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Updates and changes in the treatment of cervical cancer

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Summary Recently, a number of randomized controlled trials regarding the therapy of cervical cancer have been published. Thus, the aim of the current review is to provide an overview of the most recent studies that will likely have a substantial influence on clinical practice. In general, checkpoint inhibitors (CPIs) have been evaluated in a variety of clinical settings. The use of CPIs will be expanded to a variety of clinical scenarios due to a number of positive randomized clinical trials. In particular, the combination of taxane-based combination chemotherapy and pembrolizumab ± bevacizumab represents the new standard in the treatment of primary metastatic or recurrent programmed cell death ligand 1 (PD-L1)-positive cervical cancer. With respect to locally advanced cervical cancer, two new treatment escalation regimes on top of chemoradiation have been evaluated (neoadjuvant chemotherapy and adjuvant CPI therapy). Additionally, antibody–drug conjugates (ADCs), such as tisotumab vedotin (TV), could represent a promising therapeutic option in the future treatment of cervical cancer.

Keywords PD-L1-positive cervical cancer · Advanced cervical cancer · Immune checkpoint inhibitors · Tisotumab vedotin · Antibody-drug conjugates

Abbreviations

ADC	antibody–drug conjugate
CPIs	immune checkpoint inhibitors
CRT	chemoradiation
FIGO	International Federation of Gynecology and Obstetrics
HR	hazard ratio
ORR	objective response rate
OS	overall survival
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
TV	tisotumab vedotin

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Take home message

- The combination of the immune checkpoint inhibitor pembrolizumab with taxane-based chemotherapy doublets ± bevacizumab is the new therapeutic standard for patients with primary metastatic or recurrent PD-L1-positive cervical cancer.
- The addition of pembrolizumab prolongs overall (OS) and progression-free survival (PFS) in patients with PD-L1-positive cervical cancer without additional impairment of quality of life.
- Tisotumab vedotin (TV) demonstrated clinically meaningful and durable efficacy with a manageable and tolerable safety profile in women with previously treated recurrent or metastatic cervical cancer.

Introduction

Cervical cancer is the fourth most common malignancy in women worldwide [1]. In 2012, 528,000 women were newly diagnosed with cervical cancer and 266,000 women died from it. The age distribution shows a peak between 40 and 59 years. The incidence of cervical cancer in Germany and Austria has been significantly reduced by early detection screening using cytology smear tests [2]. However, in 2013–2014, 23% of cervical carcinomas in Germany were still in Union for International Cancer Control

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Table 1 Recent clinical trials evaluating new systemic treatment strategies in locally advanced and recurrent/metastatic cervical cancer

Trial	EORTC -55994	OUTBACK	CALLA	KEYNOTE -826	BEAT cc	ENGOT -cx6	ENGOT -cx8	Xu et al. [15]
Phase	–	3	3	3	3	2	1b/2	–
Design	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter	–	–
Population	Locally advanced CC	Locally advanced CC	Locally advanced CC	Rec or met CC	Rec or met CC	Rec CC	Rec or met CC	IVB CC
Patients, *N*	626	919	770	617	410	101	142	818
Treatment	NACT + surgery vs. adjuvant CRT	CRT vs. CRT + Carbo/Paclitaxel	Durvalumab	Pembrolizumab	Atezolizumab	Tisotumab-vedotin	Tisotumab-vedotin	RT vs. surgery + RT
ORR %	–	–	–	–	–	–	54.5%	–
PFS	–	–	12-mo PFS 76%	mPFS 10.4 mo	mPFS 13.7 mo	mPFS 4.2 mo	–	–
OS	5-year OS 72% vs. 76%	5-year OS 71% vs. 72%	–	24-mo OS 52.1%	mOS 32.1 mo	mOS 12.1 mo	–	–
Safety	Short-term AEs 41% vs. 23%	Serious AEs 30% vs. 22%	–	Serious AEs 82.4%	Serious AEs 79%	Serious AEs 28%	Serious AEs 15%	–

CC cervical cancer, *NACT* neoadjuvant chemotherapy, *CRT* chemoradiotherapy, *PFS* progression-free survival, *OS* overall survival, *AEs* adverse events, *mo* months, *rec* recurrent, *met* metastatic, *m* median

(UICC) stage III and 20% in UICC stage IV at initial diagnosis [3]. For the primary advanced or recurrent stages, only limited effective treatment options have been available to date. Since the pathogenesis of cervical carcinoma is associated with human papillomavirus (HPV) infection, immune checkpoint inhibitors such as pembrolizumab represent an important new therapeutic option in the treatment of advanced, recurrent and metastatic cervical carcinoma. HPV causes immunosuppression in infected tissue, in part through the upregulation of PD-L1, the target of pembrolizumab [4]. This review aims to provide an overview of updates in the treatment of cervical cancer (Table 1.).

