections that have already occurred, whereas prophylactic vaccines are intended to prevent HPV infection. Therapeutic vaccines most commonly target E6 and E7 oncoproteins, which are involved in the harmful process of cellular transformation and stimulate T-cell immunity (especially CD8+ cytotoxic T cells) to kill infected or malignant cells. More than 20 therapeutic HPV vaccine candidates are presently in various phases of research, with several of them undergoing clinical trials. Some therapeutic vaccines, such as VGX-3100, are currently in the latter phases of clinical research and show efficacy in treating precancerous CIN 2/3 lesions, but none have yet received widespread regulatory approval for cervical lesions/cancer treatment (65). The effectiveness and safety of PDS0101, an HPV-specific T-cell-activating immunotherapy, are being assessed in the phase II IMMUNOCERV trial (NCT04580771), in combination with chemoradiotherapy for patients with locally advanced HPV-associated CC (stage IB3 to IVA). Initial findings indicated a favorable safety profile, an 88% complete metabolic response rate on post-treatment imaging, an 89% DFS after one year, and a 100% OS (66). Further updates on long-term outcomes are expected.

Therapeutic vaccines hold great promise for patients with advanced or recurrent CC, as well as for those with precancerous lesions caused by persistent HPV infection. They have the potential to become a key part of the treatment for HPV-related diseases, considerably decreasing HPV-related malignancies' incidence and mortality.

ICI + vaccine combinations

The combination of ICI and therapeutic vaccines represents an innovative and promising approach to the treatment of CC, and the effectiveness of this combination is presently being studied in clinical trials. Atezolizumab plus the HPV16 vaccine VB10.16 showed promising

results in HPV16-positive metastatic CC in a phase II study, with a preliminary median OS greater than 25 months (67). Pembrolizumab combined with another vaccine, GX-188E, has also shown manageable toxicity and encouraging activity in HPV16 and 18-positive metastatic CC (68). Likewise, cemiplimab with the HPV 16 vaccine ISA101b showed clinical benefit in a HPV16-positive metastatic CC in a phase II trial (69).

Chimeric antigen receptor (CAR) T-cell therapy

Mesothelin, a membrane protein highly expressed in cervical cancer, represents a promising target for immunotherapy. Preclinical studies have shown that anti-mesothelin CAR-NK cells exhibit significant cytotoxicity against cervical cancer cells (70). Additionally, HPV-specific targeting shows promise, particularly against the viral oncoproteins driving malignancy. A preclinical study reported that E6-targeted CAR-T cells effectively kill HPV 16-positive cervical cancer cells, highlighting a strategy to exploit viral antigen specificity (71). Clinical trials for CAR T-cell therapy for CC are still in the early stages. More clinical data is needed to establish its safety and effectiveness in this context (72).

Antibody-drug conjugates (ADC)

Apart from immunotherapy, a new and promising treatment class in oncology is ADC. These biopharmaceuticals combine monoclonal antibodies (mAbs) with chemotherapeutic agents, enabling the direct delivery of cytotoxic drugs to cancer cells while protecting healthy organs, thus lowering systemic toxicity (73). Targeting highly expressed antigens in cervical cancer offers a promising therapeutic strategy, particularly using ADC. Potential targets under investigation include folate receptor alpha (FRα), expressed in approximately 40% of cases; tissue factor (TF), found in about 77%; HER2 (human epidermal growth factor receptor 2), present in 1–12%; TROP2 (trophoblast cell-surface antigen 2), highly expressed in around 85%; and epidermal growth factor receptor (EGFR), observed in 70–90% of cases (74–78).

Several trials are examining the safety and effectiveness of ADC in CC. Tisotumab vedotin, an antibody-drug conjugate that targets TF, was the focus of the InnovaTV 204 trial, a single-arm, phase II clinical trial that assessed the effectiveness of the treatment in patients with r/m CC who had undergone up to two previous systemic therapies. The ORR was approximately 24% and was observed across histological subtypes (squamous and nonsquamous). In 28% of cases, grade 3/4 adverse events were reported, with alopecia, nausea, conjunctivitis, and fatigue being the most prevalent adverse effects (79). The findings of this study showed that tisotumab vedotin has clinically meaningful activity in heavily pretreated CC patients. In September 2021, the FDA approved it for use in treating r/m CC patients whose disease progresses during or following chemotherapy (Table 1).

