Latest in Cervical Cancer Management

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https://doi.org/10.17925/OHR.2025.21.2.1

Cervical cancer (CC) is the fourth most common cancer among women worldwide, with an estimated 604,000 new cases and 342,000 CC-related deaths in 2020. Approximately 90% of CCs are caused by infection with human papillomavirus (HPV). Even though the adoption of both primary (HPV vaccine) and secondary (Pap test and HPV DNA test) preventive measures has reduced the number of HPV-associated tumours, CC remains a prevalent issue in both developing and developed countries. The standard of care for early-stage disease is surgery, while chemoradiation is the treatment of choice in locally advanced cancers. Both treatments have a curative intent, with a 5-year overall survival (OS) around 90% and 60%, respectively. On the contrary, advanced and recurrent diseases present restricted curative alternatives and a 5-year OS of 17%. In the last decade, after the results of the GOG 240 trial, the standard treatment for patients with advanced or recurrent tumours was platinum-based chemotherapy (using cisplatin or carboplatin) combined with paclitaxel and bevacizumab, if not contraindicated. Recently, we witnessed a significant shift in the treatment paradigm for patients with recurrent or metastatic CC.

Keywords

Antibody-drug conjugates, bevacizumab, cancer management, cervical cancer, chemotherapy, Human papillomavirus, immunotherapy, programmed death ligand-1

Disclosures: Daria Spadaro and Domenica Lorusso have no financial or non-financial relationships or activities to declare in relation to this article.

Review Process: Double-blind peer review

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Received: 3 April 2025

Accepted: 12 June 2025

Published online: 26 August 2025

Citation: *touchREVIEWS in Oncology & Haematology.* 2025;21(2):Online ahead of journal publication

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Support: No funding was received in the publication of this article.

Cervical cancer (CC) is the fourth most common cancer among women worldwide, with an estimated 604,000 new cases and 342,000 CC-related deaths in 2020.[1]

Approximately 90% of CCs are caused by infection with human papillomavirus (HPV).[2] Even though the adoption of both primary (HPV vaccine) and secondary (Pap test and HPV DNA test) preventive measures has reduced the number of HPV-associated tumours, CC remains a prevalent issue in both developing and developed countries.[3] In the UK, the implementation of the cytology-based CC screening to all females between 25 and 64 years of age through the National Health Service (NHS) determined a reduction in the incidence of CC.[4]

The standard of care for early-stage disease is surgery, while chemoradiation is the treatment of choice in locally advanced cancers.[5] Both treatments have a curative intent, with a 5-year overall survival (OS) around 90% and 60%, respectively.[6] On the contrary, advanced and recurrent diseases present restricted curative alternatives and a 5-year OS of 17%.[7] Retrospective data on patients treated with second-line systemic treatment for recurrent or metastatic CC showed an objective response rate (ORR) of 13.2%, a median progression-free survival (PFS) of 3.2 months and a median OS (mOS) of 9.3 months.[8]

In the last decade, after the results of the GOG 240 trial (A Randomized Phase III Trial of Cisplatin Plus Paclitaxel With and Without NCI-Supplied Bevacizumab [NSC #704865] Versus the Non-platinum Doublet, Topotecan Plus Paclitaxel, With and Without NCI-Supplied Bevacizumab, in Stage IVB, Recurrent or Persistent Carcinoma of the Cervix; ClinicalTrials.gov identifier: NCT00803062), the standard treatment for patients with advanced or recurrent tumours was platinum-based chemotherapy (using cisplatin or carboplatin) combined with paclitaxel and bevacizumab, if not contraindicated.[9]

Recently, we witnessed a significant shift in the treatment paradigm for patients with recurrent or metastatic CC.

