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Review

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Treatment strategies in cervical cancer: treatment of advanced disease

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Abstract

Cervical cancer is the fourth most common cancer in women worldwide, with a global incidence of 604,127 and an annual death rate of 341,831 in 2020. Patients with recurrent, persistent, or metastatic disease not amenable to curative therapy represent a patient population with a dismal prognosis. Until recently, the standard of care for these patients was based on platinum doublet chemotherapy with or without bevacizumab. However, significant advances in the treatment landscape of this disease have recently been achieved with the incorporation, among others, of immunotherapy in the therapeutic armamentarium. This review summarizes the main treatment approaches developed throughout the past decades, with particular emphasis on immunotherapy and novel targeted therapies.

Keywords: Cervical cancer, advanced stage, chemotherapy, immunotherapy, antiangiogenic agents, targeted therapy

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, with a global incidence of 604,127 and an annual death rate of 341,831 in 2020[1]. Human papillomavirus (HPV) is the leading cause of this disease, detected in 99.7% of cervical cancer cases, especially in high-risk subtypes such as HPV 16 and 18[2].

Ultimately, cervical cancer is a preventable disease. Thus, most of the new cases of cervical cancer are diagnosed in developing countries mainly due to a lack of screening programs and vaccination strategies[3]. The most common histological subtypes are squamous cell carcinoma (70%) and adenocarcinoma (25%).

The treatment of newly diagnosed cervical cancer patients mainly relies on the FIGO stage. Patients with early-stage disease [FIGO 2018, stage I-IIA (< 4 cm)] could be treated with surgery and/or radiotherapy with high cure rates. However, those patients diagnosed with locally advanced cervical cancer (LACC) (FIGO 2018, stage IB3-IVA) are only candidates for concomitant chemoradiation (CCRT), with a worse prognosis[4-8]. In this sense, recurrence rates range from 16% to 30% in the early stages and increase up to 70% in the locally advanced disease. Most of these relapses occur within the first two years after initial diagnosis, and up to 50%-60% of patients will have extrapelvic diseases. Unfortunately, those patients with recurrent, persistent, or metastatic (stage FIGO IVB) disease who are unsuitable candidates for curative-intent treatment such as surgery and/or radiation therapy represent a poor prognosis population, being the only candidates for palliative systemic therapy. Nevertheless, in the past years, the addition of the anti-vascular endothelial growth factor (VEGF) agent bevacizumab to platinum-based chemotherapy has succeeded in extending median overall survival to nearly 17 months. In addition, a meaningful improvement in overall survival has recently been reported with the introduction of immunotherapy in the frontline setting. The KEYNOTE-826 trial, as discussed below, has demonstrated a dramatic increase in overall survival, reaching a median of 24 months in the intention-to-treat (ITT) population when adding pembrolizumab to platinum-doublet with or without bevacizumab[9,10].

As can be noted, substantial efforts are being undertaken to overcome the dismal prognosis of the recurrent, persistent, or metastatic cervical cancer population, with still high clinical unmet needs. In this review, we summarize the main treatment advances which have been carried out throughout the past decades, focusing on novel targeted therapies and immunotherapy.

ROLE OF CHEMOTHERAPY IN THE FIRST-LINE SETTING AND BEYOND

Chemotherapy is the cornerstone treatment choice in patients with recurrent, persistent, or metastatic disease who are not candidates for radical-intent therapies.

Cisplatin at a dose of 50 mg/m^2 every three weeks was the first chemotherapeutic agent that demonstrated a reasonable objective response rate (ORR) of nearly 50% in a single-arm phase II trial[11].

In an attempt to improve its activity, the cisplatin dose was increased up to 100 mg/m^2 every three weeks. However, higher doses did not improve progression-free survival (PFS) or overall survival (OS)[12]. Thus, cisplatin monotherapy at 50 mg/m^2 became the standard of care. Another approach to increase cisplatin's activity was adding ifosfamide. Therefore, a trial comparing cisplatin and ifosfamide *vs.* cisplatin alone was carried out. The combination arm achieved higher ORR (33% *vs.* 19%); however, no significant improvement in OS was shown, and patients in the ifosfamide-containing arm suffered from greater toxicities[13,14].

With the arrival of third-generation chemotherapeutic agents with improved toxicity profiles, various platinum-based combinations were evaluated versus cisplatin monotherapy within different clinical trials.

The GOG169 study was a randomized phase III trial comparing cisplatin monotherapy with cisplatin-paclitaxel combination in patients with stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix. The combination with paclitaxel was superior in terms of ORR (36% *vs.* 19%, $P = 0.002$) and median

PFS (4.8 *vs.* 2.8 months, $P < 0.001$). However, there was no difference in median OS (9.7 *vs.* 8.8 months). The most common reported adverse event (AE) was myelosuppression, with grade 3-4 anemia and neutropenia more common among patients receiving combination therapy. No grade 5 AEs were reported in this trial[15].

GOG179 was a randomized phase III clinical trial comparing cisplatin monotherapy with cisplatin-topotecan combination in patients with advanced (stage IVB) recurrent or persistent carcinoma of the uterine cervix not amenable for curative treatment. Histologic types included squamous, adenosquamous, and adenocarcinoma of the cervix. It is noteworthy that this trial included a third arm with a methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) regimen that was closed prematurely due to unacceptable toxicity. In total, 294 patients were enrolled in the remaining regimens: 146 for cisplatin monotherapy and 147 for cisplatin-topotecan.

Cisplatin combined with topotecan demonstrated statistically superior outcomes compared with cisplatin alone, with a median OS of 9.4 *vs.* 6.5 months ($P = 0.017$), median PFS of 4.6 *vs.* 2.9 months ($P = 0.014$), and ORR of 27% *vs.* 13%, respectively. As expected, grade 3-4 hematologic toxicity was more common in the combination regimen[16].

It should be noted that 27% of patients in GOG169 received prior cisplatin as part of concurrent chemoradiotherapy in contrast to 57% of patients in GOG179. This is of great importance since, when we analyzed the activity according to previous use of cisplatin, cisplatin-paclitaxel showed greater ORR and therefore was considered the standard therapy to compare other combinations in subsequent clinical trials[17].

The phase III randomized GOG204 trial was designed to evaluate four different platinum doublets. Initially, this trial began as a two-arm study comparing cisplatin-paclitaxel with cisplatin-vinorelbine. The third and fourth treatment arms, cisplatin-topotecan and cisplatin-gemcitabine, were added later. The primary endpoint was OS and secondary endpoints included ORR and PFS. The primary analysis consisted of three pairwise comparisons of the experimental arms (cisplatin-vinorelbine, cisplatin-gemcitabine, and cisplatin-topotecan) to the reference arm (cisplatin-paclitaxel). None of the tested regimens were statistically superior to cisplatin-paclitaxel in terms of OS. However, the combination of cisplatin-paclitaxel showed a positive trend in all efficacy outcomes (ORR of 29.1%, median PFS of 5.82 months, and median OS of 12.87 months). The cisplatin-topotecan arm had the greatest rates of myelotoxicity (grade 3 or more: anemia in 34.9%, neutropenia in 82.6%, and thrombocytopenia in 34.9%), while cisplatin-paclitaxel had greater rates of alopecia (grade 2, 54%). The other toxicities were similar for all treatment arms.

