

REVIEW

## Recurrent or primary metastatic cervical cancer: current and future treatments

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Despite screening programs for early detection and the approval of human papillomavirus vaccines, around 6% of women with cervical cancer (CC) are discovered with primary metastatic disease. Moreover, one-third of the patients receiving chemoradiation followed by brachytherapy for locally advanced disease will have a recurrence. At the end, the vast majority of recurrent or metastatic CC not amenable to locoregional treatments are considered incurable disease with very poor prognosis. Historically, cisplatin monotherapy, then a combination of cisplatin and paclitaxel were considered the standard of care. Ten years ago, the addition of bevacizumab to chemotherapy demonstrated favorable data in terms of response rate and overall survival. Even with this improvement, novel therapies are needed for the treatment of recurrent CC in first as well as later lines. In the last decades, a better understanding of the interactions between human papillomavirus infection and the host immune system response has focused interest on the use of immunotherapeutic drugs in CC patients. Indeed, immune checkpoint inhibitors (pembrolizumab, cemiplimab, and others) have recently emerged as novel therapeutic pillars that could provide durable responses with impact on overall survival in patients in the primary (in addition to chemotherapy) or recurrent (monotherapy) settings. Tisotumab vedotin, an antibody–drug conjugate targeting the tissue factor, is another emerging drug. Several trials in monotherapy or in combination with immunotherapy, chemotherapy, or bevacizumab showed very promising results. There is a high need for more potent biomarkers to better accurately determine which patients would receive the greatest benefit from all these aforementioned drugs, but also to identify patients with specific molecular characteristics that could benefit from other targeted therapies. The Cancer Genome Atlas Research Network identified several genes significantly mutated, potentially targetable. These molecular data have highlighted the molecular heterogeneity of CC.

**Key words:** cervical cancer, metastatic, chemotherapy, immunotherapy, tisotumab vedotin

### INTRODUCTION

According to GLOBOCAN 2020, cervical cancer (CC) is the fourth most common cancer in women worldwide after breast, colorectal, and lung cancers, respectively, and is the second most common cancer in developing countries, where >85% of cases occur. Worldwide, an estimated 604 000 new cases of CC and 342 000 deaths are recorded, although incidence and mortality vary widely among countries.<sup>1,2</sup> In developed countries, incidence has decreased over the past 30 years due to the introduction of screening and vaccination programs.<sup>3</sup>

A persistent infection with human papillomavirus (HPV), a sexually transmitted deoxyribonucleic acid (DNA) virus, is detected in 99% of CC cases. Although the majority of HPV infections are transitory, HPV persists in 10% of cases, leading to the development of a preinvasive or invasive lesion 15–20 years after the initial infection.<sup>4</sup>

HPVs encode two oncoproteins, E6 and E7, which play critical roles in the development of HPV-induced carcinogenesis.

The E6 protein induces principally p53 degradation and the up-regulation of vascular endothelial growth factor (VEGF) which, in turn, lead to angiogenesis. E7 inactivates the retinoblastoma protein (pRb), increasing Ki-67 protein levels. Both E6 and E7 proteins also induce AKT phosphorylation that causes cell survival and proliferation; but they also activate transcription factors inducing cellular invasion.<sup>5</sup>

Squamous cell carcinoma (SCC), adenocarcinoma (ADK), and adenosquamous carcinoma (ADSC) are the three most common histological subtypes, accounting for 70%, 25%,

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and 5% of cases, respectively. In contrast to SCC which has experienced a progressive decrease in incidence and mortality in recent decades, the incidence and mortality of ADK has increased during the same timeframe.<sup>6</sup> This evolution has been attributed to the Papanicolaou test and its ability to detect squamous, rather than glandular, neoplasia more efficiently.<sup>7</sup>

Overall survival (OS) at 5 years is approximately 92%, 65%, and 17% for early-stage, locally advanced, and metastatic disease, respectively. The prognosis of patients with recurrent disease remains very poor, with an estimated OS around 13-17 months.<sup>8</sup> Even with the major progresses made and the optimized treatment of locally advanced CC (LACC) over the past two decades, around 30% of patients will suffer from recurrent disease.<sup>9</sup> Moreover, around 6% of the women are discovered with primary metastatic disease. By a majority, patients in recurrence will benefit from systemic treatments such as chemotherapy (CT) with or without angiogenesis inhibitors. Surgery (exenteration) is an option for only a very well selected group of patients.<sup>10</sup>

In this review, we discuss historical, current, and emerging treatment options for patients with primary metastatic or recurrent CC.

## CHEMOTHERAPY

### Cisplatin monotherapy

Historically, disseminated recurrent CC was treated with cisplatin monotherapy that was considered as the standard of care (SOC) since the results of the phase II Gynecologic Oncology Group (GOG)-26 trial. Most of the patients included were chemonaive as radiotherapy (RT) alone was the established treatment of LACC patients at that time. The overall response rate (ORR) and the median OS (mOS) were 38% and 9 months, respectively.<sup>11</sup> Another GOG trial demonstrated that the 100 mg/m<sup>2</sup> single-dose schedule has produced a statistically higher ORR than the 50 mg/m<sup>2</sup> regimen, without impact on survival, but with higher toxicity.<sup>12</sup>

### Non-cisplatin agents

Several non-platinum drugs were also tested in phase II trials such as paclitaxel, irinotecan, topotecan, vinorelbine, ifosfamide, but also 5-fluorouracil, docetaxel, doxorubicin, gemcitabine, and mitomycin. An ORR of 15%-46% was observed but with median progression-free survival (mPFS) around 2-3 months and limited gains in OS.<sup>13</sup>

### Cisplatin 'doublet' combinations

Several trials were conducted with cisplatin plus ifosfamide, gemcitabine, topotecan (GOG-179), paclitaxel (GOG-169), or vinorelbine. All these combinations increased PFS but only the combination of topotecan with cisplatin statistically increased the mOS. The GOG-179 trial was conducted in parallel with the approval of cisplatin as radiosensitizing agent in locally advanced setting. Therefore, 40% of patients had not received prior cisplatin and the effect of the

combination schedule was less beneficial in the population receiving chemoradiation, despite remaining statistically significant.<sup>14</sup> In the light of these studies, the GOG-204 evaluated four platinum doublets consisting of cisplatin with paclitaxel, gemcitabine, topotecan, or vinorelbine. The first doublet demonstrated an ORR, PFS, and OS of 29.1%, 5.8, and 12.9 months, respectively. No statistical superiority between arms was demonstrated despite there was a trend in all the endpoints favoring paclitaxel with cisplatin. Nevertheless, this combination was considered the SOC, especially in women who had not received prior cisplatin-based therapy.<sup>15,16</sup>