Management of advanced/recurrent disease

The KEYNOTE-826 trial (A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial of Pembrolizumab [MK-3475] Plus Chemotherapy Versus Chemotherapy Plus Placebo for the First-Line Treatment of Persistent, Recurrent, or Metastatic Cervical Cancer [KEYNOTE-826]; ClinicalTrials.gov identifier: NCT03635567), published in 2021, evaluated the efficacy of immunotherapy in the first-line setting. In this randomized phase III trial for persistent, recurrent or metastatic CC, patients were administered a programmed cell death 1 protein (PD-1) antibody inhibitor, pembrolizumab or placebo in addition to platinum-based chemotherapy, with or without bevacizumab. The study revealed that the addition of pembrolizumab into platinum-based chemotherapy regimens (with or without bevacizumab) improved both PFS and OS rates among patients with CC.[10] Based

on these results, in October 2021, the Food and Drug Administration (FDA) approved pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent or metastatic CC whose tumours express programmed death-ligand 1 (PD-L1; combined positive score ≥1), as determined by an FDA-approved test.

In addition, in January 2024, the results of another important trial, BEATcc (A Randomized Phase III Trial of Platinum Chemotherapy Plus Paclitaxel With Bevacizumab and Atezolizumab Versus Platinum Chemotherapy Plus Paclitaxel and Bevacizumab in Metastatic [Stage IVB], Persistent, or Recurrent Carcinoma of the Cervix; ClinicalTrials.gov identifier: NCT03556839), were published.[11] The BEATcc trial enrolled and randomized patients with recurrent or metastatic CC to treatment with cisplatin plus paclitaxel and mandatory bevacizumab with or without an anti-programmed death-ligand 1 (anti-PD-L1) antibody inhibitor, namely, atezolizumab. The addition of atezolizumab resulted in significantly higher PFS and OS with a 38% reduction in the risk of progression and a 32% reduction in the risk of death. When comparing KEYNOTE-826 with BEATcc, the ORR was more pronounced in the BEATcc cohort (84%) than in the KEYNOTE-826 cohort (69%). It is likely that these observed differences are a result of the uniform use of bevacizumab in BEATcc (100% compared with 63% in KEYNOTE-826) and the synergistic effect that exists between platinum doublets, vascular endothelial growth factor inhibitors and immune checkpoint inhibitors (ICIs).

Nonetheless, after first-line treatment failure, efficacious strategies are lacking. In subsequent lines of therapy and beyond, chemotherapy (ChT) shows a suboptimal response rate, with an estimated median PFS ranging from 3 to 6 months.[12]

Over the past few years, two PD-1 antibodies, pembrolizumab and cemiplimab, demonstrated promising outcomes in managing advanced or metastatic CC and were approved in second-line therapy for metastatic or recurrent CC.[13,14]

While the introduction of immunotherapy has improved outcomes for advanced or recurrent disease in earlier lines of treatment, options in subsequent advanced lines remain restricted. This underscores a significant unmet need, particularly for patients experiencing disease progression following immunotherapy.

The identification of novel treatments with innovative mechanisms of action is of utmost importance. The emerging antibody–drug conjugates (ADCs) can be interesting targeted therapies in this scenario. Recent evidence showed the efficacy of tisotumab vedotin (TV), an ADC, in patients with recurrent or metastatic CC experiencing disease progression following chemotherapy.[15,16] Additionally, trials are currently investigating TV both as monotherapy and in combination across various clinical settings, as presented below.

The InnovaTV 204 trial (A Single Arm, Multicenter, International Trial of Tisotumab Vedotin [HuMax®-TF-ADC] in Previously Treated, Recurrent or Metastatic Cervical Cancer; ClinicalTrials.gov identifier: NCT03438396) reported clinically relevant data of TV in the a pretreated CC population. In this study, 101 patients received at least one dose of TV.[17] The confirmed ORR was 24%, resulting in 7 complete responses and 17 partial responses, with a median duration of response (mDOR) of 8.3 months. The data from the InnovaTV-204 were so interesting that the US Food and Drug Administration (FDA) provided in September 2021 an accelerated approval for TV as monotherapy in recurrent or metastatic CC with disease progression on or after chemotherapy.[18]

