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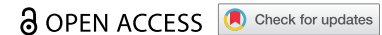
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REVIEW

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Investigational drugs for recurrent or primary advanced metastatic cervical cancer: what is in the clinical development pipeline?

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ABSTRACT

Introduction: Recurrent or primary advanced metastatic cervical cancer (R/M CC) has a poor prognosis with a 5-year-survival rate of 16.5%, demanding novel and improved therapies for the treatment of these patients. The first-line standard of care for R/M CC now benefits from the addition of the immune checkpoint inhibitor, pembrolizumab, to platinum-based chemotherapy with paclitaxel and bevacizumab. Additionally, new options for second-line treatment have become available in recent years.

Areas covered: Here, we review current investigational drugs and discuss their relative targets, efficacies, and potential within the R/M CC treatment landscape. This review will focus on recently published data and key ongoing clinical trials in patients with R/M CC, covering multiple modes of action, including immunotherapies, antibody–drug conjugates, and tyrosine kinase inhibitors. We searched clinicaltrials.gov for ongoing trials and pubmed.ncbi.nih.gov for recently published trial data, as well as recent years' proceedings from the annual conferences of the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Society of Gynaecological Oncology (ESGO), and the International Gynecologic Cancer Society (IGCS).

Expert opinion: Therapeutics currently attracting attention include novel immune checkpoint inhibitors, therapeutic vaccinations, antibody–drug conjugates, such as tisotumab vedotin, tyrosine kinase inhibitors targeting HER2, and multitarget synergistic combinations.

1. Introduction

Cervical cancer (CC) is the fourth most common female cancer following breast, colorectal and lung cancer, accounting for approximately 600,000 new cases and 340,000 annual deaths [1,2]. Human papilloma virus (HPV), the most prevalent sexually transmitted infection in the world, is responsible for 90–95% of cervical squamous cell carcinoma (SCC) making this one of the most preventable cancers [3,4]. Vaccination and screening programs in high-income countries have been very successful, with incidence more than halving since their inception [1]. However, there are major geographic discrepancies in incidence due to reduced resources, with approximately 90% of CC occurring in low-middle-income countries. In some of these regions, CC remains the second-most frequent cancer and the third largest cause of cancer death in women [1]. The age-standardized incidence of CC per 100,000 people is the highest in Africa (23.0–40.1), followed by South-Eastern Asia (17.8) and South America (15.4) with the lowest incidences in Western Asia (4.1), Australia and New Zealand (5.6), and North America (6.2) [2].

Surgery plays an important role for the treatment of early-stage CC, and remains an option for a subset of patients with recurrent CC, characterized by centrally located, previously irradiated recurrence without distant disease [5,6]. Surgery for these patients usually consists of (total) pelvic exenteration, which is associated with high postoperative morbidity, but can result in 5-year survival rates of 50% [5–7]. The following review will focus on the treatment of patients with recurrent/metastatic CC (R/M CC) for whom surgery or irradiation is not a viable curative option.

The prognosis of patients with metastatic CC is very poor, with a 5-year survival rate of only 16.5% [8]. Until recently, the standard first-line treatment for R/M CC was platinum-based chemotherapy (cisplatin or carboplatin) and paclitaxel [9] combined with bevacizumab [10,11]. However, recent approvals of the immune checkpoint inhibitor, pembrolizumab, for use in combination with chemotherapy, with or without bevacizumab, in the first-line treatment of programmed cell death ligand 1 (PD-L1)-positive tumors (combined positive score [CPS ≥1%]) changed the standard of care [12]. The approval

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Article highlights

- Cervical cancer is the fourth most common female cancer, accounting for approximately 340,000 annual deaths
- There is an unmet clinical need in the second-line therapy of recurrent/metastatic cervical cancer as there are limited options and there is currently no accepted standard of care
- Recent approvals of cemiplimab by the EMA and tisotumab vedotin by the FDA are providing alternate therapies to the armamentarium, and results from ongoing combination trials are eagerly awaited
- Many other therapeutics of interest are emerging in the development pipeline including novel immune checkpoint inhibitors, tyrosine kinase inhibitors, and multitarget synergistic combinations
- Therapies with novel mechanisms of action are also emerging, such as antibody–drug conjugates (e.g. tisotumab vedotin) and therapeutic vaccination

This box summarizes key points contained in the article.

of pembrolizumab was based on the results of the Keynote-826 study by Colombo *et al.*, where 617 patients were treated with pembrolizumab or placebo in addition to platinum-based chemotherapy with or without bevacizumab. Efficacy was mostly seen in patients with a PD-L1 CPS ≥1 (n = 548), where the median progression-free survival (PFS) was 10.4 months in the pembrolizumab group compared with 8.2 months in the placebo group, and the 24-month overall survival (OS) was 53% versus 41.7%, respectively [11]. Additionally, similar survival benefits were observed between histological subgroups to the broader population of patients in the trial [13]. As a result, the new standard of care for PD-L1-expressing R/M CC tumors is pembrolizumab in addition to cisplatin/carboplatin, paclitaxel with or without bevacizumab [14,15].