The results of this trial led to the acceptance of cisplatin-paclitaxel as the first-choice chemotherapy regimen in the advanced setting[18].

Finally, Moore *et al.* conducted a retrospective pooled data analysis of patients receiving cisplatin-combination regimens from three GOG clinical trials (GOG110, GOG169, and GOG179)[19]. After a multivariable analysis was carried out, five factors were significantly associated with poor response to cisplatin: African American ethnicity [odds ratio (OR) 0.49, 95%CI: 0.28-0.83], ECOG greater than 0 (OR 0.60, 95%CI: 0.38-0.94), pelvic recurrence (OR 0.58, 95%CI: 0.38-0.90), prior radiosensitizing chemotherapy (OR 0.52, 95%CI: 0.32-0.85), and recurrence within one year from diagnosis (OR 0.61, 95%CI: 0.39-0.95). A prognostic model with these five clinical factors was developed, and three risk groups were established: low-risk, 0-1 factors; mid-risk, 2-3 factors; and high-risk, 4-5 factors[19].

This model was externally validated using independent data from GOG protocol 149. Patients in the high-risk group had the worst treatment outcomes (ORR of 14.3%, median PFS of 3.38 months, and median OS of 5.58 months), while mid-risk and low-risk groups correlated with better outcomes accordingly (ORR of 29.4%, median PFS of 4.44 months, and median OS of 7.59 months in the mid-risk group and ORR of 42.6%, median PFS of 6.87 months, and median OS of 11.93 months in the low-risk group)[19].

Cisplatin-based doublets have remained the treatment backbone for the majority of patients with advanced cervical cancer since 2009. However, novel platinum agents have been developed and their efficacy in cervical cancer is expected to be evaluated. In this regard, the JCOG 0505 was a multicenter, open-label, randomized, non-inferiority phase III trial designed to evaluate whether cisplatin could be replaced with carboplatin as the main platinum backbone when combined with paclitaxel. The primary endpoint was OS and secondary endpoints included PFS and ORR. Patients were allowed to have received one prior platinum-based chemotherapy, including concurrent chemoradiotherapy, if no taxanes were administered in combination. The trial was run in an Asian population exclusively, enrolling 253 patients (127 received cisplatin-paclitaxel and 126 received carboplatin-paclitaxel). Carboplatin-paclitaxel was non-inferior to cisplatin-paclitaxel. Median OS was 17.5 months in the carboplatin-paclitaxel arm and 18.3 months in the cisplatin-paclitaxel arm (HR 0.994; 90%CI: 0.789-1.253; non-inferiority one-sided P = 0.032). The exploratory analysis demonstrated that median OS varied considerably among patients who had not received prior cisplatin concurrent with radiation. In this patient subgroup, median OS was shorter with carboplatin-paclitaxel (13 *vs.* 23.2 months; HR 1.571; 95%CI: 1.06-2.32). The authors concluded that, although carboplatin was non-inferior to cisplatin, cisplatin is still the key drug for patients who have not received prior platinum treatment. The toxicities reported in this study were as expected, given those in previous trials. Incidences of grade 4 neutropenia, grade 3-4 febrile neutropenia, creatinine elevation, and nausea/vomiting tended to be higher in the cisplatin-paclitaxel arm, whereas incidences of thrombocytopenia and sensory neuropathy tended to be higher in the carboplatin-paclitaxel arm[20].

The main outcomes of the trials mentioned above are summarized in Table 1.

Despite the above-mentioned results, the median OS of women diagnosed with recurrent, persistent, or metastatic (stage FIGO IVB) cervical cancer and treated with platinum-based chemotherapy alone does not cross the 12-month boundary. This is the reason multiple studies have attempted to add targeted therapy and immunotherapy to the chemotherapy backbone to raise the overall survival bar. These advances are discussed in subsequent sections.

For patients who have progressed from first-line therapy, chemotherapeutic agents can still be an option in subsequent treatment lines, provided that they maintain a good performance status and do not have any contraindications for further treatment. Multiple single agents have been evaluated in this setting within different phase II clinical trials. The main clinical trials' outcomes are summarized in Table 2[21-28].

Disappointingly, efficacy outcomes were overall poor, with a median ORR of less than 20%, median PFS of 3.3 months, and median OS of 6.7 months. This group of patients with advanced cervical cancer who have progressed from first-line platinum-based therapy represents a poor prognosis population; therefore, new therapeutic options are urgently needed.

TARGETING ANGIOGENESIS IN ADVANCED CERVICAL CANCER

Angiogenesis is a hallmark of cancer, and accumulating evidence supports its role in cervical cancer pathogenesis. This relationship seems linked to HPV's E6 and E7 oncoproteins. E6 produces p53

Table 1. Main outcomes of platinum-based combination regimens for recurrent/metastatic cervical cancer

Clinical trial	Author	Agent	*n*	ORR (%)	PFS (months)	mOS (months)	HR (95CI%)
GOG 169	Moore *et al.*[15]	CDDP-TXL	130	36*	4.8*	9.7*	NR
		CDDP	134	19	2.8	8.8	
GOG 179	Long III *et al.*[16]	CDDP-TOPO	147	27*	4.6*	9.4*	0.76 (0.593-0.979)
		CDDP	146	13	2.9	6.5	
GOG 204	Monk *et al.*[18]	CDDP-TXL	103	29.1#	5.82#	12.87#	-$
		CDDP-VNR	108	25.9	3.98	9.99	1.15 (0.79-1.67)
		CDDP-GEM	112	22.3	4.7	10.28	1.32 (0.91-1.92)
		CDDP-TOPO	111	23.4	4.57	10.25	1.26 (0.86-1.82)
JCOG 505	Kitagawa *et al.*[20]	CBDCA-TXL	126	62.6#	6.2#	17.5*	0.994 (0.789-1.253)
		CDDP-TXL	127	58.8	6.9	18.3	

ORR: Overall response rates; PFS: progression-free survival; OS: overall survival; NR: not reported; CDDP: cisplatin; CDDP-TXL: cisplatin and paclitaxel; CDDP-TOPO: cisplatin and topotecan; CDDP-VNR: cisplatin and vinorelbine; CDDP-GEM: cisplatin and Gemcitabine; CBDCA-TXL: carboplatin and paclitaxel; *$P < 0.05$; #$P \geq 0.05$; $compared to cisplatin-paclitaxel.

Table 2. Chemotherapeutic agents evaluated in clinical trials after progression from first-line therapy

Authors	Year published	Agent	*n*	ORR (%)	PFS (months)	OS (months)
Verschraegen *et al.*[21]	1997	Irinotecan	42	21	4.5	6.4
Bookman *et al.*[22]	2000	Topotecan	45	13	2.1	6.4
Muderspach *et al.*[23]	2001	Topotecan	49	19	2.4	6.6
Schilder *et al.*[24]	2005	Gemcitabine	22	5	2.1	6.5
Rose *et al.*[25]	2006	Pegylated Liposomal Doxorubicin	27	11	3.2	8.9
Garcia *et al.*[26]	2007	Docetaxel	23	9	3.8	7
Lorusso *et al.*[27]	2010	Pemetrexed	43	15	3.1	8.8
Alberts *et al.*[28]	2012	Albumin-bound Paclitaxel	35	29	5	9.4

ORR: Response rate; PFS: progression-free survival; OS: overall survival.

degradation and upregulation of VEGF, while E7 inhibits pRb and enhances hypoxia-inducible factor-1α (HIF1) and VEGF levels[29].