### Cisplatin 'triplet' combinations

In the GOG-179 trial, there was also a third comparison arm using the combination of methotrexate with vinblastine, adriamycin, and cisplatin (MVAC) regimen, but that arm was stopped early due to a higher rate of treatment-related deaths.<sup>14</sup> Two phase II trials confirmed that other triplet regimens did not improve outcome but increased toxicity.<sup>17,18</sup>

### Carboplatin

The JCOG-0505 non-inferior study randomized 253 patients with stage IVB recurrent CC between paclitaxel and carboplatin or cisplatin. Paclitaxel plus carboplatin demonstrated its non-inferiority regarding PFS and OS, and its significant reduction in toxicity. Nevertheless, a *post hoc* analysis revealed that the cisplatin doublet regimen was superior in the subgroup of patients who had not received prior cisplatin.<sup>19</sup>

## ANGIOGENESIS INHIBITORS

### Rationale

Tumor foci relapsing or persisting in the irradiated field may have compromised the blood supply, inducing hypoxia and therefore limiting the delivery of CT drugs. These characteristics may explain the limited response to retreatment with traditional CT. Moreover, we have previously described the effects of E6/E7 proteins on the angiogenic pathway.<sup>5</sup> Furthermore, VEGF has been identified as a major pro-angiogenic factor and marker of poor prognosis. In fact, overexpression of VEGF/VEGF correlates with larger tumors, parametrial infiltration, lymph node involvement, distant metastasis, and poorer OS; and was also observed in tumor samples obtained from CC patients with post-RT relapse.<sup>20-23</sup>

### Bevacizumab

Bevacizumab, a humanized monoclonal antibody targeting VEGF, was the most widely studied and used anti-angiogenic therapy in patients with CC.<sup>24</sup> Based on the favorable results in a phase II trial (GOG-227C) with heavily pretreated patients, GOG-240, a randomized phase III trial combining bevacizumab with CT (paclitaxel and cisplatin or topotecan) was started. The author demonstrated an

improvement in both PFS [8.2 versus 5.9 months; hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.54-0.82] and OS (17.0 versus 13.3 months; HR 0.71, 95% CI 0.54-0.95).<sup>25,26</sup> The Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved these combinations for patients with metastatic, persistent, or recurrent CC in 2014 and 2015, respectively.

### Other anti-angiogenic drugs

Other anti-angiogenic drugs (such as pazopanib, cediranib, apatinib, sunitinib) have been studied alone or in combination with CT. These studies demonstrated some significant benefits but with the addition of toxicities.<sup>27-30</sup> The results of the randomized phase II study including 120 patients with primary advanced (25%) or first-line recurrent (75%) CC treated by carboplatin and paclitaxel with or without nintedanib were recently presented by Vergote et al.<sup>30</sup> The majority (62%) of the patients had SCC histology and 64% received prior RT. The primary endpoint was met with a PFS at 18 months of 15.1% versus 12.8% in favor of the nintedanib arm ( $p$  minuscule = 0.057). Nevertheless, subgroup analysis demonstrated a statistical difference in PFS only in the recurrent setting: the 1-year PFS was 22.8% and 14.9% in favor of nintedanib. The mOS was 21.7 and 16.4 months for nintedanib and control arms, respectively. No new safety signals were observed.<sup>30</sup>

### EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Epidermal growth factor receptor (EGFR) overexpression is demonstrated in 80% of newly diagnosed CC and associated with reduced survival and poor response to chemoradiation.<sup>31-33</sup> Furthermore, human EGFR2 (HER2) mutations and amplifications were observed in 3%-6% and 1%-12% of CC, respectively, and were also correlated with a worse prognosis.<sup>34</sup> Although EGFR inhibition seemed a promising target in CC treatment, several phase II studies evaluating EGFR inhibitors such as cetuximab, gefitinib, erlotinib, or lapatinib showed only limited activity.<sup>27,35-37</sup> Neratinib was explored in the phase II SUMMIT trial including 16 patients (62.5% of ADK) with HER2-mutated recurrent CC progressing after platinum-based treatment. An ORR, mPFS, and mOS of 25%, 7.0, and 16.8 months, respectively, were observed.<sup>38</sup>

### IMMUNOTHERAPY

In the last decades, a better understanding of the interactions between HPV infection and the host immune system response has focused interest on the use of immunotherapeutic drugs in CC patients.

#### Rationale

Firstly, almost all cases of CC are driven by high-risk HPV infection. HPV has several mechanisms by which it induces an immunosuppressive tumor microenvironment (TME) and a deficient immunosurveillance. Of particular importance, E6 and E7 proteins modify the expression of transforming growth factor- $\beta$  (TGF- $\beta$ ) in infected cells. Up-regulation of

TGF- $\beta$  induces an immunosuppressive TME by acting notably on regulatory T (Treg) cells. Furthermore, interleukin 10 (IL-10) changes the cytokine profile from a T helper 1 (Th1) profile to a Th2 profile, which is more immunosuppressive.<sup>39</sup> Secondly, various immune inhibitory molecules such as Programmed cell death-1 (PD-1)/Programmed cell death ligand-1 (PD-L1) are expressed by CC. PD-L1 is rarely observed in normal cervical tissue. PD-L1 expression in SCC varies widely from 19% to 88% according to different series and is less frequent in ADK histology (14%).<sup>40,41</sup> Several studies have also demonstrated high expression levels of other immunomodulatory molecules such as cytokines (TGF- $\beta$ , IL-10), cytotoxic T-lymphocyte antigen-4 (CTLA-4) and surface receptors (TIM3).<sup>42,43</sup> Thirdly, the composition of the TME in CC has an impact on survival: CD8+, CD4+, and Treg cells are more abundant in CC than in normal cervical tissue, with a negative impact on survival.<sup>44,45</sup> Finally, CC has an increased total mutational burden (TMB) rate (around 5-6 mutations per megabase).<sup>46,47</sup>

### Immune checkpoint inhibitors (ICIs)

Inhibitors of PD-1 (pembrolizumab, nivolumab, cemiplimab, balstilimab) and PD-L1 (atezolizumab, avelumab, durvalumab, camrelizumab), as well as inhibitors of CTLA-4 (ipilimumab, zalifrelimab) are being evaluated in several CC trials<sup>48,49</sup> (see Tables 1-4). Table 1 summarizes the results of monotherapy clinical trials.