HPV-infected cells often harbor malfunctional p53; therefore, the DNA-damaging ability of platinum-based drugs may be limited [16]. Following the occurrence of resistance to platinum-based therapy, the standard of care for the second and later lines is not well established [17,18]. A retrospective analysis investigating R/M CC treatment regimen and duration in the USA reported that there was no majority for any second-line treatment and only a small proportion of patients remained on immunotherapy for a prolonged period, suggesting a need for improved therapy options [17]. In a retrospective review investigating the outcomes of second-line systemic therapy in a UK single center, the most common therapy was paclitaxel (28.3%), followed by carboplatin-based chemotherapy (24.5%), targeted agent monotherapy in trials (22.6%), docetaxel-based chemotherapy (13.2%), topotecan (9.4%), and gemcitabine (1.9%). The combined objective response rate (ORR; 13.2%) and median PFS (3.2 months) were poor, suggesting a need for more treatment options in the second line [18]. Recently, the antibody–drug conjugate, tisotumab vedotin (TV), was approved by the FDA for second-line use in R/M CC in the United States [19]. Interestingly, the European Medical Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has approved cemiplimab (anti-programmed cell death protein [PD1]) monotherapy for patients with R/M CC, with disease progression on or after platinum-based monotherapy, irrespective of PD-L1 expression, who have not received previous treatment with checkpoint inhibitors [20]. However, the FDA application for cemiplimab was voluntarily withdrawn; therefore, the USA currently has no approved immunotherapy for the second-line treatment of R/M CC [21].

Due to high rates of resistance and potentially reduced efficacy in PD-L1-negative tumors, there is still a need to increase the armamentarium in the therapeutic management of R/M CC. This review will focus on investigational drugs and therapies available or upcoming for the treatment of patients with R/M CC.

2. Investigational drugs for metastatic or recurrent cervical cancer

Recent advances in the molecular characterization of CC have led to the development of targeted therapies against proteins expressed specifically by the cancer cells that are involved in their growth, proliferation, and metastasis [22]. Current investigational therapies for the treatment of R/M CC include immunotherapy (in particular, immune checkpoint blockade [ICB]), anti-tyrosine kinase therapy, antibody–drug conjugates, and anti-angiogenics [22,23]. The current investigational drugs and associated trials will be discussed.

2.1. Anti-angiogenesis

Angiogenesis is a major driver of HPV-mediated cervical carcinogenesis, making vascular endothelial growth factor (VEGF) an important therapeutic target [24]. In the GOG-240 phase III trial, 452 patients with persistent R/M CC were treated with chemotherapy with or without bevacizumab (anti-VEGFR). The addition of bevacizumab to platinum-based chemotherapy led to a statistically significant improvement in median OS for those patients with R/M CC, achieving 16.8 months as compared with 13.3 months for chemotherapy with or without bevacizumab, respectively (p = 0.007). However, fistula was observed as a new specific adverse event linked to bevacizumab use. In the final analysis, the overall incidence of fistula (grade 2 and 3) was 8.6% among patients treated with bevacizumab compared with 1.4% for those without. All patients who developed fistulas had received prior radiotherapy. No fistulas resulted in surgical emergencies, sepsis, or death, and in addition to pelvic irradiation, other factors associated with fistulas included pelvic disease, preexisting hypertension, and current tobacco use [23]. The ENGOT-cx1/BGOG-cx1 double-blind phase II study investigated the first-line treatment of 120 patients with primary advanced or recurrent CC using paclitaxel and carboplatin with nintedanib or placebo. Nintedanib is an oral tyrosine kinase inhibitor targeting, among others, VEGF receptor. Recent results reported that the primary endpoint was met, as the addition of nintedanib improved PFS at 1.5 years (15.1% vs. 12.8%; p = 0.057, [α = 0.15, β = 80%]). Additionally, median OS (21.7 vs. 16.4 months) was improved as compared with placebo. It must be noted that the alpha value of this study was high, therefore further study is warranted [25]. In another study, patients with R/M CC were randomized to receive cediranib, another inhibitor of VEGF 1, 2 and 3, or placebo in combination with carboplatin and

paclitaxel. The median PFS in the cediranib group was 8.1 months compared with 6.7 months in the placebo group, although the median OS was not significantly different [26]. Investigation into cediranib in combination with olaparib is ongoing in the COMICE trial (NCT04487587) for R/M CC patients following progression after first-line therapy.