Bevacizumab is a humanized monoclonal antibody that targets all isoforms of circulating VEGF, inhibiting its binding to cell surface receptors. This antiangiogenic agent exerts its function by inhibiting new vessel growth, regression of newly formed vasculature, normalization of vascular function and tumor blood flow, etc.

The efficacy and tolerability of bevacizumab as a single agent were assessed in the phase II trial GOG-227C. Forty-six recurrent cervical cancer patients previously treated with up to two lines of systemic treatment received bevacizumab monotherapy intravenously every 21 days until disease progression or unacceptable toxicity. The primary endpoint was the PFS rate at six months since the initial expectations were that bevacizumab would be able to induce disease stabilization. The trial met its primary endpoint with a PFS rate at six months of 23% (90%CI: 14%-37%). Median PFS was 3.4 months (95%CI: 2.53-4.53 months). Moreover, five patients (10.9%; 90%CI: 4%-22%) achieved partial response, with a median duration of response (DOR) of 6.2 months. It should be noted that these efficacy outcomes were comparable to other phase II trials in the same setting (second- and third-line treatment). Regarding the safety profile, the most frequent grade 3-4 toxicities were hypertension and thromboembolism[30].

Subsequently, bevacizumab was further explored in combination with platinum-based chemotherapy. Firstly, a multicenter phase II trial assessed the combination of cisplatin, topotecan, and bevacizumab. In total, 27 recurrent or persistent cervical cancer patients with no prior lines of chemotherapy were treated until disease progression or limiting toxicity. The primary endpoint, six-month PFS rate, was 59% (80%CI: 46%-70%). Median PFS was 7.1 months (80%CI: 4.7-10.1), and median OS was 13.2 months (80%CI: 8.0-15.4). Unfortunately, this combination led to a high incidence of grade 3-4 thrombocytopenia (82%), neutropenia (56%), and anemia (63%). Importantly, 78% of the patients required hospital admissions for the management of toxicities[31].

Finally, the awaited GOG240 trial was carried out. This was a phase III, open-label, randomized clinical trial with a multifactorial design to address two questions: whether adding bevacizumab to chemotherapy would translate into an OS improvement and whether a non-platinum regimen would be superior to a platinum-based one. This was done due to the increasing use of chemoradiation as the standard of care in the LACC setting and the possible subsequent platinum resistance at recurrence. Patients with recurrent, persistent, or metastatic cervical cancer, not amenable to curative-intent therapy, were included, and they were randomly assigned to one of four regimens (1:1 randomization): cisplatin plus paclitaxel, topotecan plus paclitaxel, cisplatin plus paclitaxel plus bevacizumab, and topotecan plus paclitaxel plus bevacizumab. The trial met its primary endpoint as the addition of bevacizumab to either of these regimens demonstrated a significant increase in median OS (16.8 *vs.* 13.3 months; HR 0.77; 95%CI: 0.62-0.95; P = 0.007). Higher ORR was observed in patients receiving bevacizumab (48% *vs.* 36%). Besides, the topotecan-paclitaxel regimen showed a significantly higher risk of progression (HR 1.39; 95%CI: 1.09-1.77) compared to cisplatin-paclitaxel schema (either with or without bevacizumab) with no significant differences in terms of OS (HR 1.20; 99%CI: 0.82-1.77). Scores in the health-related quality of life survey were 1.2 points lower in patients who received antiangiogenic therapy (99%CI: -4.1 to 1.7; P = 0.30)[32]. In 2017, the final survival analysis with extended follow-up demonstrated a sustained benefit of the addition of bevacizumab in terms of median OS (16.8 *vs.* 13.3 months; HR 0.77; 95%CI: 0.62-0.95; P = 0.0068) and PFS (HR 0.68; 95%CI: 0.56-0.84; P = 0.0002). Regarding the safety profile, the addition of bevacizumab was associated with an increased risk of grade 2 or higher hypertension (25% *vs.* 2%), grade 3 or higher thromboembolic events (8% *vs.* 1%), and grade 3 or higher fistulas of gastrointestinal or genitourinary origin (6% *vs.* 0%). It is worth noting that all patients who suffered from fistulae had previously been irradiated. Factors associated with fistula formation included pelvic metastases, prior hypertension, and tobacco use.

Patients with this complication did not require emergent surgery and were not septic at clinical presentation. No grade 5 fistula formation was reported[9,32].

Based on GOG240, the FDA (August 2014) and EMA (April 2015) approved the addition of bevacizumab at a dose of 15 mg/kg every three weeks to either cisplatin plus paclitaxel or topotecan plus paclitaxel as first-line therapy in patients with advanced cervical cancer.

Additionally, the combination of carboplatin plus paclitaxel and bevacizumab was evaluated in the CECILIA trial. This was a global single-arm phase II trial that enrolled 150 patients with recurrent or metastatic cervical cancer who were not candidates for radical therapy and without previous systemic therapy for this condition. The median PFS was 10.9 months (95%CI: 10.1-13.7 months), median OS was 25 months (95%CI: 20.9-30.4 months), and ORR was 61% (95%CI: 52%-69%). The incidence of fistulae or gastrointestinal perforation was similar to that observed in the GOG240 trial. Only 17 patients (11.3%) presented grade 1 or higher perforation/fistula event, of whom 16 were previously irradiated[33].

Following the efficacy data of bevacizumab, different antiangiogenic agents have been assessed in different clinical trials.

Sunitinib is an oral multitargeted tyrosine kinase inhibitor (TKI) whose targets include VEGF receptor (VEGFR), c-Kit, and platelet-derived growth factor receptor (PDGFR). Its efficacy was evaluated in a phase II trial that enrolled previously treated patients with both locally advanced and metastatic cervical carcinoma. Patients received sunitinib at a dose of 50 mg/day for four weeks, followed by two weeks off treatment. Sixteen of 19 patients enrolled reached stable disease, but no objective responses were observed. Reported AEs included fatigue (74%), diarrhea (74%), and nausea (58%). It is worth noting the finding of an unexpectedly high incidence of fistulae (26%). Unfortunately, the safety profile of sunitinib and modest clinical activity did not warrant further studies[34].

Pazopanib is another oral multitargeted TKI with anti-VEGFR, -PDGFR, and -c-Kit activity. This drug and lapatinib (anti-EGFR and -HER2/neu) were evaluated in a randomized phase II study conducted to compare pazopanib 800 mg/day, lapatinib 1500 mg/day, or a combination of both (lapatinib 1000 mg/day plus pazopanib 400 mg/day or lapatinib 1500 mg/day plus pazopanib 800 mg/day) in patients with previously treated advanced cervical cancer. The combination arm was discontinued due to futility in the interim analysis, so 152 patients were assigned to either pazopanib (74 patients) or lapatinib (78 patients). Pazopanib showed clinical benefit based on prolonged PFS (HR 0.66; 90%CI: 0.48-0.91; $P = 0.013$) and OS (HR 0.67; 90%CI: 0.46-0.99; $P = 0.045$). ORR was 9% in the pazopanib arm and 5% in the lapatinib arm. Toxicities seen with pazopanib included decreased appetite, diarrhea, nausea, and increased blood pressure. Three patients suffered from fistula formation[34]. An update of this trial showed no significant differences in OS between the pazopanib and lapatinib arms[35].

