Emerging therapies in gynaecological cancers (part 1) : Locally advanced and metastatic cervical cancer

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SUMMARY

Although progress has been made through screening and vaccination against human papillomavirus (HPV), locally advanced (LACC) and metastatic cervical cancer continue to present significant therapeutic challenges. Indeed, the treatment strategies have remained largely unchanged for almost twenty years. In the LACC setting, recent research has focused on improving standard treatment (chemoradiation followed by brachytherapy), including neo-adjuvant chemotherapy (INTERLACE trial) or addition of an immune checkpoint inhibitor (ICI) (ENGOT-Cx11 study). In metastatic disease, immunotherapy is also making strides, encompassing ICIs in the first-line treatment; but also, tumour-infiltrating lymphocyte (TIL) transfer and therapeutic vaccination are still in clinical trials. The antibody-drug conjugate (ADC) tisotumab vedotin has demonstrated efficacy in second- or third-line therapy, while other ADCs targeting HER2 and TROP2 are under investigation. These innovative treatments offer hope for improving survival outcomes in the cervical cancer patient population.

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INTRODUCTION

According to GLOBOCAN 2022, cervical cancer (CC) is the fourth most common cancer in women worldwide, and is the second most common cancer in developing countries, where >85% of cases occur. Indeed, an estimated 660,000 new cases of CC and 350,000 deaths are recorded, although incidence and mortality vary widely among countries.[1] In developed countries, incidence has decreased over the past 30 years due to the introduction of screening and HPV vaccination programmes. In Belgium, it also ranks as the fourth most common cancer among women between 15 and 44 years old. Squamous cell carcinoma (SCC), adenocarcinoma (ADK), and adenosquamous carcinoma (ADSC) are the three most common histological subtypes, accounting for 70%, 25%, and 5% of cases, respectively. In contrast to SCC, the incidence and mortality of ADK have increased

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during the same timeframe. This evolution has been attributed to the Papanicolaou test and its ability to detect squamous, rather than glandular, neoplasia more efficiently.[2]

According to the 2018 International Federation of Gynaecology and Obstetrics (FIGO) classification, LACC corresponds to stages IB3 to IVA and accounts for approximately 40% of all CC. Moreover, around 6% of women are discovered with primary metastatic disease (stage IVB). The five-year overall survival (OS) rates approximate 92%, 65%, and 17% for early-stage, locally advanced and metastatic diseases, respectively.[2] Of note, one-third of the patients receiving chemoradiation (CRT) followed by brachytherapy for LACC will have a recurrence. The vast majority of recurrent or metastatic CC not amenable to locoregional treatments are considered incurable diseases with very poor prognosis. In this review, we discuss current and emerging treatment options for patients with LACC and primary metastatic or recurrent CC.

METASTATIC/RECURRENT CERVICAL CANCER (M/R CC):

By a majority, patients with a primary metastatic (FIGO 2018 stage IVB) or recurrent CC will benefit from systemic treatments.[3]

CHEMOTHERAPY

Historically, CC was treated with cisplatin monotherapy following the results of the phase II Gynaecologic Oncology Group **(GOG)-26** trial. The majority of the patients included were chemotherapy-naive. The overall response rate (ORR) was 38%, and the median overall survival (mOS) reached nine months.[4]

Furthermore, the phase III **GOG-204** trial evaluated four cisplatin-based combinations in 513 patients: cisplatin with paclitaxel, gemcitabine, topotecan, or vinorelbine. Although mOS, ranging from 9.9 to 12.9 months, did not differ statistically across the arms, a higher ORR was observed in the cisplatin-paclitaxel combination. Thus, this doublet became the new standard of care in M/R CC.[5,6] Moreover, the phase III **JCOG-0505** trial compared cisplatin or carboplatin with paclitaxel in 253 patients and emphasised the development of acquired platinum resistance in patients who had previously received cisplatin-based treatment.

BEVACIZUMAB

The phase III **GOG-240** study compared the combination of chemotherapy (cisplatin with paclitaxel or topotecan) with or without bevacizumab in 452 patients. The addition of the Vascular Endothelial Growth Factor (VEGF) inhibitor increased the mOS by around 4 months, from 13.3 to 17.0 months (HR 0.71; 98% CI 0.54-0.95); a higher ORR of 48% *vs.* 36% in the control arm was also described.[7] The Food and Drug Administration (FDA) in 2014 and the European Medicines Agency (EMA) in 2015 both approved this combination for patients with M/R CC.