2.2. Immunotherapy

Immunotherapy reverses immune evasion strategies of cancer cells to destroy them. Since most CCs have a viral origin, they are associated with an immunogenic profile, making CC an attractive candidate for immunotherapy [27]. However, HPV has also been associated with the induction of PD-L1 expression in head and neck squamous cell carcinoma [27]. ICB therapy blocks inhibitory surface receptors on immune cells [28], which under healthy conditions, function to modulate the immune system via a negative feedback system that ensures self-tolerance and prevents auto-immune reactions. However, dysregulation in the tumor microenvironment, including the upregulation of immune checkpoint proteins such as PD-1, PD-L1, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), allows evasion of the antitumor immune response [29]. Blocking immune checkpoint proteins has potent anti-tumor effects in various tumor types; however, since ICBs 'release the brakes' on immune activation, they often result in toxicity and immune-related adverse events, sometimes requiring discontinuation of treatment [30,31].

2.2.1. Passive immunotherapy

Upon activation, PD-L1 and, to a lesser extent, PD-L2, can reduce immune responses. The interaction between PD-L1 and PD-L2 in tumors with PD1 on tumor-infiltrating lymphocytes (TILs) has been recognized as a major mechanism of tumor immune evasion and thus has become a valuable target for therapy [30]. Variable PD-L1 expression rates (anti-PD-L1 clone E1L3N) are observed between SCC and adenocarcinoma tumor cells (not including immune cells) with positivity rates of 54% and 14%, respectively, when using a cutoff of >5%. Rates of PD-L1 expression by immune cells (predominantly tumor-associated macrophages) followed a similar pattern, with 53% and 12% for SCC and adenocarcinoma, respectively [32]. Additional immune checkpoint targets include CTLA-4, which provides inhibitory action to CD4+ helper T cells; while boosting regulatory T cells and creating a pro-tumor phenotype [33]; lymphocyte activation gene 3 (LAG-3), which has an inhibitory effect on CD8+ T cell function and increases the immune inhibitory action of regulatory T cells [34,35]; T cell immunoglobulin and mucin domain-containing-3 (TIM-3), which can inhibit anti-tumor immunity via interaction with its four ligands [36], and T cell immunoglobulin and ITIM domain (TIGIT), which also has a broad range of immunosuppressive targets [37,38].

Investigatory drugs targeting PD-(L)1 include pembrolizumab [11,39,40], nivolumab [41,42], atezolizumab [43], cemiplimab [44,45], camrelizumab [46,47], and tislelizumab and bastilimab (Table 1) [48,49]. Support for the approval of cemiplimab comes from the EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 phase III trial, which compared cemiplimab

treatment (n = 300) to chemotherapy (n = 290) in women with recurrent CC following disease progression after first-line platinum-based chemotherapy and regardless of PD-L1 status [45]. Median OS was higher in the cemiplimab group (12 months) compared with the chemotherapy group (8.5 months) as was the ORR (16.4% vs. 6.3%, respectively); however, median PFS was not improved [45]. Benefits in global health status (GHS), quality of life (QoL), and physical functioning have also been observed in those receiving cemiplimab treatment [44].

Recently, the phase I/II Checkmate-358 trial using 240 mg nivolumab every 2 weeks for the treatment of R/M CC (N = 19) reported an ORR of 26.3%, 24-month OS of 49.8%, and median PFS of 5.1 months [42]. However, the phase II trial (NCT02257528/NRG-GY002) in R/M CC patients that had progressed following systemic therapy (N = 26), showed low antitumor activity (4% partial response), although the safety profile was acceptable [41].

Camrelizumab is another PD-1-targeted antibody currently being investigated. In an open-label, prospective phase II trial, 35 patients with R/M CC with no prior systemic chemotherapy received camrelizumab, albumin-binding paclitaxel, and carboplatin as the first-line treatment strategy. The single-armed study resulted in promising efficacy: ORR was 40% and the disease control rate (DCR) was 92% [47]. Additionally, camrelizumab in combination with the tyrosine kinase inhibitor (TKI), apatinib, has also shown promising antitumor activity as a second-line therapy in this patient population (ORR: 55.6%) [46].

The possibly synergistic effect of chemotherapy was recently explored by combining doxorubicin with atezolizumab (anti-PD-L1) in the randomized phase II BGOG-cx3 trial. Atezolizumab in combination with doxorubicin (n = 23) was compared with doxorubicin alone (n = 17) in the second- or later-line therapy for recurrent CC. Recent reports describe a modestly higher PFS rate at 9 months (26% vs. 13%, respectively [p = 0.054]), OS (10.3 vs. 7.8 months [p = 0.210]) and DCR at 24 months (16% vs. 0% [p = 0.279]), although sample size was limited [43].