In October 2023, at the European Society of Medical Oncology (ESMO) meeting in Madrid, Vergote presented a planned interim analysis for the ongoing InnovaTV-301 (A Randomized, Open-Label, Phase 3 Trial of Tisotumab Vedotin vs Investigator's Choice Chemotherapy in Second- or Third-Line Recurrent or Metastatic Cervical Cancer; ClinicalTrials.gov identifier: NCT04697628) study.[19] Eligible patients had relapsed or metastatic CC with disease progression on or after treatment with standard-of-care ChT doublet plus bevacizumab plus an anti-PD-L1 therapy whenever it was possible and not contraindicated. Patients were randomized 1:1 to TV monotherapy or the investigator's choice of topotecan, vinorelbine, gemcitabine, irinotecan or pemetrexed. The primary endpoint was OS, while key secondary endpoints included PFS and confirmed ORR by the investigator. A total of 502 patients were randomized, including 253 patients in the TV arm and 249 patients in the ChT arm. Arms were well balanced for demographics and disease characteristics: 64% of patients received prior bevacizumab and 28% prior treatment with an anti-PD-L1 agent. The median survival follow-up was 10.8 months.

With a median survival follow-up of 10.8 months, the mOS was significantly longer in the TV arm: 11.5 months versus 9.5 months in the ChT arm, showing a 30% reduction in risk of death in the TV arm versus chemotherapy. Confirmed ORR was 17.8% and 5.2% in the TV and ChT arms, respectively. In addition, PFS was superior in the TV versus the ChT arm. The OS and PFS benefits in the prespecified subgroups were generally consistent with the intent to treat the population. Interestingly, in subgroup analysis, no prior bevacizumab treatment seemed to correlate with no benefits in favour of TV compared with the investigator's choice of ChT in PFS (hazard ratio [HR]: 1; 95% confidence interval [CI]: 0.66, 1.50) and OS (HR: 0.83; 95% CI: 0.59, 1.16), while OS in patients with a prior anti-PD-L1 therapy was characterized by an HR of 0.72 (95% CI: 0.46, 1.14). Further evaluations will clarify these findings for a better understanding of the best scenario to use TV.[19]

The InnovaTV 205/GOG-3024/ENGOT-cx8 (A Phase 1b/2 Open-Label Trial of Tisotumab Vedotin [HuMax®-TF-ADC] Monotherapy and in Combination With Other Agents in Subjects With Recurrent or Stage IVB Cervical Cancer; ClinicalTrials.gov identifier: NCT03786081) was a multicohort phase Ib/II trial evaluating the safety and antitumor activity of TV in combination with bevacizumab, pembrolizumab or carboplatin in patients with recurrent or metastatic CC.[20] This study enrolled 41 patients in the dose escalation arms A-C (TV plus bevacizumab, TV plus carboplatin and TV plus pembrolizumab) and 101 patients in dose-expansion arms D-F (TV plus carboplatin in the first line, TV plus pembrolizumab in the first line, TV plus pembrolizumab in the second-third line). The recommended phase II dose was TV 2 mg/kg intravenously once every 3 weeks in combination with bevacizumab 15 mg/kg, pembrolizumab 200 mg or carboplatin AUC 5 (each also administered once every 3 weeks).

The maximum tolerated dose was not reached in any arm during the dose escalation phase. For patients treated with TV plus carboplatin in the first line, the ORR was 55% and the mDOR was 8.6 months. With a median follow-up of 17.8 months, the median PFS was 6.9 months. The PFS rate was 28% and 5% at 1 year and 2 years, respectively. The mOS was not reported at the data cutoff. This encouraging antitumour activity, together with good tolerability of TV plus carboplatin, warrants further evaluations of this combination in the first-line setting. For chemo-naive patients who received TV plus pembrolizumab in the first line, the ORR was 41% and the mDOR was NR. With a median follow-up of 21.7 months, the median PFS was 5.3 months; the PFS rate was 37% and 29% at 1 year and 2 years, respectively. The mOS was NR. Among patients who

received second- or third-line treatment with TV plus pembrolizumab, the ORR was 35%. Responses were maintained in 4 of the 12 responders at the last assessment, 3 of whom remained on study treatment. An interesting response, considering that the mDOR was 14.1 months. With a median follow-up of 15.0 months, the median PFS was 5.6 months. The PFS rate was 35% and 15% at 1 year and 2 years, respectively. The mOS was 15.3 months.