Cediranib is a TKI with potent activity against VEGFR1-3 and c-KIT. Its efficacy in combination with carboplatin plus paclitaxel was evaluated in a randomized, double-blind phase II trial. Sixty-nine patients with recurrent-metastatic cervical cancer were eligible and later randomized 1:1 to receive cediranib 20 mg or placebo orally once daily plus carboplatin AUC 5 and paclitaxel 175 mg/m^2 every 21 days. Unfortunately, the trial was prematurely closed in July 2012 due to drug supply withdrawal. Cediranib achieved a longer PFS (HR 0.58; 80%CI: 0.40-0.85; $P = 0.032$), but no significant difference in terms of OS was demonstrated (HR 0.94; 80%CI: 0.65-1.36; $P = 0.42$). The incidence of AEs was higher in the cediranib arm. The most common grade 3 or superior toxicities were diarrhea (16% *vs.* 3%), fatigue (13% *vs.* 6%), and neutropenia (31% *vs.* 11%)[36].

IMMUNOTHERAPY IN THE TREATMENT OF METASTATIC CERVICAL CANCER

Introduction and treatment rationale

Immune checkpoint proteins and their signals function as regulators of the so-called "cancer immunity cycle". These proteins are involved in multiple steps required to develop an effective immunity against tumor cells. Two of the most studied immune checkpoints are programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen (CTLA-4) that mediate negative co-regulatory signals during initial T cell activation triggered by antigen presentation and the inflammatory response by effector T cells in tissues, respectively. Blockade of these immune checkpoint signals inhibits the cancer cell's ability to evade the immune response. Thus, immune checkpoint inhibitors (ICI) have become efficacious therapeutic targets in multiple tumor types including cervical cancer[37].

Approximately 75%-80% of women are exposed to HPV during their lifetime. Fortunately, most of them develop an effective antiviral response and will be able to clear the infection without major consequences. In

some women, however, immune surveillance is bypassed by HPV-infected cells through immune editing. This results in the selection of cancer clones with resistance to immune detection and elimination and the development of cervical cancer. The activation of the PD-1/PD-L1 pathway is important in this regard. An enhanced expression of PD-1 and PD-L1 checkpoints is seen in cervical cancer patients, which correlates to the progression of cervical intraepithelial neoplasia (CIN) to invasive carcinoma, tumor grade, and prognosis[38]. The level and patterns of PD-L1 expression vary across cervical cancer histological subtypes. In this regard, overexpression of PD-1/PD-L1 has been demonstrated in 54%-67% of squamous carcinoma and only 12% of patients with adenocarcinoma histology[39].

Moreover, recent reports are offering a deeper understanding of the molecular basis of PD-1/PD-L1 expression in cervical cancer. Indeed, oncoproteins of high-risk HPV (E5, E6, and E7) seem to be directly involved in the PD-1/PD-L1 axis activation, consequently leading to compromised immunity[40].

The evidence mentioned above constitutes a robust biological rationale supporting the clinical development of ICI in cervical cancer. Throughout the last few years, several clinical trials have explored the efficacy and safety of ICI monotherapy and combination strategies in advanced cervical cancer. For the purpose of this review, we focus on the most relevant clinical data published on ICI in recurrent, persistent, and metastatic cervical cancer.

Immune checkpoint inhibitors monotherapy

The first evidence for clinical activity of an ICI in advanced cervical cancer patients was obtained from the phase Ib KEYNOTE-028 trial. This study was designed to assess the safety and efficacy of the anti-PD-1 monoclonal antibody pembrolizumab in 20 cohorts of patients with PDL-1-positive metastatic solid tumors. The definition of positive PD-L1 included membranous staining on ≥ 1% modified tumor proportion score (TPS) or interface pattern as assessed using the 22C3 antibody. Twenty-four PD-L1-positive cervical cancer patients (96% squamous cell carcinoma) were enrolled in the trial and received pembrolizumab at a dose of 10 mg/kg every two weeks. Patients continued treatment until confirmed disease progression, unacceptable toxicity, or for up to two years. The confirmed ORR was 17% (95%CI: 5%-37%); four patients (17%) achieved a partial response, with a median DOR of 5.4 months (95%CI: 4.1-7.5 months). Three patients (13%) had stable disease as the best response. No grade 4-5 AEs occurred, and only two patients discontinued pembrolizumab due to grade 3 AEs (colitis and Guillain-Barré syndrome)[41].

Subsequently, KEYNOTE-158 was a phase II basket trial that included a cohort of patients with pretreated advanced cervical cancer, regardless of PDL-1 status. Ninety-eight patients (94% squamous cell carcinoma) were enrolled and received three-weekly pembrolizumab at a flat dose of 200 mg for a maximum two-year duration. Eighty-two patients (83.7%) had PD-L1 positive tumors, defined as a combined positive score (CPS) of ≥ 1% based on 22C3 assay. Of note, this method evaluates the number of PD-L1-staining cells (malignant cells, lymphocytes, and macrophages) relative to all viable tumor cells. The ORR of the cervical cancer cohort was 12.2% (95%CI: 6.5%-20.4%), only observing responses in the PDL-1-positive subgroup, with a confirmed ORR of 14.6% (95%CI: 7.8%-24.2%). Interestingly, after a median follow-up of 36.9 months, the median DOR has not yet been reached (range, ≥ 3.7 to ≥ 18.6 months). Treatment-related AEs occurred in 65.3% of patients, the most common being hypothyroidism (10.2%), decreased appetite (9.2%), and fatigue (9.2%). Only 12.2% of patients suffered from a grade 3-4 AE[42]. Following this efficacy and safety data, pembrolizumab gained FDA approval in pretreated PDL-1-positive (CPS ≥ 1% based on 22C3 assay) advanced cervical cancer in 2018.

The phase I/II CheckMate-358 trial evaluated the clinical activity of the anti-PD-1 monoclonal antibody nivolumab at a flat dose of 240 mg every two weeks in HPV-related squamous vulvar, vaginal, and cervical tumors, regardless of PDL-1 status. HPV testing was not mandatory for enrollment. However, a history of a negative HPV result was enough for exclusion. Nineteen patients with metastatic squamous cervical cancer previously treated with up to two prior lines of therapy were included in this trial. The primary endpoint ORR in the cervical subgroup was 26.3% (95%CI: 9.1%-51.2%), and the median DOR was not reached (range, 23.3-29.5 months). Interestingly, it seems that chemo-naive patients had higher ORR (28.6%) and disease control rate (71.4%) as compared with the global population (26.3% and 68.4%, respectively). Among the key secondary endpoints, the median OS was 21.9 months (95%CI: 15.1 months to not reached) and the median PFS was 5.1 months (95%CI: 1.9-9.1 months) in this cohort. The status of PD-L1 was assessed with the 28-8 pharmDx assay. Tumor PD-L1 expression was defined as the percentage of tumor cells exhibiting any intensity of plasma membrane staining. Based on this, 62.5% of cervical cancer patients had ≥ 1% tumor cell PD-L1 expression. It should be noted that responses were not limited to the PD-L1-positive tumors. Indeed, ORRs of 20.0% and 16.7% were reported in the ≥ 1% and < 1% PD-L1 subgroups, respectively. Regarding the safety profile, any-grade treatment-related AEs were reported in 63.2% of patients in the cervical cohort, with diarrhea being the most common reported AE. Grade 3-4 AEs occurred in 15.8% of cervical cancer patients[43].