Several scoring systems and cut-offs have been developed to assess PD-L1 expression by immunohistochemistry. These systems have been used as biomarkers in clinical trials testing immune checkpoint inhibitors (ICIs) in CC. In tumor proportion score, PD-L1 expression in tumors is evaluated by the ratio of PD-L1-stained tumor cells (TCs) to the total number of viable TCs. The combined positive score (CPS) is defined as the total number of PD-L1-stained cells (including TCs, lymphocytes, and macrophages) divided by the number of all viable TCs, then multiplied by 100.<sup>50</sup>

#### Monotherapy trials

**Pembrolizumab.** KEYNOTE-028 was a phase Ib study testing pembrolizumab in 24 patients with SCC expressing PD-L1. An ORR of 17% was reported.<sup>51</sup>

KEYNOTE-158, a phase II basket trial, evaluated the safety and efficacy of pembrolizumab, in 98 previously treated patients. The median duration of response (mDOR) was not reached and the ORR was of 12.2%. All responses were observed in the PD-L1 CPS  $\geq 1$  cohort. Fifty percent of responses were ongoing after  $\geq 24$  months.<sup>52,53</sup> These results led to FDA approval of pembrolizumab in the treatment of recurrent or metastatic PD-L1-positive CC patients with disease progression during or after CT. The drug is not approved by EMA in this setting.

**Nivolumab.** CheckMate-358 is an ongoing phase I/II trial evaluating nivolumab in recurrent and metastatic squamous cell cervical, vulvar, and vaginal cancers. Results from 19 CC patients were published, with an ORR of 26.3% (regardless

**Table 1. Monotherapy clinical trials**

Drug	Trial	Phase	N	Population	Histology (%)	Prior RT (%)	Prior bevacizumab (%)	PD-L1 expression (%)	Number of prior lines (%)	ORR (%)	mDOR (months)	mPFS (months)	mOS (months)	Grade 3-4 TRAEs (%) Discontinuation (%)
Pembrolizumab	KEYNOTE-028	Ib	24	Locally advanced or metastatic; PD-L1+; progression after prior therapy	SCC = 96 ADK = 4	92	42	TC = 75 TC + stroma = 25	1 = 38 2 = 25 ≥3 = 38	17	5.4	2	11	20.8 8.3
	KEYNOTE-158	II	98	Advanced disease; progression during or intolerance to ≥1 lines of prior therapy	SCC = 93.9 ADK = 5.1 ADSC = 1.0	86.7	41.8	CPS ≥1 = 83.7	1 = 30.6 2 = 34.7 ≥3 = 30.6	All = 12.2 PD-L1+ = 14.6 PD-L1- = 0	NR	2.1	9.4	12.2 4.1
Nivolumab	CheckMate-358	I/II	19	Recurrent or metastatic; HPV+; SCC	SCC = 100	89.5	31.6	CPS ≥1 = 62.5	1 = 42.1 2 = 42.1 3 = 15.8	26.3	NR	5.1	21.9	21.1 5.3
	NRG-GY002	II	26	Persistent, recurrent, or metastatic disease; progression after 1 prior line of CT	SCC = 60 ADK = 24 ADSC = 16	92	—	CPS ≥1 = 77.3	1 = 100	4	3.8	3.5	14.5	32 —
Balstilimab	NCT03104699	II	161	Metastatic, persistent, or recurrent disease; after a first line	SCC = 62.7 ADK = 32.3 ADSC = 4.3	—	29.2	CPS ≥1 = 61.5	1 = 100	All = 15 SCC = 17.6 ADK = 12.5 PD-L1+ = 20 PD-L1- = 7.9	15.4	NE	NE	11.8 4.3
Cemiplimab	EMPOWER-Cervical 1/ GOG-3016/ ENGOT-cx9	III	Cemiplimab arm = 304 CT arm = 304	Recurrent and metastatic resistant to platinum-based CT ≥2 lines	SCC = 77.8 ADK = 19.1 ADSC = 3.1	—	48.7	Cemiplimab arm/CT arm TC = 41.4/42.1	1 = 56.9 >1 = 42.6	Cemiplimab arm/CT arm (all) 16.4/6.3	Cemiplimab arm/CT arm (all) 16.9/6.9	All = 2.8	All = 12	Cemiplimab arm/CT arm 45/53.4 8.7/5.2
Ipilimumab	NCT01693783	I/II	42	Metastatic disease; progression after at least 1 line of platinum CT	SCC = 69 ADK = 31	83	—	PD-L1+ = 19	2 or 3 = 50	8.8	NE	2.5	8.5	28.5 —

ADK, adenocarcinoma; ADSC, adenosquamous carcinoma; CPS, combined positive score; CT, chemotherapy; HPV, human papillomavirus; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; N, number of patients included; NE, not evaluable; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand-1; RT, radiotherapy; SCC, squamous cell carcinoma; TC, tumor cell; TRAEs, treatment-related adverse events.

Outcomes	SCC		All population		ADK <sup>a</sup>		PD-L1 TC $\geq 1\%$		PD-L1 TC $< 1\%$	
	Cemiplimab	CT	Cemiplimab	CT	Cemiplimab	CT	Cemiplimab	CT	Cemiplimab	CT
PFS										
Median, months	2.8	2.9	2.8	2.9	2.7	2.8	3	2.9	1.9	2.9
HR (95% CI, <i>P</i> value)	0.71 (0.58-0.86, <i>P</i> < 0.001)		0.75 (0.63-0.89, <i>P</i> < 0.001)		0.91 (0.62-1.34)		0.76 (0.53-1.08, NS)		1.00 (0.62-1.60, NS)	
OS										
Median, months	11.1	8.8	12.0	8.5	13.3	7	13.9	9.3	7.7	6.7
HR (95% CI, <i>P</i> value)	0.73 (0.58-0.91, <i>P</i> = 0.006)		0.69 (0.56-0.84, <i>P</i> < 0.001)		0.56 (0.36-0.85, <i>P</i> < 0.005)		0.70 (0.46-1.05, NS)		0.98 (0.59-1.62, NS)	
ORR										
Rates, %	17.6	6.7	16.4	6.3	12.3	4.5	18.3	7.5	11.4	8.3
OR (95% CI)	—		2.98 (1.71-5.22)		—		2.72 (0.99-7.46)		1.80 (0.40-8.18)	

ADK, adenocarcinoma; CT, chemotherapy; NA, not available; NS, non-significant; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; SCC, squamous cell carcinoma; TC, tumor cell.

<sup>a</sup>Assessment not a prespecified endpoint (*post hoc* analysis).

of PD-L1 expression) and a DOR not reached (minimum of 23.3 months). Concerning the five patients with vaginal/vulvar cancers, only one response was observed with a DOR of 5.0 months.<sup>54</sup>

NRG-GY002 was a phase II study evaluating nivolumab in 26 previously treated patients. Santin et al.<sup>55</sup> showed 4% of partial responses (PR) and 36% of stable disease (SD). Estimated mPFS and mOS were 3.5 and 14.5 months, respectively.<sup>55</sup>

**Balstilimab.** A phase II trial, including 161 women with recurrent and/or metastatic CC who had relapsed after a prior platinum-based treatment regimen, was recently published by O'Malley et al.<sup>56</sup> The ORR was 15%, 20% and 7.9% in the overall population, PD-L1 positive and negative tumors, respectively. The mDOR was 15.4 months.<sup>56</sup>

**Cemiplimab.** The EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 phase III study included 608 patients with recurrent or metastatic CC, either SCC, ADK, or ADSC, progressing after platinum-based CT. Patients were enrolled regardless of PD-L1 TC expression. The women were randomized between treatment with cemiplimab or CT of investigator's choice (pemetrexed, gemcitabine, topotecan, irinotecan, or vinorelbine). Ninety-four percent (94.4%) and 5.6% of the patients were in the metastatic or recurrent/persistent settings, respectively. The first step of this hierarchical statistical design concerned the SCC population, with a median duration of follow-up of 16.8 months.