Human epidermal growth factor receptor 2 (HER2) is a transmembrane receptor tyrosine kinase belonging to epidermal growth factor receptors. HER2 is overexpressed in 15–20% of breast cancers, 15–20% of gastric tumours and approximately 5% of CC.[21–23] Trastuzumab deruxtecan (T-Dxd; Enhertu®, Daiichi-Sankyo, Chuo City, Tokyo, Japan) combines a monoclonal antibody (trastuzumab) targeting HER2 with a cytotoxic payload (deruxtecan) consisting of a topoisomerase I inhibitor.[24] T-Dxd is currently approved for the treatment of advanced breast cancer expressing HER2, as well as advanced gastric or gastroesophageal junction adenocarcinoma and non-small cell lung cancer that are HER2-positive, in both the USA and the European Union.

In January 2024, T-Dxd was granted Priority Review by the FDA in the USA for patients with metastatic HER2-positive solid tumours, after the receipt of breakthrough therapy designation in August 2023.[25] The supplemental Biologics License Application is based on data from the DESTINY-PanTumor02 (A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan [T-DXd, DS-8201a] for the Treatment of Selected HER2 Expressing Tumors [DESTINY-PanTumor02]; ClinicalTrials.gov identifier: NCT04482309), an ongoing phase II study including metastatic HER2-expressing solid tumours. Primary results recently published revealed an ORR of 50% for all patients with CC, 75% for IHC 3+ and 40% for IHC 2+.[26] In the near future, T-Dxd may join the list of available ADCs for the treatment of CC, in particular in cases in which the cancer is positive for HER2.

Trophoblast cell-surface antigen 2 (TROP-2) is a cell membrane glycoprotein encoded by the tumour-associated calcium signal transducer 2 gene. It contributes to tumour development and progression through its interaction with several fundamental molecular signalling pathways involved in cancer proliferation, invasion and metastasis.[27,28] Initially described in trophoblastic tissue, TROP-2 was later found to be highly expressed in several solid tumours, with prevalence ranging from 44% to 88.7%.[29] Its limited expression in normal tissues makes it an appropriate target for ADCs in cancer treatment.

Sacituzumab govitecan (Trodelvy®, Gilead Sciences, Foster City, CA, USA) is an ADC comprising a humanized antibody targeting TROP-2 linked to the active metabolite of irinotecan, SN-38. It is currently the only FDA- and European Medical Association (EMA)-approved anti-TROP-2 ADC and is indicated for the treatment of unresectable or metastatic triple-negative breast cancer as well as hormone receptor-positive, HER2-negative breast cancer.[30]

Considering that the expression rate of TROP-2 in CC (88.7%) surpasses that in triple-negative breast cancer (78.1%), TROP-2-positive CCs could emerge as a promising area for future research, and an ongoing randomized trial, ENGOT-cx20/MK-2870-020 (A Phase 3 Randomized, Active-controlled, Open-label, Multicenter Study to Compare the Efficacy and Safety of MK-2870 Monotherapy Versus Treatment of Physician's Choice as Second-line Treatment for Participants With Recurrent or Metastatic Cervical Cancer [TroFuse-020/GOG-3101/ENGOT-cx20]; ClinicalTrials.gov identifier: NCT06459180), is evaluating its efficacy with respect to standard chemotherapy.[31]

Management of locally advanced disease

Chemoradiotherapy in locally advanced cervical cancer

Chemoradiotherapy (ChRT) with a cisplatin-based schema has remained the cornerstone of treatment for patients with IB3-IVA since the publication of five large randomized trials in the late 1990s.[32–35] Subsequently, a meta-analysis found that the addition of ChRT improved 5-year OS and disease-free survival (DFS) rates by 6% and 8%, respectively.[36]