The phase II C-700-01 trial evaluated the efficacy and safety of balstilimab, an anti-PD-1 monoclonal antibody, in patients with previously treated recurrent or metastatic cervical cancer, regardless of PD-L1 expression. In total, 161 patients were enrolled in the study (62.7% squamous cell carcinoma and 36.6% adenocarcinoma/adenosquamous). They were treated with balstilimab at a dose of 3 mg/kg every two weeks for a maximum of two years. Of these, 140 patients were finally evaluated as part of the efficacy analysis, as they met the eligibility criteria of measurable disease at baseline and had relapsed after one prior platinum-based treatment regimen in the metastatic setting. The primary endpoint ORR in the overall population was 15% (95%CI: 10.0%-21.8%). Five patients achieved a complete response and 16 a partial response. The observed median DOR was 15.4 months (95%CI: 5.7 months to not reached). The investigators analyzed baseline PD-L1 expression centrally in archival tumor biopsy specimens with the 22C3 pharmDx assay. PD-L1 positivity was defined by a CPS ≥ 1%, and its association with clinical response was part of an exploratory analysis. Patients with PD-L1-positive tumors (85 patients) had an ORR of 20% (95%CI: 12.9%-29.7%). In addition, confirmed responses to balstilimab were found in patients with PD-L1-negative tumors (3/38, 7.9%). Interestingly, responses were not restricted to squamous tumors (ORR of 17.6%), finding an ORR of 12.5% in the adenocarcinoma subgroup. Regarding safety data, balstilimab has a manageable toxicity profile comparable to other anti-PD-1 antibodies. The most common grade 3 or higher treatment-related AEs were colitis (3.1%) and diarrhea (1.9%)[44].

As these data on the activity of checkpoints inhibitors in cervical cancer were merging, the EMPOWER-Cervical 1 was launched. This was an open-label, randomized, multicenter, phase III trial evaluating the efficacy and safety of cemiplimab, an anti-PD-1 antibody, *vs.* the investigator's choice of single-agent chemotherapy in patients with recurrent/metastatic cervical cancer that has progressed following first-line platinum-based treatment. Patients were included regardless of PD-L1 status. Following 1:1 randomization, 304 patients were treated with cemiplimab at a flat dose of 350 mg every three weeks and 304 received pemetrexed, vinorelbine, gemcitabine, irinotecan, or topotecan for up to 96 weeks. Stratification factors included histology (77.8% squamous cell carcinoma and 22.2% adenocarcinoma or adenosquamous) and previous bevacizumab use. The primary endpoint was OS, which was analyzed hierarchically in patients with squamous cell carcinoma, followed by the total study population. PFS, ORR, quality of life (QoL), and safety were included as secondary endpoints.

Regarding the primary endpoint, among 239 squamous cell carcinoma patients on cemiplimab, the median OS was 11.1 months compared to 8.8 months in 238 patients receiving chemotherapy (HR 0.73; 95%CI: 0.58-0.91; $P = 0.006$). Median OS in the total population was 12.0 months with cemiplimab compared to 8.5 months with chemotherapy (HR 0.69; 95%CI: 0.56-0.84; $P < 0.001$). In the adenocarcinoma subgroup, the 65 patients receiving cemiplimab demonstrated a median OS of 13.3 months compared to 7.0 months in the 66 patients receiving chemotherapy (HR 0.56; 95%CI: 0.36-0.85). Regarding secondary endpoints, PFS, ORR, and DOR in both overall and squamous cell carcinoma populations favored cemiplimab over chemotherapy. Note that confirmed objective responses with cemiplimab were seen in both histological subgroups: an ORR of 12% (95%CI: 6-23) in the adenocarcinoma subgroup and an ORR of 17.6% (95%CI: 13.0-23.0) in the squamous cell carcinoma subgroup. Moreover, treatment with cemiplimab provided a statistically significant benefit in GHS/QoL and physical functioning versus chemotherapy in both the squamous cell carcinoma and overall populations.

Concerning the PD-L1 expression status at baseline, it should be stressed that it was not an eligibility criterion or a stratification factor of the trial. However, it was analyzed retrospectively. PD-L1 expression positivity, using the SP263 monoclonal antibody, was defined by an expression ≥ 1% per tumor cell (TPS). Of 608 randomized patients, only 254 (41.7%) had valid baseline PD-L1 samples (126 in the cemiplimab arm and 128 in the chemotherapy arm). Among these patients, PD-L1 expression of ≥ 1% was more common among patients with squamous-cell carcinoma (70.7%) compared to adenocarcinoma or adenosquamous carcinoma (32.6%). The association between efficacy outcomes and PD-L1 expression was evaluated as part of an exploratory analysis. Based on available tumor samples, a numerical OS benefit of cemiplimab versus chemotherapy was seen in patients with PD-L1 < 1% (7.7 months; 95%CI: 4.3-12.3 months), although the benefit was greater in patients with PD-L1 ≥ 1% (13.9 months; 95%CI: 9.6 to not reached). Besides, ORR to cemiplimab were observed in patients with both PD-L1 expression of ≥ 1% (18%; 95%CI: 11%-28%) and < 1% (11%; 95%CI: 4%-25%). Regarding safety profile, grade 3 or higher adverse events occurred in 45.0% of the patients who received cemiplimab and in 53.4% of those who received chemotherapy. Overall, 8% of patients treated with cemiplimab discontinued due to AEs versus 5% of patients on investigator's choice of chemotherapy[45]. 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, Regeneron finally decided to withdraw the biologics license application for cemiplimab following discourse with the FDA in January 2022.

Immune checkpoint inhibitors combination approaches

ICI monotherapy has provided promising but modest efficacy results in advanced cervical cancer patients with significant rates of primary resistance. Recently, increasing pre-clinical and clinical data are supporting the use of ICI combination approaches in different tumor types as a potential strategy to overcome resistance, expecting to increase immune cell activation and reverse T cell exhaustion[46]. Several phase II trials that combined an anti-PD1/PDL1 and anti-CTLA4 therapy in advanced cervical cancer patients are discussed below.

CheckMate-358 also included a treatment arm that evaluated the efficacy and safety of nivolumab combined with ipilimumab (anti-CTLA-4) in patients with recurrent or metastatic squamous cervical cancer with up to two prior lines of therapy, regardless of PD-L1 expression status. Patients were randomly assigned to receive either: (A) nivolumab 3 mg/kg every two weeks plus ipilimumab 1 mg/kg every six weeks; or (B) nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every three weeks for four doses followed by nivolumab maintenance 240 mg every two weeks, for up to two years. The ORR (primary endpoint) seemed higher in Combination B *vs.* A (41.3% *vs.* 26.7%). Interestingly, patients with no prior systemic therapy for the recurrence/metastatic setting showed better efficacy outcomes across both treatment regimens, as compared

with those previously treated. Thus, ORR was higher among those not previously treated (31.6% *vs.* 23.1% and 45.8% *vs.* 36.4% with Combinations A and B, respectively), and median DOR was not reached for either regimen in patients without prior systemic therapy. Of note, despite having few patients in subgroups, responses were seen regardless of tumor cell PD-L1 expression. Regarding secondary endpoints, the OS rate at 12 months in patients with no prior systemic therapy was 83.5% and 78% for Combinations A and B, respectively. Concerning the toxicity profile, no new safety signals were detected. The higher incidence of any-grade treatment-related AEs and serious AEs leading to discontinuation with Combination B (19.6% and 10.9%, respectively) compared with Combination A (13.3% and 4.4%, respectively) should be noted. Besides, the incidence of treatment-related gastrointestinal, endocrine, and musculoskeletal events was greater in the Combination B arm compared with the Combination A arm, which could be explained by a higher dose of ipilimumab[47].