Research is also underway that combines checkpoint blockade therapies. Although balstilimab's (anti-PD-1) biologic license application for use in patients with R/M CC has recently been withdrawn [50], its combination with zalifrelimab (anti-CTLA-4) was recently investigated in a phase II trial of 155 patients with R/M CC that had relapsed following platinum-based therapy. The ORR was 25.6% with improved response observed for patients with PD-L1-positive (32.8%) compared with those with PD-L1-negative tumors (9.1%). Additionally, the median PFS was 2.7 months, and the median OS was 12.8 months [49]. Further investigations of balstilimab and zalifrelimab compared with balstilimab monotherapy are ongoing in the randomized phase II, RaPiDS trial (NCT03894215) for the second-line treatment of recurrent CC.

Several types of lymphocytes express the inhibitory receptor, TIGIT, including TILs [51]. TIGIT is an inhibitory receptor expressed on activated CD4+, CD8 + T cells, natural killer cells, regulatory T cells and follicular T helper cells and blocking of TIGIT restores the ability of CD8 + T-cells to produce cytokines [52]. The ongoing KEYVIBE-001 trial is investigating two doses

Table 1. Recently published data from clinical trials of investigative drugs in R/M CC.

Interventions	Study ID	NCT number	Phase	Study design	N	Status/citation	Primary outcome
Immunotherapy							
Cemiplimab (anti-PD-1) vs. chemotherapy	EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9	NCT03257267	III	Multi-center, randomized, parallel-arm, open-label	608	Tewari et al., 2022 [45] Oaknin et al., 2022 [44]	Median OS: 12.0 vs. 8.5 months
Pembrolizumab (anti-PD-1) + chemotherapy vs. placebo + chemotherapy	KEYNOTE-826	NCT03635567	III	Multi-center, double-blind, placebo-controlled	548	Colombo et al., 2021 [11]	PFS: 10.4 vs. 8.2 months; OS: 53% vs. 41.7%
Pembrolizumab	KEYNOTE-158	NCT02628067	II	Multi-center, single-arm, open-label, basket	98	Chung et al., 2019 [40]	ORR: 12.2%
Pembrolizumab		NCT02721732	II	Open-label, multi-cohort, basket	6	Frumovitz et al., 2020 [39]	% alive at 27 weeks and progression free: 0
Nivolumab (anti-PD-1)	NRG-GY002	NCT02257528	II	Single-arm, open-label	26	Santin et al., 2020 [41]	ORR: 4% PR, 36% SD
Nivolumab			II	Multi-center, open-label, prospective	20	Tamura et al., 2019 [53]	ORR: 25%
Camrelizumab + apatinib	CLAP	NCT03816553	II	Multi-center, single-arm, open-label	45	Lan et al., 2020 [46]	ORR: 55.6%
Camrelizumab + carboplatin + albumin-binding paclitaxel			II	Single-arm, open-label, prospective	35	Zhang et al., 2022 [47]	ORR: 40%; DCR: 92%
Balstilimab (anti-PD-1)		NCT03104699	II	Single-arm, open-label	161	O'Malley et al., 2021 [54]	ORR: 15%
Balstilimab (anti-PD-1) + **zalifrelimab** (anti-CTLA-4)		NCT03495882	II	Single-arm, open-label	155	O'Malley et al., 2022 [49]	ORR: 25.6% (32.8% in PD-L1+ tumors)
Pembrolizumab + **GX-188E** (DNA vaccine)		NCT03444376	II	Single-arm, open-label	36	Won Youn et al., 2020 [55]	ORR: 42% (15% CR, 27% PR)
Ipilimumab (anti-CTLA4)		NCT01693783	II	Multi-center, single-arm, open-label	42	Lheureux et al., 2018 [56]	Safety: well tolerated; ORR: prespecified RR of 20% not met
Atezolizumab + bevacizumab		NCT02921269	II	Multi-center, open-label	10	Friedman et al., 2020 [57]	ORR: 0%
Axalimogene filolisbac (ADXS-HPV)	GOG-0265	NCT01266460	II	Single-arm, open-label	50	Huh et al., 2020 [58]	Safety: tolerable; OS at 12 months: 38%
ISA101 (HPV vaccine) + chemotherapy		NCT02128126	I/II	Multi-center, single-arm, open-label	77	Melief et al., 2020 [59]	Safety: similar to chemotherapy alone; HPV-specific immune response: mounted to all doses
Nivolumab	CheckMate 358	NCT02488759	I/II	Multi-center, open-label, multi-cohort	19	Nauman et al., 2019 [42]	ORR: 26.3%
Cemiplimab (anti-PD-1) vs. cemiplimab + hfRT		NCT02383212	I	Multi-center, non-randomized, open-label, dose escalation/dose expansion	20	Rischin et al., 2020 [60]	Safety/tolerability: TEAEs (≥Grade 3) 10% monotherapy, 30% combined therapy
Chemotherapy + radiotherapy with sequential **Ipilimumab** (anti-CTLA4)			I	Multi-center, single-arm, open-label, prospective	34	Mayadev et al., 2019 [61]	Safety: max tolerable dose = 10 mg/kg
Sintilimab (anti-PD-1) + **anlotinib** (VEGFR TKI)			II	Multi-center, single-arm, open-label	42	Xu et al., 2022 [62]	ORR: 54.8%
Atezolizumab (anti-PD-L1) + **navoximod** (IDO inhibitor)	GO29779	NCT02471846	Ib	Non-randomized, open-label, dose escalation	157	Jung et al., 2019 [63]	Safety: acceptable; MTD was not reached
Antibody–drug conjugates (ADC)							
Tisotumab vedotin (TV)	innovaTV 204/GOG-3023/ENGOT-cx6	NCT03438396	II	Multi-center, single-arm, open-label	102	Coleman et al., 2021 [64]	ORR: 24% (7% CR; 17% PR)
TV	innovaTV 201	NCT02001623	I/II	Multi-cohort, open-label, dose escalation/expansion	55	De bono et al., 2019 [65] Hong et al., 2020 [66]	Safety/tolerability: manageable