The InnovaTV 301/ENGOT-cx12/GOG-3057, a phase III clinical trial, evaluated the efficacy of tisotumab vedotin in treating r/m C following progression on first-line systemic therapy. Results demonstrated that tisotumab vedotin significantly improved PFS and OS compared to chemotherapy, with a mOS of 11.5 months compared to 9.5 months for chemotherapy (HR 0.70; 95% CI, 0.54 to 0.89; two-sided P = 0.004). The mPFS was 4.2 months with tisotumab vedotin versus 2.9 months with chemotherapy (HR 0.67; 95% CI, 0.54 to 0.82; two-sided P<0.001). Grade >3 treatment-related side effects were less common with tisotumab vedotin (29.2%) than with chemotherapy (45.2%), and were tolerable (80). The FDA approved tisotumab vedotin in April 2024 for the treatment of patients with r/m CC whose disease progresses during or following chemotherapy (Table 1).

In the DESTINY-PanTumor02 study, a multicenter, phase 2, open-label clinical trial, patients with advanced or metastatic solid tumors that have progressed on previous therapies are evaluated for the safety and effectiveness of trastuzumab deruxtecan (T-DXd), an ADC that targets HER2. The ORR for all patients was 37.1%; for CC patients it was 50%, the mDOR was 9.8 months, and the PFS was seven months; in IHC 3+ cases the ORR and PFS NR were

75%, 40.8% of patients experienced drug-related side effects of grade ≥3 (81). Based on results from the DESTINY-PanTumor02 trial and supporting data from studies in lung and colorectal cancer, the FDA, in August 2024, granted tumor-agnostic approval for fam-trastuzumab deruxtecan-nxki (82,83). The indication includes patients with HER2-positive (IHC 3+) unresectable or metastatic solid tumors who have received prior systemic therapy.

Sacituzumab govitecan (SG) is an ADC that works by combining an anti-Trop-2 monoclonal antibody with the cytotoxic agent SN-38, a topoisomerase I inhibitor, allowing targeted delivery of chemotherapy to Trop-2 expressing tumors(84). CC often exhibits high Trop-2 expression, making SG a plausible candidate for treatment (85)**.** Patients with advanced CC who are resistant or intolerant to chemotherapy are being recruited for trial EVER-132-003, a multicenter, multi-cohort clinical phase II trial that includes SG in the treatment of patients with various solid malignancies. An interim review revealed a 50% ORR and no new warning signs (72). For r/m CC patients, SG might be a new targeted treatment option for CC patients who overexpress Trop-2.

Like other cancers, the role of ADC in CC treatment is promising. ADC could revolutionize the treatment landscape for CC by offering a more precise and effective option and may provide new hope as first- or second-line treatments, especially for patients who have limited responses to conventional approaches. The combinations between ADC and existing therapies like immunotherapy, radiation, or other targeted therapies could enhance their effectiveness, and in the future, research into combinations with these treatment modalities could provide answers. As novel therapies like ADC emerge, identifying biomarkers that predict response to various treatments becomes even more critical.

Association between immune biomarkers and outcomes in CC: Implications for immunotherapy

Biomarkers play a critical role in predicting clinical outcomes in CC, especially in the context of immunotherapy (Figure 2). Several studies have highlighted predictive and prognostic biomarkers that can help guide treatment decisions.