The mOS was 11.1 and 8.8 months with cemiplimab and CT, respectively. After the second interim analysis (85% of total OS events had occurred), the independent data monitoring committee recommended the trial be stopped early for efficacy. In the overall population (second step), the mOS results were almost similar with 12.0 versus 8.5 months. The OS benefit of cemiplimab was observed across all prespecified subgroups. Nevertheless, in patients with more than one prior line in the metastatic setting, the benefit is not statistically significant (HR 0.81; 95% CI 0.59-1.10). Full details concerning mPFS, mOS, and ORR in the SCC-overall and ADK populations, as well as in patients with PD-L1 TC  $\geq 1$  or  $< 1\%$  are described in Tables 1 and 2.

For patients receiving cemiplimab, treatment improved or maintained quality of life (QoL) from baseline, whereas with CT, QoL generally deteriorated. In fact, no new safety signals were observed in this analysis.<sup>57</sup> Following results of this trial, the FDA granted a priority review (28 September 2021) but biologic license application was voluntarily withdrawn by Sanofi/Regeneron following discourse with the FDA (January 2022). The submission to EMA is ongoing.

**Ipilimumab.** Lheureux et al.<sup>58</sup> showed the results of a phase I-II study in 42 recurrent or metastatic CC patients treated by ipilimumab. The mPFS and mOS were 2.5 and 8.5 months, respectively. Best responses included one PR and ten SD.<sup>58</sup>

### Combination trials

Several trials have tested the efficacy of combinatorial approaches with anti-PD-1/PD-L1 agents and either CT, other ICIs, or angiogenesis inhibitors. Table 3 summarizes the results of combination clinical trials.

**ICIs + CT.** The KEYNOTE-826 phase III trial was a randomized, double-blind, placebo-controlled study comparing platinum-based CT (paclitaxel + cisplatin or carboplatin up to six cycles with or without bevacizumab) plus or minus pembrolizumab (up to 35 cycles) for patients with persistent, recurrent, or metastatic CC not previously treated by CT and not amenable to curative treatment. The study enrolled 617 patients with SCC, ADK, or ADSC histologies. The dual primary endpoints were PFS and OS, each tested sequentially in patients with a PD-L1 CPS  $\geq 1$ , in the all-comer population, and in patients with a PD-L1 CPS  $\geq 10$ . Overall, 56.4% received previous chemoradiotherapy with or without surgery, and 19.8% had previously untreated metastatic disease at trial entry. Median PFS, mOS, and mDOR were significantly and statistically longer in the pembrolizumab than in the placebo arm in the three subgroups. The HR for OS and PFS for the subgroup without concomitant bevacizumab were slightly higher than those for the subgroup with concomitant bevacizumab and the 95% CI crossed 1. In the small subgroup of 69 patients with

**Table 3. Combination clinical trials**

Regimen	Trial	Phase	N	Population	Histology (%)	Prior RT (%)	Prior bevacizumab (%)	PD-L1 expression (%)	Number of prior lines	ORR(%)	mDOR (months)	mPFS (months)	mOS (months)	Grade 3-4 TRAEs (%) Discontinuation (%)
					Pembro/placebo	Pembro/ placebo	Pembro/ placebo	Pembro/placebo						Pembro/placebo
Chemotherapy (carboplatin or cisplatin + paclitaxel) + pembrolizumab ± bevacizumab	KEYNOTE-826	III	Pembro arm = 308 Placebo arm = 309	Persistent, recurrent, or metastatic not previously treated by CT and not amenable to curative treatment	SCC = 76/68.3 ADK = 18.2/27.2 ADSC = 4.9/4.5	73.7/71.6	63.6/62.5	CPS <1 = 11.4/11 CPS 1-<10 = 37.3/37.5 CPS ≥10 = 51.3/51.5	0	All = 65.9	All = 18	All = 10.4	All = 24.4	68.4/64.1 Any agent 31.3/22.3 All treatment 3.3/1.9
Ipilimumab plus nivolumab	CheckMate-358	I/II	Combo A: IPI 1 + NIVO 3 mg/kg = 45 Combo B: IPI 3 + NIVO 1 mg/kg = 45	Recurrent or metastatic; with or without prior systemic therapies (PST)	SCC = 100	Combo A/B 84.4/84.8	Combo A/B 53.3/54.3	Combo A/B TC ≥1 = 62.2/67.6	Combo A/B 0 42.2/52.2 ≥1 57.8/47.8	Combo A/B No PST = 31.6/45.6 PST = 23.1/36.4	Combo A/B No PST = NR/NR PST = 14.6/9.5	Combo A/B No PST = 13.8/8.5 PST = 3.6/5.8	Combo A/B No PST = NR/NR PST = 10.3/25.4	Combo A/B 28.9/37 4.4/13
Cadonilimab	NCT04380805	II	21	Recurrent or metastatic						47.6				
Zalifrelimab plus balstilimab	NCT03495882	II	155	Recurrent and/or metastatic disease; after a first-line platinum-based CT	SCC = 70.3 ADK = 27.1 ADSC = 2.6	89	32.9	CPS ≥1% = 56.8	Median = 1 (0-2)	All = 25.6 SCC = 32.6 ADK = 8.8 PD-L1+ = 32.8 PD-L1- = 9.1	NR	2.7	12.8	20.0 7.7
Atezolizumab plus bevacizumab	NCT02921269	II	11	Recurrent, persistent, or metastatic. Progression after 1-2 prior therapies at least containing Bevacizumab	SCC = 55 ADK = 45	73	100	CPS ≥1 = 37.5	1 = 45 2 = 55	0	—	2.9	8.9	36.4 18.1
Camrelizumab plus apatinib	NCT03816553 (CLAP)	II	45	Metastatic, recurrent, or persistent; progression after at least 1 line systemic therapy	SCC = 66.7 ADK = 33.3	88.9	22.2	CPS ≥1 = 66.7	1 = 42.2 2 = 42.2 ≥3 = 15.5	All = 55.6 SCC = 77.8 ADK = 28.6 PD-L1+ = 69 PD-L1- = 50	NR	8.8	NR	71.1 —
Bintrafusp alfa	NCT02517398 NCT03427411	I/II	39	Recurrent/metastatic; pretreated	SCC = 64.1 ADK = 30.8 ADSC = 2.6	82.1	64.1	TC ≥1% = 30.8	1 = 33.3 2 = 25.6 ≥3 = 41	All = 28.2 SCC = 25 ADK = 41.7	11.7	2.1	13.4	23.1 —

ADK, adenocarcinoma; ADSC, adenosquamous carcinoma; CPS, combined positive score; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; N, number of patients included; NR, not reached; ORR, objective response rate; PD-L1, programmed cell death ligand-1; RT, radiotherapy; SCC, Squamous cell carcinoma; TC, tumor cell; TRAEs, treatment-related adverse events.