In the last two decades, technological progress has enhanced imaging and radiotherapy delivery techniques, improving the treatment of locally advanced cervical cancer (LACC). External beam radiotherapy has evolved from conventional multiple field techniques (3D technique) to intensity-modulated radiotherapy/volumetric modulated arc therapy (IMRT/VMAT), with a clear benefit in the toxicity profile. Nevertheless, the most advanced techniques focused high doses to grossly involved pelvic and/or para-aortic nodes by simultaneous boost, sparing organs at risk. Two randomized studies in the adjuvant setting, comparing the 3D technique versus image-guided intensity-modulated radiotherapy (IG-IMRT), revealed less grade (G) ≥2 toxicity with IG-IMRT (57% versus 78%), and quality-of-life (QoL) improvements with no difference in tumour control rates.[37,38] Moreover, a meta-analysis comparing IMRT to 3D or 2D technique for definitive treatment of CC showed no significant differences in 3-year OS and DFS between IMRT and conventional techniques. However, IMRT significantly reduced the incidence of acute and chronic gastrointestinal (GI) and genitourinary (GU) toxicities (GI: G ≥3; OR = 0.55; 95% CI: 0.32, 0.95; p=0.03; GU: G ≥3; OR = 0.31; 95% CI: 0.14, 0.67; p=0.003).[39]

Most advances in improving outcomes were done in brachytherapy (BT) treatment. In the 2000s, the Gynaecological (GYN) Groupe Europeen De Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) working group published the recommendations for target contouring, implant technique and treatment planning with magnetic resonance imaging (MRI)-based image-guided adaptive brachytherapy (IGABT).[40–42] The validation of GEC-ESTRO and ICRU 89 recommendations was conducted through the prospective, multicentre EMBRACE I study (A International Study on MRI-guided Brachytherapy in Locally Advanced Cervical Cancer; ClinicalTrials.gov identifier: NCT00920920), which evaluated the outcomes of 1,341 patients treated with standard ChRT followed by MRI-based IGABT for LACC. With a median follow-up of 51 months, the 5-year actuarial overall local tumour control rate across all stages was 92% (95% CI: 90, 93), while the 5-year OS rate was 74% (95% CI: 72, 77).[43] Furthermore, the application of IGABT treatment led to a 14–17% increase in local and pelvic control for FIGO (International Federation of Gynaecology and Obstetrics) 2014 stage IIIB/IVA disease. Key treatment characteristics included a median dose received by 90% of the high-risk clinical target volume of 90 Gy (85–94) and a median overall treatment time of 46 days (42–49). Importantly, these excellent outcomes were achieved without an increase in treatment-related toxicity or deterioration in QoL. The actuarial cumulative 5-year rates of G3/4 morbidity were as follows: GU 6.8%:1%, GI 8.5%:3%, vaginal 5.7%:0.5% and fistulae 3.2%:2.1%.[44] Given these results, MRI-based IGABT has become the cornerstone of the standard treatment for LACC.[6]

With the rationale of improving disease outcomes in high-risk LACC (IIIB/IVA and/or node-positive) disease, the combination of standard ChRT

and ICIs was evaluated in two randomized phase III clinical trials.[45,46] The randomized, double-blind CALLA trial (A Phase III, Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With and Following Chemoradiotherapy Compared to Chemoradiotherapy Alone for Treatment in Women With Locally Advanced Cervical Cancer; ClinicalTrials.gov identifier: NCT03830866) analysed the combination of an anti-programmed death ligand-1 (durvalumab) or placebo concomitant with standard ChRT, followed by durvalumab in maintenance for up to 24 cycles.[45] The study did not achieve statistical significance for the primary endpoint of improving PFS in a biomarker unselected population (76% versus 73.3%; HR: 0.84; [95% CI: 0.65, 1.08; p=0.17]). However, an exploratory subgroup analysis of CALLA trial has shown that patients with PD-1 tumour area positivity >20% (51%) showed a reduced risk of progression (HR: 0.62; 95% CI: 0.42, 0.91).