The phase II C-550-01 trial evaluated the combination of balstilimab and zalifrelimab (anti-CTLA-4) in patients with recurrent or metastatic cervical carcinoma with disease progression after first-line platinum-based chemotherapy, regardless of PD-L1 status. In total, 155 patients were enrolled in the trial and received the combination of balstilimab 3 mg/kg every two weeks and zalifrelimab 1 mg/kg every six weeks. The maximum duration of therapy was two years. Of these, 119 patients (69% squamous cell carcinoma and 31% adenocarcinoma/adenosquamous) met the eligibility criteria and were included in the efficacy analysis. The primary endpoint ORR was 25.6% (95%CI: 14%-28%). At the time of the data cut-off (95%CI: 1.3-15.4 months), the median DOR was not reached. Besides, ORR was seen across all histological subtypes (ORR of 32.6% in squamous cell carcinoma and 8.8% in adenocarcinoma/adenosquamous subgroups). Regarding PD-L1 expression status, 56.8% of cervical tumors had a CPS ≥ 1%, 25.2% had a CPS < 1%, and 18.1% were not evaluable or unknown. Once again, responses were demonstrated in both CPS < 1% (ORR of 9.1%) and CPS ≥ 1% (ORR of 32.8%) subgroups with this combination treatment. Regarding the safety profile, the combination of balstilimab and zalifrelimab was well tolerated. Note that, among immune-related AEs of any grade, the incidence of gastrointestinal disorders, laboratory abnormalities (creatinine, lipase, aminotransferases, electrolytes, and thyroid-stimulating hormone levels abnormalities), and endocrine disorders was higher with the combination compared with balstilimab monotherapy[48]. In addition, the RaPiDS study (NCT03894215) is a phase II randomized clinical trial aiming at assessing the efficacy and safety of balstilimab monotherapy and combined with zalifrelimab in women with recurrent or metastatic cervical cancer with relapse or progression after first-line platinum-based chemotherapy. This trial began inclusion in June 2019 and has an anticipated end date in 2024.

Immune checkpoint inhibitors in the frontline setting

The solid biological rationale for the use of ICI and the encouraging results in previously treated advanced cervical cancer patients mentioned above has led investigators to assess immunotherapy early on in the disease course when the host immune system is more robust. Interestingly, some preliminary clinical data show a better efficacy outcome of ICI in patients treated in the first-line setting, as discussed above in the CheckMate-358 trial's results. Besides, it is well known that platinum-based chemotherapy and bevacizumab (anti-VEGF-A) may modulate the immune tumor microenvironment favoring the synergism with anti-PD-1 and -PD-L1 monoclonal antibodies[49,50].

Currently, there are three phase III trials exploring the synergistic combination of ICI and first-line standard of care therapy based on platinum doublet (platinum and paclitaxel) with or without the addition of bevacizumab for recurrent, persistent, or metastatic cervical cancer patients: KEYNOTE-826 (NCT03635567), BEATcc (NCT03556839), and FERMATA (NCT03912415) trials. Thus far, KEYNOTE-826 is the only of these trials that have published its results.

KEYNOTE-826 was a phase III randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of the addition of pembrolizumab to frontline chemotherapy with or without bevacizumab in previously untreated persistent, recurrent, or metastatic cervical cancer patients. In total, 617 eligible adult patients (72% squamous cell carcinoma and 28% adenocarcinoma/adenosquamous) were randomly assigned in a 1:1 ratio to receive pembrolizumab 200 mg flat dose or placebo every three weeks for a total of 35 cycles plus platinum-based chemotherapy for up to six cycles and bevacizumab at the investigators' discretion. Stratification factors included metastatic status at diagnosis, prior bevacizumab exposure, and PD-L1 expression at baseline in either an archival tumor tissue sample or a fresh biopsy. The assessment of PD-L1 expression was done centrally during the screening period with PD-L1 IHC 22C3 pharmDx assay and measured according to CPS. The dual primary endpoints were PFS and OS, each tested sequentially in the PD-L1 CPS ≥ 1% population, then the ITT population, and, finally, in patients with a PD-L1 CPS ≥ 10%. The results presented come from the protocol-specified first interim analysis after a median follow-up of 22.0 months (range, 15.1-29.4 months). In 548 patients with a PD-L1 CPS ≥ 1% (89% of the overall population), the median PFS was 10.4 months in the pembrolizumab group and 8.2 months in the control group (HR 0.62; 95%CI: 0.50-0.77; $P < 0.001$). In the ITT population (617 patients), median PFS was 10.4 and 8.2 months, respectively (HR 0.65; 95%CI: 0.53-0.79; $P < 0.001$). In the 317 patients with a PD-L1 CPS ≥ 10%, median PFS was 10.4 and 8.1 months, respectively (HR 0.58; 95%CI: 0.44-0.77; $P < 0.001$). Whereas median OS was not reached in either PD-L1-selected population for pembrolizumab, it was 24.4 months in the ITT population for pembrolizumab, and it ranged from 16.3 to 16.5 months in the placebo arm. OS rate 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% in the PD-L1 CPS ≥ 1%, ITT group (HR 0.67; 95%CI: 0.54-0.84; $P < 0.001$), and 54.4% and 44.6% in the PD-L1 CPS ≥ 10% group (HR 0.61; 95%CI: 0.44-0.84; $P = 0.001$). Regarding the protocol-specified subgroup analysis (ITT population), the OS benefit provided by the addition of pembrolizumab was generally consistent across all patient subgroups. However, the PD-L1 CPS < 1% subgroup (11% of the overall population) seems to obtain the least survival benefit among the PD-L1-selected subpopulations (HR 1.00; 95%CI: 0.53-1.89). Besides, concomitant use of bevacizumab (63%) may have a significant impact on OS (HR 0.63; 95%CI: 0.47-0.87). Even though the trial met its primary endpoint in the ITT population based on the aforementioned subgroup analysis, the FDA has recently approved the use of pembrolizumab added to platinum-based chemotherapy with or without bevacizumab for those patients whose tumors are CPS ≥ 1%. Regardless, further studies are required to better understand the performance of pembrolizumab in these particular patient subgroups. Regarding key secondary endpoints, the confirmed ORR, according to the investigator review, was higher in the pembrolizumab group than in the placebo group among those with PD-L1 CPS ≥ 1% (68.1% *vs.* 50.2%), those in the ITT population (65.9% *vs.* 50.8%), and those with a PD-L1 CPS ≥ 10% (69.6% *vs.* 49.1%). Regarding the safety profile, the toxicity of this combination treatment was manageable. The observed AEs were expected based on the profile of the individual drugs. Anemia (30.3% in the pembrolizumab group *vs.* 26.9% in the placebo group) and neutropenia (12.4% *vs.* 9.7%) were the most common grade 3-5 AEs reported in this trial. The most common any-grade immune-related AEs were hypo- and hyperthyroidism (18.2% and 7.5%), 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[10].