**Table 4. KEYNOTE-826 trial**

Outcomes	PD-L1 CPS $\geq 1$		All-comer		PD-L1 CPS $\geq 10$	
	Pembro	Placebo	Pembro	Placebo	Pembro	Placebo
PFS						
Median, months	10.4	8.2	10.4	8.2	10.4	8.1
HR (95% CI, <i>P</i> value)	0.62 (0.50-0.77, <i>P</i> < 0.001)		0.65 (0.53-0.79, <i>P</i> < 0.001)		0.58 (0.44-0.77, <i>P</i> < 0.001)	
OS						
Median, months	NR	16.3	24.4	16.5	NR	16.4
HR (95% CI, <i>P</i> value)	0.64 (0.50-0.81, <i>P</i> < 0.001)		0.67 (0.54-0.84, <i>P</i> < 0.001)		0.61 (0.44-0.84, <i>P</i> = 0.001)	
ORR						
Rates, %	68.1	50.2	65.9	50.8	69.6	49.1
DOR						
Median, months	18.0	10.4	18.0	10.4	21.1	9.4

CPS, combined positive score; DOR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; Pembro, pembrolizumab; PFS, progression-free survival.

a PD-L1 CPS <1 (11.2% of all the population), it is difficult to draw clear conclusions, but the effect, if any, appears small. Time to QoL deterioration was longer with pembrolizumab than with placebo (12 month estimate of patients free from deterioration, 58.2% versus 44.8%; HR 0.75; 95% CI 0.58-0.97).<sup>59</sup> Full details regarding mPFS, mOS, mDOR, ORR and toxicities are provided in Tables 3 and 4.

Two other phase III trials are evaluating the addition of ICIs to CT. The BEATcc/ENGOT-Cx10 trial compared the association of cisplatin, paclitaxel and bevacizumab with or without atezolizumab in metastatic, persistent, or recurrent CC. This study is now closed for recruitment. Similarly, the FERMATA trial evaluated BCD-100 (PD-1 inhibitor). The results of these two phase III trials are eagerly awaited.

**PD-1 or PD-L1 + CTLA-4 inhibitors.** The results of the CheckMate-358 trial including 91 patients with SCC who had received or not prior systemic therapies for recurrent or metastatic disease were presented in 2019. Nivolumab + ipilimumab ‘high-dose’ showed more efficacy for patients who had previously received treatment. There were also promising results in the ‘low-dose’ arm when the patient had not received CT before.<sup>60</sup>

O’Malley et al.<sup>61,62</sup> recently published the results of a phase II trial including 155 patients treated with a combination of balstilimab and zalifrelimab. The median follow-up was 19.4 months. The ORR was 25.6% with 16.8% and 8.8% of PR and complete responses (CR), respectively. The mDOR was not reached in the combination arm.<sup>61,62</sup>

Cadonilimab (AK104) is a novel humanized first-in-class tetrameric bi-specific antibody targeting PD-1 and CTLA-4, recently accepted by China in the treatment of relapsed or metastatic CC. This approval is based on the data from the phase II study (NCT04380805) testing cadonilimab in 21 patients with recurrent or metastatic CC: the ORR and disease control rate (DCR) were 47.6% and 66.7%, respectively. The toxicity seems significantly reduced compared with the traditional combination therapy of both drugs. Currently, the results of this study have not yet been published or presented in a large international meeting. A

phase III (NCT04982237) trial evaluating this drug with a platinum-based CT with or without bevacizumab as first-line treatment of persistent, recurrent, or metastatic CC, is ongoing. Of note, the FDA also granted fast track and orphan drug designations.<sup>63,64</sup>

**ICIs + angiogenesis inhibitors.** Tumor vascular remodeling could enhance the efficacy of immunotherapy. In fact, TCs rapidly outgrow their blood supply, leading to hypoxia in the TME, promoting immunosuppressive mechanisms. Hypoxia stimulates hypoxia-inducible factor (HIF-1) which in turn up-regulates VEGF. This later induces malformed and mal-functional vasculature that can stop the penetration of CD8+ tumor-infiltrating lymphocytes (TILs) into the tumor.<sup>65</sup>

In a phase II trial, Friedman et al.<sup>66</sup> tested the combination of atezolizumab and bevacizumab in 11 heavily pre-treated CC patients. The author showed no responses but 60% of DCR.<sup>66</sup>

The CLAP trial is a multicenter, single-arm, phase II study that enrolled 45 patients with advanced CC progressing after at least one line of CT. The trial tested the combination of camrelizumab and apatinib. The ORR in the overall population was 55.6%. Median DOR and OS were not reached.<sup>67</sup>

**Bintrafusp alfa.** As previously mentioned, the TME is invaded by different immunomodulating molecules such as cytokines and notably TGF- $\beta$ . Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF- $\beta$ -RII receptor which functions as a TGF- $\beta$  ‘trap’ fused to an PD-L1 inhibitor.<sup>68</sup> Strauss et al.<sup>69</sup> reported pooled (phase I and II) safety and efficacy of 39 patients with ICI-naive, recurrent/metastatic CC treated with this drug. The ORR was 28.2% in the all-comer population and responses occurred irrespective of tumor histology or prior bevacizumab or radiation treatment. Any-grade, grade 3, and grade 4 treatment-related adverse events (TRAEs) occurred in 33 (84.6%), 8 (20.5%), and 1 patient (2.6%), respectively.<sup>69</sup> The results of the phase II study (INTR@PID CERVICAL 017) are awaited.

**ICIs + other checkpoint inhibitors.** Tiragolumab is a humanized antibody targeting T-cell immunoreceptor with Ig and ITIM domains (TIGIT). TIGIT is an inhibitory immune checkpoint; blocking TIGIT's binding to its ligand (CD155) enhances T- and NK-cell activity.<sup>70</sup> Tiragolumab is being investigated in the phase II SKYSCRAPER-04 (NCT04300647) trial that compares atezolizumab with or without tiragolumab in patients with metastatic and/or recurrent PD-L1-positive CC.