Recently, results of the phase III ENGOT-cx11/GOG3047/KEYNOTE-A18 trial (A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer [KEYNOTE-A18/ENGOT-cx11/GOG-3047]; ClinicalTrials.gov identifier: NCT04221945) were published.[46] In that trial, patients with high-risk LACC were randomized to receive pembrolizumab (anti-PD-1) or placebo plus concurrent ChRT (radiotherapy and image-guided BT) followed by maintenance pembrolizumab or placebo for 15 cycles. Data from the second interim analysis at 36 months showed a significant improvement in PFS (69.3% versus 56.9%) and OS (82.6% versus 74.8%), with a HR for death of 0.67 (95% CI: 0.50, 0.90; p=0.0040). Based on the PFS results obtained in that trial, pembrolizumab concomitant with ChRT and used as maintenance therapy was approved by the US FDA in January 2024 for FIGO 2014 stage III-IVA disease, and the EMA also approved pembrolizumab for this high-risk subgroup.

Neoadjuvant/induction chemotherapy

Several phase III trials have explored new strategies on neoadjuvant (NA) and adjuvant ChT treatment that have yielded mixed results. A randomized phase III trial conducted by Gupta et al. reported that NA ChT followed by radical surgery was inferior in DFS compared to ChRT alone, although OS was comparable.[47] Similar results were shown in the EORTC-55994 (Randomized Phase III Study Of Neoadjuvant Chemotherapy Followed By Surgery Vs. Concomitant Radiotherapy And Chemotherapy In FIGO Ib2, IIa>4 cm or IIb Cervical Cancer; ClinicalTrials.gov identifier: NCT00039338) randomized phase III study comparing NA cisplatin-based ChT followed by radical hysterectomy to standard ChRT in patients with stage Ib2-IIB.[48] Without any benefit in terms of survival rates, the surgery arm in both trials showed the worst toxicity profile.

The concept of NA ChT plus ChRT and BT has been widely explored and discussed in recent years. A meta-analysis of individual patient data from 18 randomized trials failed to perform a comprehensive analysis due to differences in trial design.[49] However, it highlighted cycle length and platinum dose intensity as key factors influencing the effect of NA ChT on treatment outcomes. More recently, the results of the randomized phase III GCIC INTERLACE trial (A Phase III Multicentre Trial of Weekly Induction Chemotherapy Followed by Standard Chemoradiation Versus Standard Chemoradiation Alone in Patients With Locally Advanced Cervical Cancer; ClinicalTrials.gov identifier: NCT01566240) were published.[50] This academic study compared standard ChRT to induction ChT (IC) with weekly carboplatin/taxol for six cycles followed by standard ChRT. The 5-year OS rate was 80% in the experimental arm versus 72% in the control arm (HR: 0.60 [95% CI: 0.40, 0.91; p=0.015]). While those results appear to support the use of induction chemotherapy, these findings must be considered in the context of the trial limitations, particularly concerning patient selection and treatment techniques. The population included in this study was mainly FIGO 2014 stage IB2-IIB disease (86%), and only 43% of the cohort had positive lymph nodes excluding para-aortic lymph node involvement, representing a good prognostic subgroup. An important limitation of the INTERLACE trial is the large proportion of patients who did not receive IGABT (70%), the current standard of care. Moreover, the mean dose to the cervical tumour was 79.4 Gy at point A in the full cohort (i.e. patients treated with and without IGABT). This dose is notably lower than what can be achieved with MRI-based IGABT and is likely insufficient for optimal local control. In conclusion, compared with the standard arm, IC appears to compensate for suboptimal BT in a specific subgroup of LACC patients.[51,52] *Table 1* summarizes the findings of the cited trials on the management of LACC and recurrent/metastatic CC.