PD-L1 expression, assessed by IHC, is the most widely used biomarker to predict response to immunotherapy (86). While general literature reports PD-L1 expression in approximately 30–70% of cervical cancers, clinical trials have demonstrated even higher positivity rates, particularly at the advanced stage (25). It is also considered a potential surrogate marker for HPV infection. Indeed, in the KEYNOTE-826 study, which evaluated pembrolizumab in recurrent or metastatic cervical cancer, PD-L1 expression was observed in 89% of tumors (41). Similarly, the KEYNOTE-A18 trial investigating treatment in LACC reported PD-L1 expression in 95% of patients (87). PD-L1 expression is also a predictive biomarker of response to pembrolizumab in first-line and later-line treatment of CC. In first-line treatment, subgroup analyses demonstrated improved PFS and OS in patients with PD-L1–positive tumors compared to those without expression (41). However, in the LACC, adding pembrolizumab to chemoradiotherapy provided clinical benefit regardless of PD-L1 expression, suggesting that PD-L1 may not be an optimal biomarker for ICI in CC (87).

The number of mutations found in the coding parts of the cancer genome is known as the tumor mutational burden (TMB). It can serve as a predictive biomarker for how likely a cancer is to evoke an immune response, influencing its potential sensitivity to immunotherapy with ICI. Higher TMB often correlates with a more robust response to certain ICIs (88,89). The prognostic value of TMB has been demonstrated in CC (90). Patients with high TMB showed significantly improved 5-year survival compared to those with low TMB. In the KEYNOTE-158 study, which evaluated immunotherapy in advanced solid tumors, including CC, TMB was

investigated as a possible immunotherapy response biomarker (91). The study found that high TMB (≥10 mutations per megabase) was present in 13% of all solid tumor patients analyzed. Small cell lung cancer (33%) and CC (16%) showed the highest prevalence of high TMB. Clinical implications of TMB have also been shown in another study with squamous CC (92). The 5-year survival rate was considerably higher for patients with high TMB than for those with low TMB. Interestingly, the threshold for TMB (high vs. low) was based on the median TMB in the cohort (92). Among the clinical data, 69% of patients had T1 or T2 CC, while metastatic status was unknown for 59% of patients. In a retrospective study of 44 patients with FIGO IB-IVA squamous LACC treated with chemoradiotherapy or radiotherapy, high TMB combined with low CD8 TIL density was associated with poor OS, PFS, and distant metastasis-free survival ($p = 0.012$, $p = 0.27$, and $p = 0.047$, respectively) (93). Treatment intensification may be beneficial for these patients, including chemoimmunoradiotherapy and consolidation immunotherapy, as per the KEYNOTE A-18 protocol.

Microsatellite instability (MSI) implies genetic hypermutability due to defects in the DNA mismatch repair (MMR) system. Tumors that exhibit high levels of MSI, referred to as MSI-High (MSI-H), tend to accumulate numerous mutations throughout repetitive DNA sequences known as microsatellites (94–96). MSI-H cancers tend to exhibit strong responses to immunotherapies, such as ICI, due to their increased neoantigen load. The highest prevalence of MSI-H has been demonstrated in colorectal, endometrial, and gastric adenocarcinomas. A retrospective study investigated the frequency of mismatch repair deficiency/high microsatellite instability (MMRd/MSI-H) and its role as a predictive biomarker of response to immunotherapy in gynecological cancers, including CC (97). MMRd/MSI-H was identified in ~10% of gynecologic cancers with squamous cell carcinoma morphology. Among patients treated with ICI, a response was observed in 8 of 37 cases (22%), suggesting that MMRd/MSI-H may serve as a potential biomarker for predicting immunotherapy response in CC.

Homologous recombination deficiency (HRD) refers to an inability of cells to properly repair double-strand DNA breaks through the homologous recombination pathway. HRD causes genetic instability and the accumulation of mutations (98, 99). Cancers exhibiting HRD often rely on alternative, less accurate DNA repair mechanisms, making them particularly susceptible to treatments such as poly (ADP-ribose) polymerase (PARP) inhibitors (98, 99). HRD and subsequent genomic instability also make cancers more sensitive to immunotherapy with ICI (100). NGS analysis revealed that 16% of CC patients have somatic pathogenic variants associated with HRD, highlighting the potential for evaluating the efficacy of HRD-targeted therapies and immunotherapy (101).