Relatlimab, a humanized antibody targeting the immune checkpoint lymphocyte-activation gene 3 (LAG-3), is being evaluated in combination with nivolumab in a phase I/II trial.<sup>71</sup>

### Therapeutic cancer vaccines

Various types of therapeutic cancer vaccine exist such as dendritic cell-based, TC-based, peptide protein-based, nucleic acid-based, and live vector-based vaccines.<sup>72</sup> Traditionally, CC has been the main focus for research on HPV-associated disease and development of prophylaxis and therapy against such.<sup>73</sup>

ISA101, a synthetic long peptide of HPV16 E6 and E7 in combination with CT, was tested in 77 patients with advanced, metastatic, or recurrent CC. The treatment resulted in regression and SD, both in 43% of the patients. Moreover, vaccine-specific T-cell responses correlated with increased probability of survival.<sup>74</sup>

The DNA-based vaccine GX-188 combined with pembrolizumab showed lesion regression in 42% of the 26 HPV-positive CC patients, with PR and CR in seven and four patients, respectively.<sup>75</sup> The VB10.16 phase I/II trial is currently ongoing with no reports on preliminary results.<sup>76</sup>

Axalimogene filolisbac (ADXS11-001 or AXAL) is a *Listeria monocytogenes*-derived, live attenuated vaccine targeting the HPV-16 E7 protein.<sup>77</sup> The GOG-0265 phase II study evaluated this vaccine to treat patients who progressed on or after at least one prior line of CT. ADXS11-001 was administered as monotherapy in 50 patients and obtained an ORR, DCR, and 12-month OS of 2%, 32%, and 38%, respectively. Adverse events of grade 3 were developed by 36% of patients, mainly symptoms of cytokine release.<sup>78</sup> This vaccine has also been investigated in a randomized phase II study in monotherapy or in combination with cisplatin, including 110 Indian patients (69 assessable) with recurrent or persistent CC. The two cohorts showed similar results in terms of ORR (17.1% and 14.7%, respectively) and TRAEs.<sup>48,79</sup> Of note, a phase III study in a locally advanced setting was closed for futility and slow recruitment. Finally, durvalumab alone or in combination with ADXS11-001 was tested in 54 patients with persistent, recurrent, or metastatic CC. The ORR (9%-10%) was similar for both groups. Median PFS was longer in the durvalumab alone arm (5.0 versus 2.1 months). The incidence of grade  $\geq 3$  TRAEs was lower in patients in the monotherapy group (7.4% versus 25.9%).<sup>80</sup>

### Adoptive cell transfer

The ultimate goal of adoptive cell transfer (ADCT) is to generate a robust immune-mediated antitumor response

via the infusion of *ex vivo* manipulated T cells. ADCT-based drugs can be divided into two principal techniques: (i) the isolation of naturally occurring tumor-specific T cells from existing tumor samples (TILs); (ii) the genetic modification of blood-derived T cells to allow for specific recognition of TCs. In both settings, T cells are manipulated *in vitro* followed by an expansion and reinfusion back into the lymphodepleted patient. Lymphodepletion by CT before ADCT is an important component of the treatment as it eliminates Treg and other lymphocytes, which compete with the transferred cells. Administration of high-dose IL-2 after cell-transfer is also recommended.<sup>81</sup>

**ADCT using TILs.** Stevanović et al.<sup>82</sup> showed the results of nine patients with metastatic CC receiving a single infusion of TILs selected for HPV E6 and E7 reactivity. Two patients experienced a sustained CR and one patient showed a PR.<sup>82</sup>

The initial and updated efficacy findings of a phase II trial investigating the TIL therapy LN-145 concerned 27 patients with SCC (44%) and ADK (44%) histologies. The prior treatments received were platinum-based CT, bevacizumab, and ICI for 100%, 82%, and 15% of patients, respectively. The ORR was 44%, including one CR. Additionally, 40.7% of patients experienced SD, for an overall DCR of 85.2%. The mDOR was not yet reached. Most of the AEs were related to the expected effects of lymphodepleting CT and IL-2.<sup>83</sup> O'Malley<sup>84</sup> presented preliminary results of the NCT03108495 phase II trial including 24 CC patients treated with a combination of pembrolizumab and ADCT with TILs: the ORR and DCR were 57.1% and 92.7%, respectively.<sup>84</sup>

**Chimeric antigen receptor T-cell therapy.** This second technique is based on the transfer of genetic material encoding either a cloned T-cell receptor or a synthetic chimeric antigen receptor (CAR) targeting tumor specific antigens. These CAR-T cells have demonstrated major results in hematological cancers. The most impressive results were observed in acute lymphoblastic leukemia, with CR rates of 70%-90% in heavily pretreated patients.<sup>85</sup> The results concerning the use of CAR-T cells in solid tumors are more disappointing. Unlike hematological cancers, solid tumors are located in specific sites (not always near blood vessels) and are frequently surrounded by an immunosuppressive TME that can negatively influence this drug. Moreover, the antigens expressed by solid tumors are often non-specific, which is the basis of the 'on-target/off-tumor' toxicity. The development of CAR-T cell technology in gynecological cancers is still in its early stages, with three ongoing studies.<sup>86</sup>

Firstly, the NCT01583686 trial tested anti-mesothelin CAR in various tumor types expressing mesothelin, including CC. Of the 15 patients enrolled, only one SD was observed. This study is closed due to slow accrual. Secondly, the NCT04556669 trial is testing anti-PD-L1 armored anti-CD22 CAR-T/CAR-TILs targeting patients with solid tumors, including CCs. The final data collection is scheduled for August 2023. Thirdly, the NCT03356795 trial was activated to collect peripheral blood mononuclear cells of



patients with GD2-, PSMA-, Muc1- or mesothelin-positive CCs.

### TISOTUMAB VEDOTIN

Tisotumab vedotin (TV) is an investigational antibody–drug conjugate (ADC) directed against tissue factor (TF). TF is aberrantly expressed in a broad range of solid tumors and its expression in CC is 94%-100%.<sup>87</sup> TF expression has been associated with poor clinical features. TV binds TF on to target cells; the resulting complex is internalized and trafficked to the lysosome where the linker is cleaved, releasing the monomethyl auristatin E (MMAE) intracellularly. MMAE then binds to tubulin and disrupts microtubule polymerization, resulting in cell cycle arrest and apoptosis. This cytotoxicity may be increased by MMAE which can also diffuse into the TME, where it could induce bystander killing of neighboring dividing cells. These antitumor effects are further enhanced by the capacity of TV to fix to adjacent natural killer cells, which leads to antibody-dependent cellular cytotoxicity. MMAE-based ADCs have also been shown to induce immunogenic cell death, which can activate innate and adaptive immune responses to tumor antigen.<sup>88</sup> Table 5 summarizes the results of trials with TV in CC.