Adjuvant chemotherapy

A large randomized phase III trial (A Phase III Trial of Adjuvant Chemotherapy Following Chemoradiation as Primary Treatment for Locally Advanced Cervical Cancer Compared to Chemoradiation Alone: The OUTBACK Trial; ClinicalTrials.gov identifier: NCT01414608) investigated the impact of adjuvant ChT with carboplatin/paclitaxel for four cycles following standard ChRT in LACC. The results showed a 5-year OS of 72% in the adjuvant ChT group compared to 71% in the ChRT-only group (HR: 0.90; 95% CI: 0.70, 1.17; p=0.81).[53] These results indicate that adjuvant ChT did not improve OS and was associated with increased grade (G) 3–4 toxicity . Moreover, Horeweg et al. conducted a meta-analysis focused on adjuvant ChT after standard ChRT and showed that those strategies not only failed to significantly improve OS (HR: 0.78; 95% CI: 0.45, 1.33; p=0.36) and PFS (HR: 0.85; 95% CI: 0.65, 1.10; p=0.22), but they also increased toxicity.[54]

Conclusions

The treatment of CC, and in particular of advanced and recurrent disease, has rapidly evolved in recent years. The introduction of immunotherapy in first-line treatment has significantly improved survival outcomes. The approval of pembrolizumab in LACC represents a new standard of care. However, despite the progress brought by ICIs, therapeutic options in cases of progression after immunotherapy remain limited. ADCs, such as TV, have shown encouraging results, suggesting a potential role for ADC combinations in both frontline and salvage settings. Agents targeting HER2 (e.g. trastuzumab deruxtecan) and TROP-2 (e.g. sacituzumab govitecan) represent promising therapeutic options in selected populations. Moreover, the diffused use of IGABT has led to improved tumour control and reduced toxicity in advanced stages. The innovations in the landscape of CC treatment highlight the importance of biomarker-driven approaches and tailored therapies to improve outcomes across all disease stages. ❑

Table 1: Summary of the latest developments in locally advanced and recurrent/metastatic cervical cancer management

Setting	Therapy	Key trials	Findings
Locally advanced cervical cancer	Advanced RT techniques (IGABT)	EMBRACE I	Improved tumour control and reduced toxicity
	ChRT + immunotherapy	CALLA (durvalumab)	No significant PFS improvement (biomarker-unselected population)
		KEYNOTE-A18 (pembrolizumab)	Improved PFS and OS (HR death: 0.67); 5-year OS: 82.6%
	Induction chemotherapy + ChRT	INTERLACE	Improved OS (80% versus 72%); HR death: 0.70 (70% of patients did not receive IGABT)
Recurrent/metastatic cervical cancer	Chemotherapy + bevacizumab	GOG-240	Improved ORR, PFS, OS versus chemotherapy alone
	+ Immunotherapy (PD-1/PD-L1 inhibitors)	KEYNOTE-826 (pembrolizumab)	OS and PFS benefit (HR death: 0.64)
		BEATcc (atezolizumab)	Better ORR (84%) and OS versus KEYNOTE-826
	ADC: TV	InnovaTV 204	ORR: 24%; median duration of response: 8.3 months
		InnovaTV-301	OS: 11.5 months (TV) versus 9.5 months (chemotherapy); HR death: 0.70
	TV + chemotherapy or ICI	InnovaTV-205	ORR: 55% (TV + carboplatin), 41% (TV + pembrolizumab)
	ADC: T-Dxd	DESTINY-PanTumor02	ORR of 50% in HER2-expressing tumours
	ADC: sacituzumab govitecan (anti-TROP-2)	ENGOT-cx20	Ongoing

ADC = antibody–drug conjugate; ChRT = chemoradiotherapy; HER2 = human epidermal growth factor receptor 2; HR = Hazard Ratio; ICI = immune checkpoint inhibitor; IGABT = image-guided adaptive brachytherapy; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RT = radiotherapy; T-Dxd = trastuzumab deruxtecan; TROP-2 = tumor-associated calcium signal transducer 2; TV = tisotumab vedotin.

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