Locally advanced cervical carcinoma

EORTC-55994

Locally advanced cervical carcinoma is defined as patients with stage IIB–IVa cervical carcinoma. Nowadays, patients with stage IB2 and IIA2 with several histologically proven risk factors (tumor characteristics or affected pelvic lymph nodes) are also considered to have locally advanced cervical cancer [2].

This randomized, multicenter study investigated the value of neoadjuvant chemotherapy before surgery compared to adjuvant chemoradiotherapy in stage IB2-IIB cervical cancer. A total of 626 patients were randomly assigned to either neoadjuvant chemotherapy followed by surgery or standard chemoradiotherapy. The primary endpoint was 5-year overall survival (OS). After a median follow-up period of 8.7 years, 198 patients (31.6%) died.

The 5-year OS did not differ significantly between neoadjuvant chemotherapy followed by surgery (72%; 95% confidence interval [CI] 66–77) and standard chemoradiotherapy (76%; 95% CI 70–80). Thus, no superiority in favor of the neoadjuvant chemotherapy group could be demonstrated in this study. Of note, additional radiotherapy after completion of neoadjuvant chemotherapy followed by surgery was performed in 48% of patients and additional surgery in 8% of patients after completion of standard chemoradiotherapy. Morbidity and quality of life were comparable in both groups as short-term adverse events ≥ grade 3 occurred more frequently with neoadjuvant chemotherapy followed by surgery (41% vs. 23%), whereas long-term adverse events occurred more frequently with standard chemoradiotherapy (21% vs. 15%) [5].

Therefore, concomitant cisplatin-based chemotherapy and radiotherapy with brachytherapy remains standard therapy for locally advanced cervical carcinoma [2].

OUTBACK trial

The multicenter, open-label, randomized phase 3 OUTBACK trial investigated whether additional adjuvant chemotherapy after chemoradiotherapy improves survival in patients with locally advanced cervical cancer. Patients with FIGO 2008 stages IB1 with lymph node metastases or IB2, II, IIIB or IVA were 1:1 randomized to receive either standard cisplatin-based chemoradiotherapy only ($n=456$) or standard cisplatin-based chemoradiotherapy followed by four cycles of carboplatin and paclitaxel ($n=463$). The study failed to demonstrate a significant survival difference between both treatment groups; The 5-year overall survival rate was 71% (66–75) in the chemoradiotherapy-only group (116 deaths) and 72% (95% CI 67–76) in the adjuvant chemotherapy group (105 deaths, difference 1% (95% CI 6–7); hazard ratio 0–90 [95% CI 0–70 to 1–17]; $p=0.81$).

The most common clinically significant adverse events were grade 3–4 decreased neutrophil count (71 [20%] in the adjuvant chemotherapy group ver-

sus 34 [8%] in the chemoradiotherapy-only group) and anemia (66 [18%] versus 34 [8%]). Serious adverse events occurred in 107 (30%) in the adjuvant chemotherapy group versus 98 (22%) in the chemoradiotherapy-only group, most commonly due to infectious complications.

Adjuvant platinum-based chemotherapy after standard chemoradiotherapy increases short-term toxicity and does not improve overall survival in patients with unselected locally advanced cervical cancer and therefore is not recommended in routine clinical practice [6].

CALLA trial

This multicenter, randomized, placebo-controlled, phase III trial evaluated the concomitant administration of the PD-L1 inhibitor durvalumab (AstraZeneca, Cambridge, UK) in the context of primary chemoradiation (CRT) for locally advanced cervical cancer. The 12-month progression-free survival (PFS) was 76.0% (71.3–80.0) with durvalumab and 73.3% (68.4–77.5) with placebo. Thus, this trial failed to demonstrate a relevant benefit of additional checkpoint inhibitor administration to CRT in a biomarker unselected, all-comers population with locally advanced cervical cancer. The additional administration of durvalumab to CRT was well tolerated [7].

Thus, the efficacy of additional checkpoint inhibitor administration to CRT in patients with locally advanced cervical cancer remains controversial.