The innovaTV 201 phase I/II trial is investigated TV in multiple types of tumors in recurrent, advanced, or metastatic settings. This trial was not powered to evaluate antitumor activity, but encouraging preliminary responses were reported.<sup>88</sup> In the cohort of 55 CC patients, the ORR, mDOR, and 6-month PFS rate were 24%, 4.2 months, and 29%, respectively.<sup>89</sup>

The innovaTV 204 phase II trial evaluated TV in 101 patients with recurrent or metastatic CC that had progressed during or after treatment with standard first-line therapy. At a median follow-up of 10 months, the assessment confirmed that ORR was 24%, with 7% and 17% patients achieving CR and PR, respectively (DCR of 72%). The mPFS, mOS, and mDOR were 4.2, 12.1, and 8.3 months, respectively. Responses were observed regardless of tumor histology, lines of prior therapy, response to prior systemic regimen, TF expression level, and use of bevacizumab. The most common TRAEs included alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), and fatigue (26%). Peripheral neuropathy grade 3 TRAEs occurred in 7% of patients.<sup>90</sup>

Furthermore, the results of the phase Ib/II ENGOT-Cx8/GOG-3024/innovaTV 205 trial, combining TV with carboplatin, bevacizumab, or pembrolizumab in recurrent and stage IVB CC, were recently presented.

Monk et al.<sup>91</sup> presented the results of the escalation phase of TV with bevacizumab (arm A), pembrolizumab (arm B), or carboplatin (arm C). A maximum tolerated dose was not reached with any combination. In arms A/B/C, grade  $\geq 3$  AEs occurred in 5 (33%), 12 (92%), and 8 (62%) patients, respectively. The recommended phase II dosing (RP2D) of TV was 2.0 mg/kg in the three arms.<sup>91</sup>

In addition, Lorusso et al.<sup>92</sup> reported ORR/mDOR of 54.5%/8.6 months, 40.6%/not reached, and 38.2%/14 months in the first-line TV combined with carboplatin (33

patients), first-line TV with pembrolizumab (33 patients), and second-/third-line TV associated with pembrolizumab (35 patients) cohorts, respectively. Most TEAEs were grade 1 or 2. The observed safety profiles were generally consistent with those known for each individual agent. The major prespecified AEs of interest included ocular, peripheral neuropathy, and bleeding events.<sup>92</sup>

The innovaTV 301 phase III trial comparing TV with the investigator's choice CT has just started; the estimated study completion date is 2024.<sup>93</sup> Patients have to experience disease progression during or after a doublet CT associated with bevacizumab (if eligible). Patients could have received one or two prior systemic therapy regimens for recurrent and/or metastatic settings.

### DISCUSSION

Despite screening and vaccination, CC remains a major cause of mortality worldwide, with a 5-year OS rate of only 17% in metastatic/recurrent disease.

Historically, cisplatin monotherapy and then a combination of cisplatin and paclitaxel were considered the SOC, with a mOS of 12 months. In 2014, platinum-based CT combined with bevacizumab became the new standard first-line treatment providing an mOS of around 17 months. Despite this improvement in OS, novel therapies are clearly needed for the treatment of recurrent CC in first as well as later lines. This dream has come true since the recent positive results of phase II and also phase III randomized trials with ICIs. Indeed, a better understanding of the interactions between HPV infection and the host immune system response has clearly positioned the use of immunotherapeutic drugs in CC patients. In fact, ICIs are changing the SOC. Firstly, pembrolizumab was approved (FDA) for second-line treatment of PD-L1-expressing tumors (phase II). Secondly, pembrolizumab was also approved (FDA/EMA) for first-line treatment, in combination with CT (with or without bevacizumab), for patients with persistent, recurrent, or metastatic PD-L1-positive CC. Indeed, this combination led to a mOS of 24 months in the all-comer population, although not reached in the sub-populations of patients with CPS  $>1$  or 10. Finally, approvals (FDA/EMA) of cemiplimab to treat patients with recurrent or metastatic disease whose disease progressed on or after CT, are ongoing.

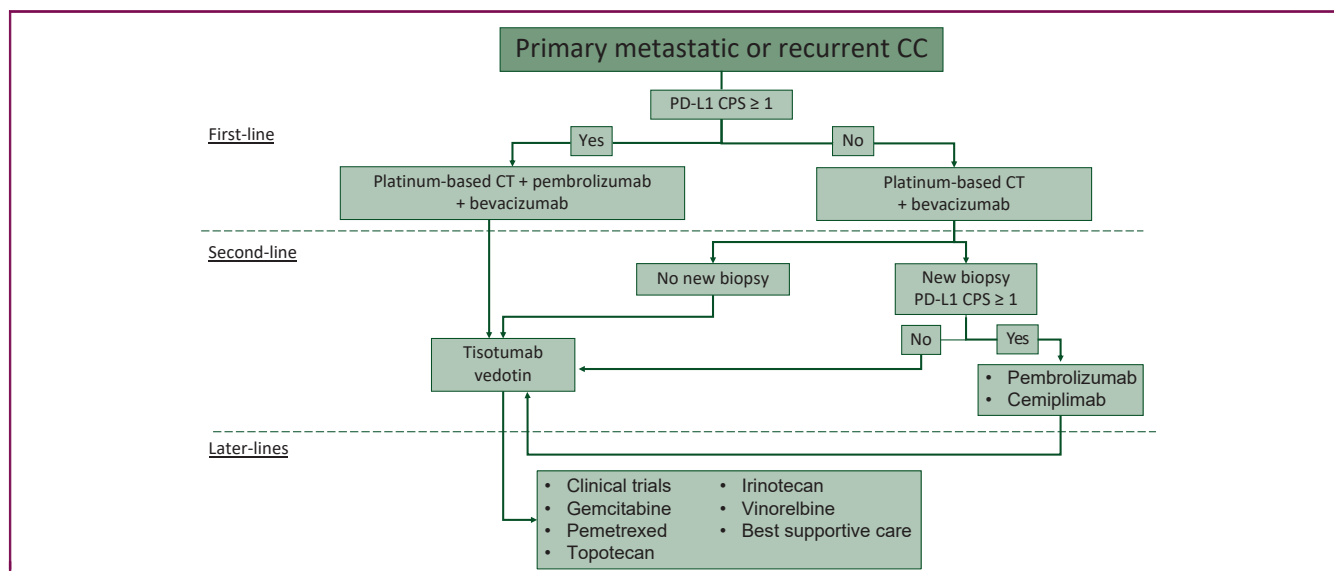
Additionally, other immunotherapeutic approaches such as therapeutic vaccination, ADCT, and CAR-T cells, will undoubtedly have a major place in the arsenal of weapons developed to fight CC, but probably not in monotherapy. Indeed, the profound immunosuppressive TME that reduces their clinical efficacy in monotherapy can now be modified by combinations with CT, antiangiogenic therapies, or ICIs. In many other published studies, they have been combined with RT or CT, also with promising results. Of note, their development in daily practice will probably be difficult due notably to manufacturing issues.<sup>94</sup>