An important clinical trial worth mentioning is BEATcc. This was a randomized, open-label phase III trial designed to assess the safety and efficacy of the addition of atezolizumab, an anti-PD-L1 monoclonal antibody, to cisplatin plus paclitaxel and bevacizumab in metastatic, persistent, or recurrent cervical cancer patients, regardless of PD-L1 expression. The co-primary endpoints were OS and PFS. Secondary endpoints included ORR per RECIST 1.1, safety and tolerability of the experimental arm, and the assessment of patient-reported outcomes (PROs). BEATcc enrolled patients with squamous cell, adenocarcinoma, or adenosquamous recurrent, persistent or metastatic 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 ineligible if they had received prior systemic therapy in the advanced setting or had disease infiltration of bladder or rectum at baseline pelvic magnetic resonance imaging (MRI) or any other contraindication of bevacizumab use since it was mandatory for all enrolled patients. Available archival or fresh tumor samples for PD-L1 expression assessment were mandatory. Patients were randomized in a 1:1 ratio to receive cisplatin 50 mg/m^2 plus paclitaxel 175 mg/m^2 plus bevacizumab 15 mg/kg every three weeks with or without atezolizumab 1200 mg flat dose in a 21-day cycle. Treatment was continued until disease progression, unacceptable toxicity, or death. In cases of developing prohibitive toxicity or achieving complete response after ≥ 6 cycles, chemotherapy could be dropped out, continuing only on bevacizumab and/or atezolizumab after discussion with the principal investigator. Randomized patients were stratified by three factors: (1) Prior concomitant chemoradiation; (2) histology (squamous cell carcinoma versus adenocarcinoma and adenosquamous); and (3) chemotherapy backbone (cisplatin *vs.* carboplatin). It is worth noting that PD-L1 expression status was not included as a stratification factor of the trial; 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 JGOG being GEICO the lead group on behalf of ENGOT. The trial was launched in 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 2022[51].

ENGOT-cx13/AGO/FERMATA is an international randomized, double-blind, placebo-controlled clinical trial designed to test the safety and efficacy of the addition of BCD-100, an anti-PD-1 monoclonal antibody, to platinum-based chemotherapy with or without bevacizumab, in advanced squamous cervical cancer patients, irrespective of PD-L1 expression status. The primary hypothesis of the study is that the combination of BCD-100 with standard treatment prolongs OS compared to placebo when combined with first-line treatment. The primary endpoint of the study is OS. PFS, ORR per RECIST 1.1, and immune-related RECIST will be among the key secondary endpoints. Women diagnosed with cervical cancer with squamous histology, having recurrent or progressing disease after primary treatment with curative intent, or stage FIGO IVB, not previously treated with a palliative systemic therapy, will be eligible. Determination of PD-L1 status by evaluation of a fresh tumor biopsy before randomization will be mandatory. Eligible patients will be randomized in a 1:1 ratio to receive either platinum-based chemotherapy (cisplatin 50 mg/m^2 or carboplatin AUC5 plus paclitaxel 175 mg/m^2) with or without bevacizumab 15 mg/kg at the investigator's discretion, in combination with BCD-100 3 mg/kg or placebo every three weeks until progression of the disease or unacceptable toxicity. If no dose-limiting toxicity is reached, chemotherapy will be continued for a minimum of six cycles. After this, chemotherapy can be stopped upon the investigator's decision or patient's wish, and therapy with BCD-100/placebo with or without bevacizumab would be maintained for the remainder of the clinical trial. Stratification factors will include stage of the disease (initial stage FIGO IVB, recurrent disease, or disease progressing during or shortly after curative therapy), use of bevacizumab (yes or no), tumor PD-L1 expression status (positive (CPS ≥ 1) or negative (CPS < 1)), and ethnicity (non-Asian or Asian descent). In total, 316 subjects from sites in Russia, China, Georgia, and Turkey will be included.

The planned duration of the clinical study is approximately 60 months (Q4 2019-Q4 2024), including about 24 months for enrollment and 36 months for final efficacy evaluation.

New immunotherapy approaches in advanced cervical cancer

Beyond ICI, several immunotherapy approaches are under evaluation in metastatic cervical cancer. Cancer vaccines and cell-based therapy are among the most promising strategies.

The well-known etiology implication of HPV in cervical cancer makes HPV-related oncoproteins an attractive target for vaccine-based therapies. ADXS11-001 is a live attenuated *Listeria monocytogenes* vector vaccine designed to liberate an HPV 16 E7 fusion protein targeting HPV-transformed cells. This would induce antitumoral T cell response and may break immune tolerance. The GOG/NRG0265 trial reported safety and efficacy preliminary results of the ADXS11-001 in previously treated persistent, recurrent, and metastatic cervical cancer (squamous and non-squamous). ADXS11-001 was globally well tolerated. The 12-month OS rate was 38.5%, suggesting clinical activity in this setting[52]. Besides, the combination of ADXS11-001 with cisplatin has been explored in a randomized phase II clinical trial. This study reported an encouraging 12-month OS rate of 34.9%, warranting further investigation[53]. AIM2CERV, a phase III randomized, placebo-controlled trial, was launched to evaluate the efficacy of ADXS11-001 administered in the adjuvant setting after completion of chemoradiation in patients with high-risk LACC. Unfortunately, the trial closed prematurely due to the lack of budget.

Peptide vaccines are already in clinical development. ISA101 contains 12 synthetic long peptides from HPV 16 E6/E7 proteins, capable of inducing HPV-specific T cells. A single-arm phase II trial explored the ORR of ISA101 combined with nivolumab in patients with incurable HPV 16-positive solid tumors. Of the 24 patients enrolled in this study (only one patient diagnosed with advanced cervical cancer), the ORR was 33% (90%CI: 19%-50%), with a median DOR of 10.3 months (95%CI: 10.3 months to inestimable), which compares favorably with response rates achieved with anti-PD-1 alone[54]. Therefore, a phase II open-label study (NCT04646005) has been launched to evaluate the efficacy and safety of ISA101b plus cemiplimab in patients with recurrent or metastatic, HPV 16-positive cervical cancer with disease progression from first-line therapy.

Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has shown inspiring responses in patients with recurrent or metastatic cervical cancer. C-145-04 (NCT03108495) is an ongoing, open-label, multicenter phase II clinical trial that aims to assess the efficacy and safety of LN-145 TILs in patients with previously treated metastatic cervical cancer. Prior ICI exposure is an important exclusion criterion to take into account. For TIL obtention, surgically removed tumor samples were harvested at local institutions and then sent to central facilities for TIL generation. The manufacturing process lasted 22 days. LN-145 TIL was then cryopreserved and shipped to study sites. Patients receive one week of lymphodepleting chemotherapy (cyclophosphamide and fludarabine). After this, patients received a single LN-145 infusion, followed by a maximum of six doses of IL-2 (600,000 IU/kg). Preliminary efficacy results were impressive. At a median follow-up of 3.5 months, the ORR was 44% and the disease control rate achieved was 89%. Note that 11 of 12 patients still maintained response at the moment of data cut-off[55]. Therefore, the encouraging efficacy outcomes of LN-145 led to FDA breakthrough therapy designation for pretreated advanced cervical cancer patients in 2019. Besides, the combination of LN-145 and pembrolizumab have been explored in treatment-naïve persistent, recurrent, or metastatic cervical cancer patients, showing an ORR of 57.1% and a disease control rate of 92.9% (median study follow-up of 7.6 months) with a manageable toxicity profile[56].

Regarding engineered T cell therapy, namely chimeric antigen receptors T cells (CAR-T) and T cell receptor-modified T cells (TCR-Ts), its clinical development in cervical cancer is still underway. Several early-phase trials showed preliminary efficacy data of TCR-Ts targeting different tumor-specific antigens such as proteins E6 (NCT02280811, NCT03578406) and E7 (NCT02858310) of HPV and MAGE-A3

(NCT02153905, NCT02111850). Besides, CAR-T therapies targeting antigens such as mesothelin (NCT01583686), CD22 (NCT04556669), or others (NCT03356795) are still under development.

NEW THERAPIES IN CERVICAL CANCER

Antibody-drug conjugates

Antibody-drug conjugates (ADC) are new therapeutic agents composed of a monoclonal antibody attached to a biologically active cytotoxic molecule through chemical linkers with labile bonds. The ADCs are designed to target specific antigens of tumor cells, such as tissue factor, HER2, AXL NaPi2B, or mesothelin. After binding to the target, the ADC releases a cytotoxic drug into the cancer cell. The cytotoxicity of ADC might be augmented by bystander effects on adjacent tumor cells and effects on the immune system[57]. Currently, several ADCs are under clinical development in advanced cervical cancer.

Tisotumab vedotin (TV) targets tissue factor (TF), highly prevalent in cervical cancer of both squamous and adenocarcinoma histological subtypes.

InnovaTV204 was a multicenter phase II clinical trial designed to evaluate the activity of TV in patients with recurrent or metastatic cervical cancer who had received up to two prior lines of chemotherapy in the advanced disease setting. Patients received TV 2.0 mg/kg every three weeks until unacceptable toxicity or progression of disease. In total, 102 patients were enrolled. The reported ORR was 24% (95%CI: 16%-33%). Seven patients achieved a complete response. The median DOR was 8.3 months (95%CI: 4.2 months to not reached) with a median PFS of 4.2 months (95%CI: 3.0-4.4 months) and a median OS of 12.1 months (95%CI: 9.6-13.9 months). TV showed tolerability aligned with ADC safety characteristics. The most common all-grade treatment-related AEs were alopecia, epistaxis, nausea, and conjunctivitis. Ocular events appeared as an emergent AE related to TV and need to be considered. Common ocular treatment-related AEs included conjunctivitis (26%), xerophthalmia (23%), and keratitis (11%). To reduce ocular adverse events, primary prophylactic with topical corticosteroid and vasoconstrictor eye drops and cooling masks during infusion were used. Despite the mitigation measures, ocular treatment-related AEs happened in 54 patients (25 with grade 1 and 27 with grade 2 events). Two patients suffered from a grade 3 AE (ulcerative keratitis)[58].

Based on these results, on 21 September 2021, the FDA approved TV in patients with persistent, recurrent, or metastatic cervical cancer with disease progression after chemotherapy. In Europe and Asia, the randomized phase III innovaTV301 clinical trial (NCT04697628) was recently launched to compare TV *vs.* physician's choice of chemotherapy in this setting.

The multi-cohort phase Ib/II InnovaTV205 trial was designed to evaluate the efficacy and safety of several TV combination approaches in patients with metastatic or recurrent cervical cancer. Preliminary results from Cohorts D (TV in combination with carboplatin in the first-line setting) and F (TV in combination with pembrolizumab in the second- or third-line setting) were presented at the ESMO 2021 congress and subsequently updated at the ASCO 2022 congress. Thirty-three patients were treated in the carboplatin combination cohort, achieving an ORR of 55% (95%CI: 36%-72%) with a DCR of 91% (95%CI: 76%-98%), while 32 patients were finally enrolled in the pembrolizumab combination cohort, showing an ORR of 38% (95%CI: 22%-56%). Recently, at the ASCO 2022 congress, results of Cohort E (TV in combination with pembolizumab in patients with recurrent or metastatic cervical cancer who have not received prior systemic therapy) were presented. Thirty-two evaluable patients achieved an ORR of 41% (95%CI: 24%-59%). This comprised five complete responses, eight partial responses, and 14 cases of stable disease. The safety profile was acceptable and the incidence of pre-specified AEs of interest was similar to those observed in the

InnovaTV204 trial[59,60]. Besides, a new cohort has been added to the InnovaTV205 trial, evaluating the combination of TV 2 mg/kg plus carboplatin AUC5 plus pembrolizumab 200 mg with or without bevacizumab 15 mg/kg every three weeks in patients with metastatic or recurrent cervical cancer with no prior systemic therapy[61].

Other ADCs are currently being investigated in several early-phase clinical trials, namely enapotamab vedotin, an AXL-targeting ADC (NCT02988817), and trastuzumab-deruxtecan, a HER2-directed ADC (NCT04482309).

Targeted therapies

Since the approval of TV, no further targeted therapies have been approved for patients with recurrent or metastatic cervical cancer who have progressed to first-line platinum-based therapy.

HER-2 mutations are found in 3%-6% of cervical cancer patients, preferentially in the adenocarcinoma histological subtype, and are associated with poor prognosis. Neratinib is an oral, irreversible, pan-HER TKI whose safety and efficacy profile were evaluated in the phase II SUMMIT basket trial. Sixteen HER2-mutant cervical cancer patients who had progressed to platinum-based treatment were included. Patients received neratinib 240 mg/day with loperamide prophylaxis during the first cycle. Neratinib showed evidence of clinical activity with an ORR of 25% (95%CI: 5.5%-57.2%). Median PFS and OS were 7.0 (95%CI: 0.7-18.3 months) and 16.8 months (95%CI: 4.1 months to not evaluable), respectively. The most common adverse events were diarrhea (75%), nausea (44%), and decreased appetite (38%)[62].

CONCLUSIONS

Cervical cancer is still one of the most burdensome cancers worldwide, even though it is a largely preventable disease. Therefore, the implementation of screening and vaccination programs remains of paramount importance. Regarding the persistent, recurrent and metastatic disease setting, there has been a large unmet medical need for active treatments aiming to overcome the dismal prognosis of this population. Fortunately, in recent years, major therapeutic breakthroughs have been achieved with the introduction of antiangiogenic agents, immunotherapy, and novel treatments such as ADCs. However, further efforts in basic and translational research are still needed to develop new therapeutic agents and better select our patients.

DECLARATIONS

Authors' contributions

Contributed in the conception, design, information collection, interpretation, and manuscript writing: Valdivia A, Grau-Béjar JF, García-Durán C, Oaknin A

Final approval was obtained for: Valdivia A, Grau-Béjar JF, García-Durán C, Oaknin A

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