(Continued)

Table 1. (Continued).

Interventions	Study ID	NCT number	Phase	Study design	N	Status/citation	Primary outcome
TV + bevacizumab or pembrolizumab or carboplatin; **TV** monotherapy; **TV** + pembrolizumab + carboplatin +/- bevacizumab	innovaTV 205/ ENGOT Cx8/ GOG-3024	NCT03786081	I/II	Multi-center, multi-cohort, open-label, dose escalation/expansion	33 35	Vergote et al., ESMO 2021 1 L TV + carboplatin 2 L/3 L TV + pembro dose-expansion cohorts [67] Lorusso et al., ASCO 2022 (1 L TV + pembro dose-expansion cohort) [68]	ORR: 55% ORR: 35% (interim data) ORR: 41% (9% CR; 31% PR) (interim data)
TV	innovaTV 206	NCT03913741	I/II	Single-arm, open-label, dose escalation/expansion	6/17	Yonemori et al., 2022 [69]	DLT: none; MTD: not reached
Anti-angiogenic							
Apatinib (VEGF TKI)			II	Single-arm	20	Zhang et al., 2020 [70]	ORR: 15%; DCR: 35%
Apatinib +/- chemotherapy/chemo-brachytherapy	ChiCTR1900024143		II	Randomized controlled, prospective	59	Guo et al., 2020 [71]	PFS: 10.1 vs. 6.4 months
Carboplatin + paclitaxel +/- **cetuximab** (anti-EGFR)	MITO CERV-2	NCT00997009	II	Multi-center, randomized,	108	Pignata et al., 2019 [72]	EFS: 4.7 months without and 6.0 months with cetuximab
Bevacizumab (VEGF inhibitor) + carboplatin + paclitaxel	CECILIA	NCT02467907	II	Single-arm	150	Redondo et al., 2020 [73]	Incidences of fistula: 11.3%
Bevacizumab + carboplatin + paclitaxel			II	Single-arm	34	Suzuki et al., 2019 [74]	ORR: 88% (50% CR; 38% PR)
Paclitaxel + carboplatin +/-bevacizumab vs. **dose-dense paclitaxel + carboplatin** +/- bevacizumab	JGOG1311		II/III	Randomized, parallel-arm	122	Ishikawa et al., 2021 [75]	RR conventional + bevacizumab = 67.9%; RR dose-dense + bevacizumab = 60.7%
Bevacizumab + carboplatin + paclitaxel	JGOG1079		II	Multi-center, open-label	69	Tanigawa et al., 2022 [76]	PFS: 11.3 months
Other							
Selinexor (Exportin 1 inhibitor)		NCT02025985	II	Multi-cohort, single-arm	25	Vergote et al., 2020 [77]	DCR: 24%; PR: 4%
Irinotecan (anti-neoplastic) + **S-1** (chemotherapy)			II	Single-arm	19	Mabuchi et al., 2019 [78]	RR: 29.4%
Neratinib (pan-HER TKI)	SUMMIT	NCT01953926	II	Non-randomized, parallel-arm, open-label, basket	16	Oaknin et al., 2020 [79]	ORR: 25%
Trametinib (MEK inhibitor) + **GSK2141795** (AKT inhibitor)			II	Single-arm	35	Liu et al., 2019 [80]	Best tumor response: no confirmed responses

AE, adverse event; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; DLT, dose-limited toxicity; EFS, event-free survival; EGFR, endothelial growth factor receptor; MTD, maximum-tolerated dose; OS, overall survival; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TEAEs, treatment-emergent adverse events; TILs, tumor-infiltrating lymphocytes; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

(200 or 700 mg every 3 weeks) of the anti-TIGIT therapy, vibostolimab, in combination with pembrolizumab in PD-L1 inhibitor-naïve advanced or metastatic CC. Recent results report that antitumor activity was comparable between doses and efficacy was seen irrespective of PD-L1 status [81]. As a result of this success, the ongoing KEYVIBE-005 trial (NCT05007106) is evaluating this combination in CC irrespective of PD-L1 tumor status at the recommended dose of 200 mg every 3 weeks. Investigation into the combination of anti-PD1 antibody, tislelizumab, with or without another anti-TIGIT antibody, and ociperlimab, is also currently ongoing (NCT04693234) in patients with previously treated R/M CC.