ENGOT-cx11 trial

Building on the promising therapeutic effects of pembrolizumab (Merck & Co., Inc., Rahway, NJ, USA) in the palliative setting, ENGOT-cx11 is the first multicenter, randomized, placebo-controlled, phase III trial to investigate pembrolizumab as an adjuvant therapy after primary CRT for newly diagnosed locally advanced cervical cancer. Patients received 5 cycles of pembrolizumab (200 mg) or placebo every 3 weeks plus CRT, followed by 15 cycles of pembrolizumab (400 mg) or placebo every 6 weeks.

Median progression-free survival was not reached in either group; rates at 24 months were 68% in the CRT plus pembrolizumab group versus 57% in the CRT plus placebo group. The HR for disease progression or death was 0.70 (95% CI 0.55–0.89, $p = 0.0020$). Overall survival at 24 months was 87% in the CRT plus pembrolizumab group and 81% in the CRT plus placebo group. The HR for death was 0.73 (0.49–1.07).

CRT followed by pembrolizumab showed a statistically significant and clinically meaningful improvement in PFS and a favorable trend in OS compared to CRT plus placebo in patients with locally advanced high-risk cervical cancer and had a manageable safety profile.

This study will lead to an approval for adjuvant pembrolizumab for patients with locally advanced cervical cancer undergoing primary CRT [8].

INTERLACE trial

A feasibility study demonstrated a good response rate to short course weekly induction chemotherapy (IC) delivered before standard chemoradiation (CRT). The INTERLACE trial investigated whether this approach improves both progression-free survival (PFS) and overall survival (OS).

This randomized, multicenter phase III trial enrolled 500 patients with FIGO (2008) stage IB1 node positive, IB2, II, IIIB, and IVA. Patients were randomized (1:1) to receive either CRT alone (5 cycles weekly cisplatin) or IC (6 cycles of weekly carboplatin AUC2 and paclitaxel 80 mg/m^2) followed by CRT in week 7.

The 5-year PFS rate was 73% with the combination of IC/CRT and 64% with CRT alone (HR 0.65; 95%CI 0.46–0.91, $p = 0.013$). The corresponding 5-year OS rates are 80 and 72% (HR 0.61; 95%CI 0.40–0.91, $p = 0.04$).

Grade ≥ 3 adverse events were seen in 59% (IC/CRT) vs. 48% (CRT alone).

Induction chemotherapy followed by CRT significantly improves PFS and OS in locally advanced cervical cancer and should be considered a new standard of care [9].

Metastatic or recurrent cervical carcinoma

KEYNOTE-826 trial

A total of 617 patients with persistent, recurrent or primary metastatic cervical cancer without prior systemic therapy or after radio(chemo)therapy were included. Patients received pembrolizumab (200 mg q3w) versus placebo together with paclitaxel + cisplatin or carboplatin ± bevacizumab. This multicenter, randomized, placebo-controlled phase III trial showed that the addition of pembrolizumab resulted in significantly longer overall and progression-free survival. Patients with PD-L1 positive cervical carcinomas showed significantly longer progression-free survival in case pembrolizumab was added to standard therapy (10.5 months vs. 8.2 months, HR 0.58 [0.47–0.71], $p < 0.001$). Overall survival was also significantly longer in case pembrolizumab was added to standard therapy (survival after 24 months 53.5% vs. 39.4%, HR 0.60 [0.49–0.74], $p < 0.001$). Interestingly, results in the biomarker unselected intention-to-treat population—comprising the small subset of patients with PD-L1 < 1 tumors—were comparable to the PD-L1-positive cohort: the all-comer population showed significantly longer progression-free survival in case pembrolizumab was added to standard therapy (10.4 months vs. 8.2 months, HR 0.61 [0.5–0.74], $p < 0.001$). In the all-comer population, overall survival was also

significantly longer in case pembrolizumab was added to standard therapy (survival after 24 months 52.1% vs. 38.7%, HR 0.63 [0.52–0.77], $p<0.001$).

With respect to subgroup analyses, the efficacy of pembrolizumab seems to be independent of the additional administration of bevacizumab. Thus, even patients who cannot receive bevacizumab benefit from the addition of pembrolizumab. The small subgroup of patients with PD-L1 <1 tumors did not seem to benefit from the addition of pembrolizumab. The HR for OS was 0.87 [0.50–1.52]; however, the 95% CI was wide and overlapped that of the total population.