In a phase 1 study exploring sequential immunotherapy with ipilimumab following chemoradiotherapy for LACC elevated levels of tumor-promoting cytokines (TNFα, IL6, and IL8) post-chemoradiotherapy were significantly associated with worse PFS (102). The presence of CD4+ ICOS+ and CD4+ ICOS+ PD-1+ immune cell subsets was linked to significantly improved PFS. These findings highlight the potential role of these immune markers in predicting treatment outcomes for CC.

A potential biomarker for therapy intensification is circulating tumor HPV DNA (ctHPV DNA), which can be used to assess residual disease after chemoradiotherapy for LACC (103). The persistence of ctHPV DNA was associated with worse outcomes, with patients who had detectable ctHPV DNA four to six weeks after treatment showing a 2-year PFS of 15%, compared to 82% for those with undetectable disease ($P < 001$).

In summary, these potential predictive biomarkers provide valuable insights for personalizing treatment strategies, especially in guiding immunotherapy and other targeted treatments.

ACCESSIBILITY AND GLOBAL DISPARITIES

Despite the impressive strides in personalized therapy for CC, global access to biomarker testing and targeted treatments remains markedly uneven (104). Low- and middle-income countries, which bear a disproportionately high burden of CC, often lack the infrastructure, specialized laboratories, and funding necessary to implement complex diagnostic assays (e.g., TMB, MSI testing) at scale. Although PD-L1 IHC is more readily available than some of the newer genomic assays (e.g., next-generation sequencing), its routine use can still be limited by staffing, reagent costs, and quality assurance challenges. These obstacles are further compounded by the high costs of immunotherapies and novel agents such as antibody-drug conjugates, which frequently lie beyond the reach of most public health budgets.

Consequently, patients in these regions are often diagnosed at later stages and have fewer therapeutic options once diagnosed (105). To bridge this gap, multi-stakeholder approaches involving government policy, industry-led tiered pricing, philanthropic initiatives, and international cooperation are needed. By subsidizing assay costs, establishing local testing networks, and negotiating reduced drug prices, it may be possible to extend the benefits of advanced biomarker-driven therapy to populations where CC incidence and mortality are most pronounced. Emphasizing capacity-building, education, and early detection strategies—such as HPV vaccination and screening—will also be critical in ensuring a more equitable global fight against CC. Continued international collaboration and commitment are needed to turn these proposals into reality.

CONCLUSION

In conclusion, immunotherapy has significantly transformed CC treatment, substantially improving outcomes from second-line to first-line and locally advanced settings. However, to fully maximize its benefits in practice and improve tailored treatment strategies, identifying and implementing reliable predictive biomarkers are essential. Ongoing basic and clinical research

will further reveal the interplay between the immune system and CC, ultimately advancing more effective and personalized treatment approaches.

Conflicts of interest: Gordan Srkalović received honoraria from the Recordati Rare Diseases Speakers' Bureau. Other authors declare no conflicts of interest.

Funding: Authors received no specific funding for this work.

Submitted: 24 April 2025

Accepted: 22 May 2025

Published online: 22 May 2025

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TABLES AND FIGURES WITH LEGENDS

Table 1. Summary of clinical trials with FDA-approved immunotherapy and ADC regimens in the treatment of cervical cancer.