Additional ongoing immunotherapy trials in R/M CC include the phase I trial of bintrafusp alfa (NCT04708470), a bifunctional fusion protein composed of the extracellular domain of the human TGF-β receptor II (TGF-β trap), and an anti-PD-L1 antibody plus chemotherapy; the bispecific PD-1/CTLA-4 antibody AK104 (cadonilimab) in combination with chemotherapy with or without bevacizumab (NCT04220307); the study of LN-145 (NCT03108495), an adoptive cell transfer (ACT) therapy utilizing autologous TIL, and the SKYSCRAPER-04 trial (NCT04300647) using tiragolumab plus atezolizumab monotherapy in PD-L1 positive R/M CC.

2.2.2. Active immunotherapy

Adoptive cell therapy using TILs has received attention recently for the treatment of advanced CC in patients who have progressed following several lines of therapy [82]. Previous trials using this therapy for CC have reported an ORR of 33% [83], and there are also a number of ongoing trials investigating TILs therapy for R/M CC (NCT01585428; NCT04674488).

Therapeutic use of HPV vaccination has also shown promise in advanced, R/M CC in combination with chemotherapy [30], which was found to deplete myeloid suppressive cells, allowing the generation of tumor-specific immune responses. In the CervISA study, patients were treated with standard-of-care chemotherapy and precisely timed ISA101. Prolonged OS is associated with strong antigen-specific T cell responses – so-called high responders [59]. In patients with relapsed head and neck cancer, the percentage of patients with a meaningful tumor response with ISA101 and nivolumab was twice the rate achieved with nivolumab monotherapy [84]. The ISA-HPV (ISA101b, NCT04646005) vaccine trial in combination with cemiplimab is ongoing for the second-line treatment of R/M CC.

In a phase II trial (GOG-0265) the therapeutic vaccine, axalimogene filolisbac (ADXS-HPV), used to treat patients with advanced CC resulted in a 12-month OS of 38%, median OS of 6.1 months, and median PFS of 2.8 months [58]. However, the AIM2CERV (NCT02853604) phase III study of this drug has been placed on partial clinical hold and is no longer recruiting.

2.3. Antibody–drug conjugates

Tissue factor (TF) is highly prevalent in many solid tumors, including CC, and is associated with a poor prognosis [66,85]. It is a transmembrane protein expressed in some extravascular cells following growth factor and cytokine stimulation and contributes to angiogenesis and metastatic processes in tumors [85]. Tisotumab vedotin (TV) is the first tissue factor-directed antibody therapy and consists of a human monoclonal antibody conjugated to the microtubule disruptive agent, monomethyl auristatin E (MMAE), via a protease cleavable linker [64]. TV has been investigated for the treatment of locally advanced and metastatic tumors in the innovaTV trials[64–66]. InnovaTV 201 was a phase I/II dose-escalation and dose-expansion study investigating the safety and efficacy of TV treatment in 147 patients with a range of relapsed, advanced, or metastatic cancer, including 55 patients with CC [65]. In a sub-analysis, the CC patient data showed an ORR of 24%, median duration of response (DOR) of 4.2 months, and 6-month PFS was 29% [66]. The approval of TV by the FDA was based on the pivotal phase II innovaTV 204/ENGOT-cx6/GOG-3023 trial, in which TV was investigated in 101 previously treated patients with R/M CC. Therapy achieved a DOR of 8.3 months and an ORR of 24%, with seven (7%) complete and 17 (17%) partial responses [64]. A global phase III trial of TV in previously treated R/M CC is ongoing (innovaTV 301/ENGOT-cx12/GOG-3057).

The phase Ib/II innovaTV 205/ENGOT-cx8/GOG-3024 trial is also underway, which is evaluating combinations of TV with pembrolizumab, bevacizumab, or carboplatin, including a population of previously untreated R/M CC patients where first-line use was investigated. Interim data show promising results [86]. In the 33 previously untreated patients (except chemoradiation) using TV plus pembrolizumab, an ORR of 41% was observed, with 9% (n = 3) complete responders and 31% (n = 10) partial responders. The median DOR has not been reached with a response ongoing for 7 of 13 patients. Additionally, the median PFS was 5.3 months, and the median OS was not reached. An acceptable safety profile was displayed; the most common treatment-emergent adverse events (TEAEs) associated with TV were alopecia, diarrhea, epistasis, conjunctivitis, and nausea. Specific prespecified adverse events (AEs) (grade 1–2/grade≥3) included ocular (58%/9%), peripheral neuropathy (45%/3%), and bleeding (61%/6%) [68]. Ocular toxicity from TV is believed to occur due to TF expression by the conjunctiva, but the implementation of an ocular care plan has been shown to substantially reduce ocular AE [87].