Another emerging drug is the ADC targeting TF, named tisotumab vedotin, already approved (FDA) for patients with recurrent or metastatic CC with disease progression on or

**Table 5. Tisotumab vedotin trials**

Reference	Trial	Phase	N	Population	Histology (%)	Prior RT (%)	Prior bevacizumab (%)	Number of prior lines (%)	ORR (%)	mDOR (months)	mPFS (months)	mOS (months)	Grade 3-4 TRAEs (%) Discontinuation (%)
Hong et al. <sup>89</sup>	InnovaTV 201	I/II	55	Recurrent or metastatic progressed on platinum-based CT ≤4 prior treatments for advanced disease	SCC = 51 ADK = 35 ADSC = 11 Others = 4	NA	73	0 = 7 1 = 42 2 = 31 3 = 11 4 = 9	24 (Investigator) 22 (IRC) SCC = 29 ADK = 16	4.2 (Investigator) 6.0 (IRC)	4.2 (Investigator) 4.1 (IRC)	NA	56 NA
Coleman et al. <sup>90</sup>	InnovaTV 204	II	101	Recurrent or metastatic disease, progressed during or after standard first line	SCC = 68% ADK = 27% ADSC = 5%	54 (radiochemotherapy)	63	1 = 70, 2 = 30	IRC = 24	8.3	4.2	12.1	28 12
Monk et al. <sup>91</sup>	InnovaTV 205 ENGOT-Cx8/ GOG-3024	Ib/II	Arm A TV + beva = 15 Arm B TV + pembro = 13 Arm C TV + carbo = 13	Recurrent or metastatic disease, progressed on or after ineligible for or intolerant to standard therapy	Arm A/B/C SCC = 53.3/ 53.8/46.2 ADK = 46.7/ 46.2/ 46.2 ADSC = 0/0/7.7	NA	Arm A/B/C 40/46.2/30.8	Arm A/B/C 0 = 6.7/0/0 1 = 40/38.5/38.5 2 = 40/30.8/38.5 3 = 6.7/23.1/15.4 4 = 6.7/7.7/15.4	Arm A/B/C 33.3/15.3/30.8	NA	NA	NA	Arm A/B/C 33/92/62 NA
Lorusso et al. <sup>92</sup>	InnovaTV 205 ENGOT-Cx8/ GOG-3024	Ib/II	Arm A 1L TV + carbo = 33 Arm B 1L TV + pembro = 33 Arm C 2L/3L TV + pembro = 35	Recurrent or metastatic disease, progressed on or after ineligible for or intolerant to standard therapy	Arm A/B/C SCC = 72.7/ 66.7/54.3 ADK = 24.2/ 33.3/42.9 ADSC = 3.0/0/0 Other = 0/0/2.9	Arm A/B/C 81.8/75.8/85.7	Arm A/B/C NA/NA/54.3	Arm A/B/C 0 = 100/100/0 1 = 0/0/71.4 2 = 0/0/28.6	Arm A/B/C 54.5/40.6/38.2	Arm A/B/C 8.6/NR/14.0	Arm A/B/C 6.9/5.3/5.6	Arm A/B/C NR/NR/15.3	Arm A/B/C NA 21.2/24.2/34.3

ADK, adenocarcinoma; ADSC, adenosquamous carcinoma; beva, bevacizumab; carbo, carboplatin; IRC, independent review committee; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; N, number of patients included; NA, not available; NE, not evaluable; NR, not reached; ORR, objective response rate; pembro, pembrolizumab; RT, radiotherapy; SCC, Squamous cell carcinoma; TRAEs, treatment-related adverse events; TV, tisotumab vedotin.



**Figure 1.** Recommended algorithm for the treatment of primary metastatic or recurrent CC (not eligible for localized treatment). CC, cervical cancer; CPS, combined positive score; CT, chemotherapy; PD-L1, programmed cell death-ligand 1.

after CT. Several trials in monotherapy or in combination with immunotherapy, CT, or bevacizumab showed very exciting results. Nevertheless, new AEs will need to be managed.

There is a great need for more potent biomarkers to more accurately determine which patients would receive the greatest benefit from all these aforementioned drugs, but also to identify patients with specific molecular characteristics who could benefit from other targeted therapies. The Cancer Genome Atlas Research Network identified several genes significantly mutated, potentially targetable. These molecular data have highlighted the molecular heterogeneity of CC. Moreover, the role of immunotherapy in CC is increasing and specific biomarkers will also need to be explored such as PD-L1 expression, microsatellite instability, mismatch repair deficiency, and TMB. PD-L1 is one potential biomarker with the majority, but conflicting data: better predictive biomarkers are clearly needed.

In summary, in the first-line setting, patients with PD-L1 CPS  $\geq 1$  tumors should receive a combination of CT with pembrolizumab and bevacizumab (except in the case of contraindications). In second and later lines, they could receive TV or be included in clinical trials.

In contrast, in the first-line setting, patients without PD-L1 CPS  $\geq 1$  tumors should receive a combination of CT with bevacizumab (except in the case of contraindications). In second and later lines, they could receive TV or be included in clinical trials. A new biopsy could exclude PD-L1 expression appearance and if so, treatment by cemiplimab or pembrolizumab (FDA only) could be used (Figure 1).

Even with all these improvements with immunotherapy, several questions remain:

- What is the best timing for use (neoadjuvant, adjuvant, or metastatic settings)?
- What is the best immunotherapy technique (ICIs, vaccination, ADSC, or CAR-T cells)?

- What is the best schedule (monotherapy or combination approaches)?
- What is the best treatment of PD-L1-negative tumors? A combination of PD1/PD-L1 inhibitors with CT or other checkpoint inhibitors (CTLA-4? LAG3? TIGIT?) could be interesting?
- What is the most appropriate treatment of ADK histology subtype, well known to have less expression of PD-L1?
- What will be the impact of immunotherapeutic drugs in patients with a locally advanced disease? Results of several phase III trials are awaited (CALLA, ATOMIC, CX-11, ...).
- What would be the impact of ICIs in earlier stages, as preinvasive setting (high-grade cervical intraepithelial neoplasia grade 2 or 3) that can eliminate malignant cells avoiding progression to invasive cancer? Favorable results concerning vaccination against HPV oncoproteins in this setting were recently published. This could probably be a better approach, avoiding toxicity of ICIs.<sup>95,96</sup>

The limitation for a rapidly expanding use of all these new therapeutic approaches is the emerging evidence of disparities in access to these highly effective but expensive treatments. These inequalities in treatment, but also in screening and HPV vaccination accesses, in many developing countries probably contribute to the absence of improvement in the global OS of this disease.

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