Drug	Trial	Patient population	Treatment	ORR	mPFS	mOS	Approval year
Bevacizumab	Phase III GOG 240(106)	r/m or persistent CC, no prior CHT	CHT + bevacizumab vs. CHT	45 % vs. 34%	8.2 vs. 6.0 months (HR 0.68)	16.8 vs. 13.3 months (HR 0.77) 24.5 vs. 16.8 months (HR 0.64) in pts not treated with prior CRT	2014
Pembrolizumab	Phase II KEYNOTE 158(30)	r/m CC (PD-L1 (CPS)≥1) with disease progression on prior systemic treatments (	Pembrolizumab for 35 cycles or disease progression or unacceptable toxicity	14.6% (95% CI, 7.8% to 24.2%)	4.1 month (95% CI, 2.4 to 4.9 months)	23.5 month (95% CI, 13.5 months to NR)	2018
Vedotin	Phase II Innova TV204(79) Phase III Innova TV 301(80)	r/m CC with disease progression on prior systemic treatment	TisotumabVedontin TisotumabVedontin vs. CHT	24 % 17.8% vs. 5.2%	Not reported 4.2 vs. 2.9 months (HR 0.67)	Not reported 11.5 vs. 9.5 months (HR 0.70)	FDA accelerated approval 2021 2024

Pembrolizumab	Phase III KEYNOTE-826(41)	r/m or persistent CC, no prior CHT, known PD L1 status prior to randomization	CHT +/- bevacizumab (investigator choice) + pembrolizumab or CHT +/- bevacizumab (investigator choice) + placebo	65.9% vs. 50.8%	10.4 vs. 8.2 months (HR 0.65)	24.4 vs. 16.5 months (HR 0.64)	2021

Table 1 ***(continued)***

Pembrolizumab	Phase III KEYNOTE-A-18(87)	Newly diagnosed, high-risk, stage IB2–IIB with node-positive disease or stage III–IVA irrespective of the nodal state (FIGO 2014)	Pembrolizumab + CRT vs. Placebo + CRT	Not reported	NR in either group (rates at 24-month 68 % vs. 57%) (HR 0.70)	36-month overall survival 82.6% vs. 74.8% (HR 0.67)	2024
Cemiplimab	Phase III EMPOWER-CERVICAL 1/ GOG-3016/ ENGOT-cs9(107)	r/m CC with disease progression on prior systemic treatment	Cemiplimab vs. investigator's choice chemotherapy	16.4% vs. 6.3%	(HR 0.75; 95% CI, 0.63 to 0.89; P<0.001)	12.0 vs. 8.5 months (HR 0.69)	FDA BLA voluntarily withdrawn January 2022 EMA approved 2022

Abbreviations: r/m or persistent CC, recurrent, metastatic or persistent cervical cancer; CHT, chemotherapy; CRT, chemoradiation; Pts, patients; ADC, antibody-drug conjugate; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; PD-L1, programmed cell death ligand-1; EMA, European Medicines Agency; FDA,

Food and Drug Administration; BLA, Biologics License Application; NR, not reached, CPS, Combined Positive Score); FIGO, International Federation of Gynecology and Obstetrics.