2.4. Inhibition of tyrosine kinase signaling

Cervical cancer is associated with activation of growth factors and signaling pathways that enable tumor cell survival. Unfortunately, despite clear rationale for their use, few clinical trials of TKIs have shown promise in R/M CC.

2.4.1. HER2

HER2 is a receptor tyrosine kinase, the overexpression of which is associated with increased activation of signaling pathways associated with cellular transformation. It is a validated therapeutic target in breast and esophageal cancers; however, mutations of HER2 are reported in approximately 5% of CC [79]. The SUMMIT phase II basket trial investigated neratinib, a pan-HER TKI, in 16 heavily pre-treated patients with HER2-positive metastatic CC.

Three of 12 Response Evaluation Criteria in Solid Tumors (RECIST)-measurable patients had confirmed partial responses (ORR 25%; 95% CI 5.5–57.2%), 3 had stable disease for ≥16 weeks (CBR 50%; 95% CI 21.1–78.9%), DOR was 5.6, 5.9, and 12.3 months, median PFS was 7 months and median OS was 16.8 months [79]. Two ongoing phase II trials are investigating the antibody–drug conjugate trastuzumab deruxtecan (T-DXd): the DESTINY-PanTumour01 trial (NCT04639219) and the DESTINY-PanTumor02 trial (NCT04482309). The former aims to investigate the efficacy and safety of T-DXd therapy across seven tumor cohorts expressing HER2 activating mutations, including CC, and the latter aims to investigate the treatment of unresectable and/or metastatic HER2-positive solid tumors by immunohistochemistry. Interestingly, in breast cancer, T-DXd has also displayed clinically meaningful improvements in PFS and OS in patients with low HER2 expression [88]; investigations in HER2-low CC are also warranted.

2.4.2. EGFR

Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase whose ligation results in the initiation of signaling cascades involved with cell division and survival [22]. EGFR is overexpressed in around 70% of cervical SCC and is associated with poorer prognosis [22]. Despite this, there has been little success to date with the use of EGFR inhibitors in patients with recurrent CC. Erlotinib and gefitinib monotherapies were found to be inactive [89,90]; lapatinib and pazopanib monotherapies and combination displayed limited anti-tumor efficacy and increased serious AE in the latter [91]; and similarly the MITO CERV-2 trial did not yield a beneficial effect of combining cetuximab with carboplatin and paclitaxel [72].

2.4.3. Multi-target tyrosine kinase inhibitors

The use of small molecules that target multiple-tyrosine kinases has attracted great interest due to their ability to combat complex cancers and potential synergistic effects [92]. The small-molecule drug, cabozantinib, targets several receptor tyrosine kinases involved in tumor growth, metastasis, and angiogenesis. The main targets are VEGFR2, MET, RET, and AXL [93]. A single-arm phase II trial (CABOCOL-01) recently reported data of 54 patients with advanced/metastatic CC, treated using cabozantinib monotherapy, for whom platinum-based treatment had failed [94]. Here, it was reported that 46.3% had 3-month disease control, ORR was 9.3% with no complete responses, and median PFS and OS were 2.8 and 8.9 months, respectively. The formation of gastrointestinal or genito-urinary fistula or perforation occurred in 11.1% (n = 6) of patients [94].

Mutations in genes encoding PI3K and KRAS are commonly found in CC. A phase II trial investigated the dual inhibition of these signaling pathways by inhibiting MEK and AKT with trametinib and GSK2141795, respectively. The study ended early due to the development of GSK2141795 being terminated; the results showed that the combination had limited anti-tumor activity [80].

2.4.4. Combinations including tyrosine kinase inhibitors

A phase II prospective trial investigated sintilimab (anti-PD-1) in combination with anlotinib (multi-kinase inhibitor with anti-angiogenic activity) for the second-line treatment of 39 patients with PD-L1-positive R/M CC [46]. The ORR was 59%, the median PFS was 9.4 months, and the disease control rate was 94.9%. The most common treatment adverse events (TAEs) were hyperthyroidism (33%), elevated aspartate aminotransferase levels (21.4%), and hypertension (19%) [62]. Similarly, the CLAP phase II trial investigated the combination of camrelizumab (anti-PD-1) with apatinib (anti-VEGFR2) in 45 patients with advanced CC who had failed to respond to first-line treatment. The ORR was 55.6% with 2 complete and 23 partial responses; the median PFS was 8.8 months [46].