The side effect profile is of particular interest in this trial, as the addition of pembrolizumab to standard therapy results in a treatment comprising four agents. The incidence of grade ≥3 adverse events was 82.4% for pembrolizumab chemotherapy and 75.4% for placebo chemotherapy. The most frequently recorded grade 3–5 adverse events in both the pembrolizumab and placebo groups were anemia (30.3% vs. 26.9%), neutropenia (12.4% vs. 9.7%) and arterial hypertension (9.4% vs. 10.7%). Substance-typical immune-associated side effects were well treatable on an outpatient basis and did not lead to any additional measurable loss of quality of life.

These results demonstrate that pembrolizumab plus chemotherapy with or without bevacizumab results in clinically meaningful improvements for survival in patients with persistent, recurrent or metastatic cervical cancer [4]. Thus, particularly in patients with primary metastatic or recurrent PD-L1-positive cervical cancer a taxane-based combination chemotherapy ± bevacizumab + pembrolizumab is the new standard of care. The benefit of this quadruple treatment for patients with PD-L1 <1 tumors in this setting remains controversial.

BEATcc

A total of 410 patients with persistent, recurrent or primary metastatic cervical cancer without prior systemic therapy or after radio(chemo)therapy were included in this randomized, open-label phase 3 trial. Patients were randomized 1:1 to standard therapy (cisplatin or carboplatin, paclitaxel and bevacizumab) with or without atezolizumab 1200 mg (Roche, Basel, Schweiz).

Median progression-free survival was 13.7 months (95% CI 12.3–16.6) with atezolizumab and 10.4 months (9.7–11.7) with standard therapy (hazard ratio [HR] = 0.62 [95% CI 0.49–0.78]; $p<0.0001$); at interim analysis of overall survival, median overall survival was 32.1 months (95% CI 25.3–36.8) and 22.8 months (20.3–28.0) (HR 0.68 [95% CI 0.52–0.88]; $p=0.0046$). Adverse events of grade 3 or worse occurred in 79% of patients in the experimental group and in 75% of patients in the standard group. Diarrhea, arthralgia, pyrexia and grade 1–2 rash occurred more frequently with atezolizumab.

The addition of atezolizumab to standard treatment with bevacizumab plus platinum in metastatic, persistent or recurrent cervical cancer significantly improves progression-free and overall survival and can be considered an option for first-line treatment [10].

ENGOT-cx6 trial

There are few effective second-line therapies for women with recurrent or metastatic cervical cancer. Established palliative therapeutic options remain limited and are mostly confined to cytotoxic monochemotherapy. Late-line chemotherapy rechallenges, typically consisting of topoisomerase I inhibitors, gemcitabine, or vinorelbine, are associated with modest prognostic benefits but significant side effects [11].

Tissue factor is highly expressed in cervical cancer and can be targeted by tisotumab vedotin (TV, Pfizer, NYC, NY, USA), an antibody–drug conjugate (ADC).

The ENGOT-cx6 trial was a multicenter, open-label, single-arm phase II trial evaluating the clinical efficacy of the antibody–drug conjugate tisotumab vedotin (2 mg/kg i.v. q3w) in 101 patients with recurrent cervical cancer during or after dual chemotherapy with bevacizumab who have already received a maximum of two prior systemic therapies. Median PFS was 4.2 (3.0–4.4) and median OS was 12.1 (9.6–13.9) months. A clinical response rate of 24% (95% CI 16–33) with a 7% complete remission rate was observed in a median follow-up of 10 months.

The most common treatment-related adverse events included alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), fatigue (26%) and dry eye (23%). Grade 3 or worse adverse events were reported in 28% of patients, including neutropenia (3%), fatigue (2%), ulcerative keratitis (2%) and peripheral neuropathy (2% each with sensory, motor, sensorimotor and peripheral neuropathy). One death due to septic shock was classified by the investigator as treatment-related.

In summary, tisotumab vedotin demonstrated clinically meaningful and durable antitumor activity with a manageable and tolerable safety profile in women with previously treated recurrent or metastatic cervical cancer. Compared to previous late-line monochemotherapy trials, which are associated with low prognostic benefit on the one hand and significant side effects on the other, tisotumab vedotin could represent a promising therapeutic option in the future [12].

ENGOT-cx8 trial

The ENGOT-cx8 trial, an open-label, multicenter phase Ib/II trial, evaluated tisotumab vedotin in combination with bevacizumab, pembrolizumab or carboplatin in recurrent or metastatic cervical cancer in terms of dose-escalation arms and toxicities.