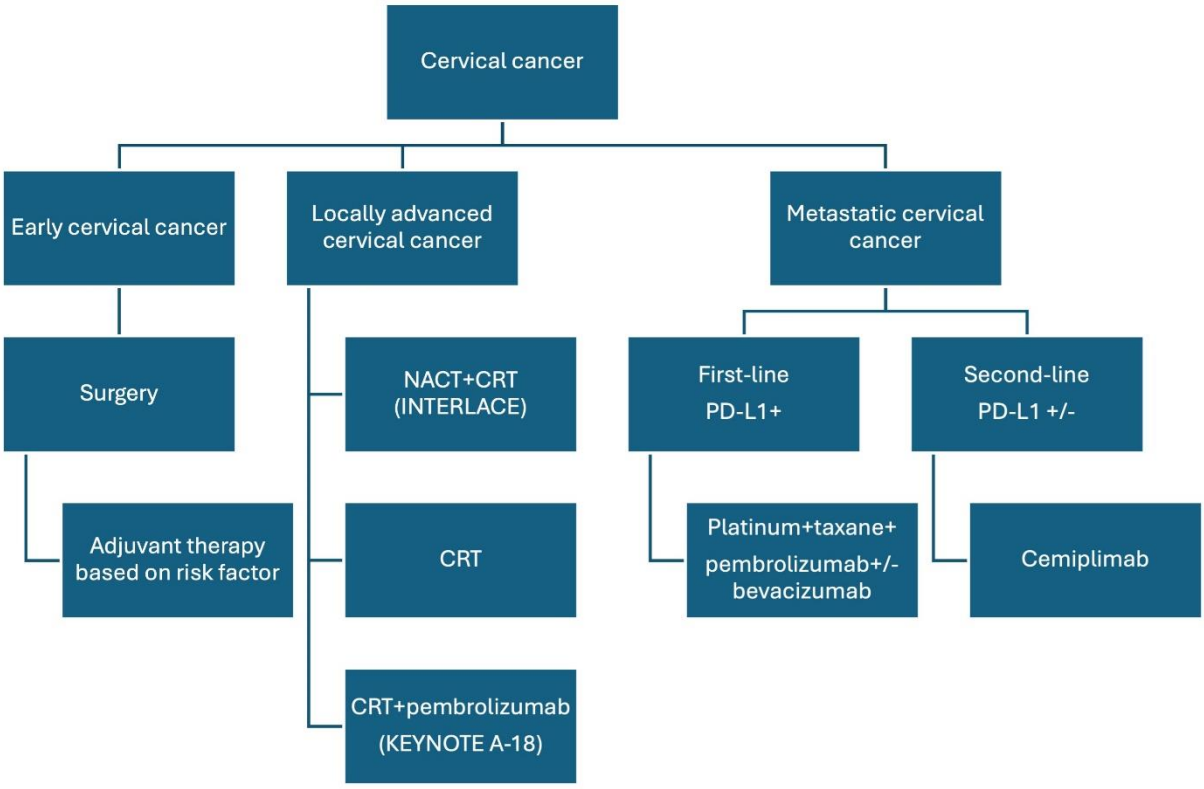

Figure 1. The proposed treatment algorithms for invasive cervical cancer based on current evidence.

NACT, neoadjuvant chemotherapy; CRT, chemoradiotherapy; PD-L1, programmed death receptor-1 ligand

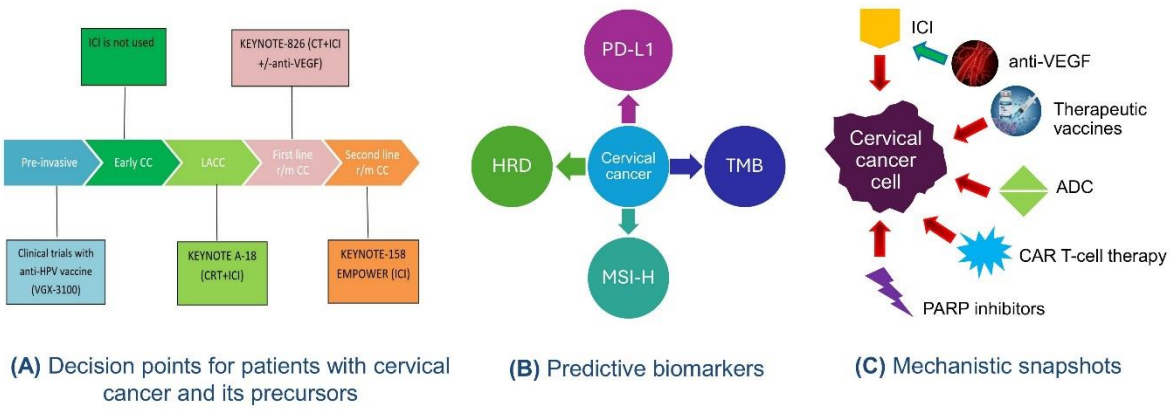

Figure 2. Potential biomarkers for immunotherapy in cervical cancer. Red arrows indicate inhibitory, while the green arrow (anti-VEGF therapies) indicates an enhancing effect (image C).

Abbreviations: TMB, tumor mutational burden; MSI-H, microsatellite instability high; PD-L1, programmed death receptor-1 ligand; HRD, Homologous recombination deficiency; ICI, immune checkpoint inhibitors; PARP, Poly (ADP-ribose) polymerase.