3. Expert opinion

The diversity of targets available in the treatment of R/M CC has been outlined here and is expanding throughout immunotherapy, antibody–drug conjugates, tyrosine kinases, and anti-angiogenics. Recently, it was shown that the addition of pembrolizumab (anti-PD1) to standard chemotherapy and bevacizumab improved survival in first-line R/M CC. As mentioned previously, there is an unmet clinical need for the second-line treatment of R/M CC, as limited effective options are currently available. However, immunotherapies and antibody–drug conjugates represent important progress and offer potential improvements to therapy in the context of R/M CC. The recent EMA approval of cemiplimab for second-line treatment adds another option to the armamentarium, although it remains to be seen as to whether patients will respond well to a second line of ICB treatment.

Additionally, therapies with alternative mechanisms of action are emerging as second-line options, such as the promising antibody–drug conjugate, TV, alone or in combination with immunotherapy, platinum-based chemotherapy, or bevacizumab. Indeed, TV has already been approved as a single agent by the FDA for second-line use in R/M CC. The results from the innovaTV 205/ENGOT cx8/GOG-3024 (NCT03786081), including pembrolizumab combination arms, are highly encouraging. Additionally, the results of the ongoing phase III innovaTV 301/ENGOT-cx12/GOG-3057 (NCT04697628) trial investigating TV therapy versus standard-of-care chemotherapy in previously treated R/M CC patients who have progressed following first- and second-line therapies are eagerly awaited.

Immunotherapies are moving earlier in the treatment line, and we must consider strategies to improve the efficacy in first line and to overcome immune resistance in later lines; for example, by using combinations of immune-stimulating therapies (anti-PD-L1, CTLA4, anti-TIM3, anti-LAG3, etc.). Some interesting reports were recently presented with the combination of nivolumab and ipilimumab or balstilimab and zalifrelimab, for example. Additionally, HPV therapeutic vaccinations in combination with immunotherapy have the potential to be effective in this setting, as does adoptive cell transfer of TILs.

Finally, the antibody–drug conjugate, trastuzumab deruxtecan, has also shown signs of anti-tumor activity. Furthermore, other upcoming therapy types of interest include inhibitors of the DNA damage response, such as poly-ADP-ribose polymerase (PARP) inhibitors, fibroblast

growth factor receptor (FGFR) inhibitors, and bispecific T cell engagers, such as B11-BiTE, are also promising candidates for the future treatment of R/M CC.

Declaration of interests

I. Vergote (IV) receives consulting fees from Agenus, Akesobio, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai, Elevar Therapeutics, Exelixis, F. Hoffmann-La Roche, Genmab, GSK, Immunogen, Jazzpharma, Karyopharm, Mersana, MSD, Novocure, Novartis, Oncoinvent, OncXerna, Regeneron, Sanofi, Seagen, Sotio, Verastem Oncology and Zentalis. I. Vergote performs contracted research (via KULeuven) for Oncoinvent AS. I. Vergote performs corporate sponsored research for Amgen and Roche. I. Vergote receives accommodation and travel expense remuneration from: Karyopharm, Genmab and Novocure.

I. Ray-Coquard receives consulting/advisory fees from PharmaMar, Merck Serono, Novartis, Agenus, Akesobio, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai, Exelixis, F. Hoffmann-La Roche, Genmab, GSK, Immunogen, Mersana, MSD, Novocure, Novartis, OncXerna, Seagen and Verastem Oncology. I. Ray-Coquard receives travel/accommodation/expense remuneration from AstraZeneca, Clovis Oncology, PharmaMar, Roche, and Tesaro/GSK. IRC receives honoraria from AstraZeneca, Clovis Oncology, Genmab, Immunogen, Merck, Roche, and Tesaro/GSK. IRC receives research funding (to institution) from, BMS, MSD, and GSK.

D. Lorusso receives consulting/advisory fees from PharmaMar, Merck Serono and Novartis. D. Lorusso performs a speaker bureau role for AstraZeneca, Clovis Oncology, PharmaMar, and Tesaro/GSK. D. Lorusso receives travel/accommodation/expense remuneration from AstraZeneca, Clovis Oncology, PharmaMar, Roche, and Tesaro/GSK. D. Lorusso performs expert testimony on behalf of Clovis Oncology. D. Lorusso receives honoraria from AstraZeneca, Clovis Oncology, Genmab, Immunogen, Merck, Roche, and Tesaro/GSK. D. Lorusso receives research funding (to institution) from Clovis Oncology, Merck, PharmaMar, and Tesaro/GSK.

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D. Cibula serves as advisory board member for Akesobio, Astra Zeneca, GSK, MSD, Novocure, Roche, Seagen and Sotio.

T.Van Gorp performs a consulting or advisory role for; AstraZeneca, Eisai Europe, GSK, Immunogen, MSD, OncXerna Therapeutics, Seagen (all fees to institution). T.Van Gorp (receives travel/accommodation/expense renumeration from AstraZeneca, GSK, Immunogen, MSD and PharmaMar. TVG performs corporate sponsored research (via institution) for: Amgen, AstraZeneca and Roche.

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