The recommended phase II dose of tisotumab vedotin in combination with bevacizumab (arm A), pembrolizumab (arm B) or carboplatin (arm C) was determined.

In the dose-escalation arms, the antitumor activity and safety of tisotumab vedotin at the recommended phase II dose was evaluated in combination with carboplatin as first-line treatment (arm D) or with pembrolizumab as first-line (arm E) or second/third-line treatment (arm F). The primary endpoint of dose escalation was the objective response rate (ORR). A total of 142 patients were included in the study. As no dose-limiting toxicities were observed during the dose-escalation phase, the recommended phase II dose was tisotumab vedotin 2 mg/kg plus bevacizumab 15 mg/kg once every 3 weeks, pembrolizumab 200 mg once every 3 weeks or carboplatin AUC 5 once every 3 weeks.

At dose escalation, the ORR was 54.5% with first-line tisotumab vedotin + carboplatin (arm D), 40.6% with first-line tisotumab vedotin + pembrolizumab (arm E) and 35.3% with second-/third-line tisotumab vedotin + pembrolizumab (arm F). The median duration of response was 8.6 months, was not reached and was 14.1 months in arms D, E and F, respectively.

Grade ≥ 3 (≥ 15%) adverse events were anemia, diarrhea, nausea, and thrombocytopenia in arm D and anemia in arm F (none ≥ 15%, arm E).

Tisotumab vedotin in combination with bevacizumab, carboplatin or pembrolizumab showed manageable safety and encouraging antitumor activity in treatment-naïve and previously treated recurrent or metastatic cervical cancer [13].

Local treatment in stage IVB

The concept of "oligometastases"—isolated recurrence restricted to defined sites, which may be treated more aggressively by local surgical resection or ablative therapies—had already been proposed in 1995 [14].

Recent studies provide further evidence that such approaches appear to be associated with significantly longer survival in recurrent gynecologic cancer patients, challenging the concept of purely palliative therapeutic approachability in case of recurrence in advanced gynecologic cancers.

The recent trial conducted by Xu et al. investigated the extent to which local treatment improves survival in patients with stage IVB cervical cancer. In this large retrospective series 818 patients with oligometastatic recurrence received local treatment (85.2%) comprising 724 (88.5%) patients with radiotherapy and 94 (11.5%) with surgery ± radiotherapy [15].

Patients undergoing radiotherapy (HR 0.643, 95% CI 0.436–0.947, $P = 0.025$) and surgery (HR 0.146, 95% CI 0.052–0.410, $P < 0.001$) had a better cause-specific survival compared to patients undergoing systemic therapy only without local treatment. Within the cohort of patients undergoing local therapy, patients with radiotherapy alone and patients with surgery alone had comparable oncologic outcomes (HR 0.756, 95% CI 0.454–1.260, $P = 0.284$).

Additional local surgery or radiotherapy appears to improve survival for stage IVB patients [15].

Conclusion

The combination of taxane-based combination chemotherapy and pembrolizumab ± bevacizumab represents a new standard in the treatment of primary metastatic or recurrent PD-L1-positive cervical cancer. Moreover, the use of checkpoint inhibitors (CPIs) will be expanded to other clinical scenarios due to a number of positive randomized clinical trials. Of note, the approvals for these additional indications are currently pending but awaited soon. With respect to locally advanced cervical cancer two new treatment escalation regimes on top of chemoradiation have been evaluated (neoadjuvant chemotherapy and adjuvant CPI therapy). As the full publication for neoadjuvant chemotherapy and the FDA/EMA approval for pembrolizumab as additional therapy to chemoradiation are currently missing, and there is currently conflicting data for the value of CPI therapy in addition to primary chemoradiation, their exact roles in clinical practice need to be further clarified. Additionally, antibody–drug conjugates, such as tisotumab vedotin, could represent a promising therapeutic option in the future treatment of cervical cancer.

Conflict of interest C. Grimm Consultant: AstraZeneca, Celgene, Clovis, Eisai, GSK, MSD, PharmaMar, Roche, Vifor Pharma, Sandoz. Speaker: Amgen, AstraZeneca, Eisai, GSK, MSD, PharmaMar, Roche. Direct research funding: AstraZeneca, Meda Pharma, Roche Diagnostics. Travel/meeting support: AstraZeneca, GSK, PharmaMar, Roche, Roche Diagnostics. M. Postl, T. Bartl and M. Danisch declare that they have no competing interests.

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