IMMUNE CHECKPOINT INHIBITORS (ICIS):

Two phase III clinical trials investigated the addition of immunotherapy to chemotherapy in first-line (1L) M/R CC. In the phase III **KEYNOTE-826** study, the addition of pembrolizumab *vs.* placebo to carboplatin/paclitaxel with or without bevacizumab was tested in 617 patients. Baseline characteristics were well balanced across the two treatment arms, with the majority of cases being SCC. Half of the patients had a Programmed Death-Ligand 1 (PD-L1) Combined Positive Score (CPS) ≥ 10, and 37% had scores between one and ten. As previous therapies, most patients (70%) received chemoradiation or radiation with or without surgery. Over 60% of patients were concomitantly treated by bevacizumab during the study. The combination of pembrolizumab and chemotherapy reduced the risk of progression (HR 0.61; 95% CI 0.5-0.74) or death (HR 0.63; 95% CI 0.54-0.84) by approximately 40% in the overall population; with an ORR of 66.2% in the pembrolizumab [including 21.4% of complete response (CR)] *versus* 50.8% in the control arms. In the CPS≥1 to <10 population, the risk of progression (HR 0.58; 95% CI 0.47-0.71) and death (HR 0.60; 95% CI 0.49-0.74) were also reduced with an ORR of 68.1% and 50.2% in the experimental and control arms, respectively. Globally, the same results were demonstrated in the CPS≥10 group.[8,9]

Pembrolizumab, in combination with chemotherapy with or without bevacizumab, received EMA approval on the 29th of April 2022, for the treatment of patients with persistent, recurrent, or metastatic CC whose tumours express PD-L1 (CPS ≥ 1). This treatment is also reimbursed in Belgium with the same indication.

The phase III **BEATcc** study investigated carboplatin/paclitaxel with or without atezolizumab (PD-L1 inhibitor), in 410 patients (15). Bevacizumab use was mandatory. Characteristics were well-balanced between the two arms (80% SCC, 73% recurrent disease with 35% of patients having distant disease only). This study revealed that the addition of atezolizumab has prolonged both Progression Free Survival (PFS) and OS. Median PFS of 13.7 months and 10.4 months was demonstrated in the atezolizumab and

control groups (HR 0.62, 95% CI: 0.49-0.78), respectively. Similarly, the mOS was 32.1 months in the atezolizumab *versus* 22.8 months in the control group (HR 0.68, 95% CI: 0.52-0.88). In the atezolizumab arm, 79% of patients experienced a grade ≥3 adverse event (AE) *vs.* 75% in the placebo arm. The addition of atezolizumab also demonstrated spectacular results in terms of ORR (84%) and CR (32%). This drug is not yet approved either by the EMA or in Belgium.[10]

The phase III **ENGOT-Cx9 (EMPOWER)** study evaluated the efficacy of cemiplimab in patients with R/M CC after progression on 1L platinum-based chemotherapy. Among the 608 randomised patients (1:1), 477 and 131 had SCC and ADK, respectively. Over 85% of patients in both arms were aged 65 years or older. In the overall population, the mOS with cemiplimab was 11.7 months, compared to 8.5 months with chemotherapy (HR 0.69; 95% CI, 0.56 to 0.84). PFS was also improved in the experimental group (HR 0.75; 95% CI 0.63-0.89). These benefits were observed regardless of histological subtypes and PD-L1 status. Cemiplimab demonstrated a reassuring safety profile, with grade 3 or higher AEs observed in 45.0% *vs.* 53.4% of patients receiving chemotherapy.

TISOTUMAB VEDOTIN (TV)

The tissue factor (TF) is a transmembrane protein expressed on the surface of endothelial and fibroblastic cells in normal conditions, playing a key role in initiating the coagulation cascade by activating factor VII. It is overexpressed on the surface of many solid tumours, particularly in 94 to 100% of CCs. Its overexpression is associated with poor prognosis due to its role in tumour angiogenesis, proliferation, metastatic dissemination, and thrombotic events. TV is an antibody–drug conjugate (ADC) directed to TF with the microtubule-disrupting agent monomethyl auristatin E (MMAE) as payload. Its mechanism of action is multimodal and acts through direct cytotoxicity, antibody-dependent cellular cytotoxicity, phagocytosis, bystander effect, and induction of immunogenic cell death.

The phase II **INNOVA-TV-204** trial evaluated TV monotherapy in 101 R/M CC patients with a disease progressing on or after doublet-chemotherapy with bevacizumab (if eligible); who had received two or fewer previous systemic regimens. An ORR of 24% was shown, with CR and partial response (PR) in 7 and 17 patients, respectively.

The phase III randomised **INNOVA-TV-301** study investigated the efficacy and safety of TV (n = 253) compared to chemotherapy (investigator's choice) (n= 249) in patients progressing during or after standard doublet-chemotherapy, with or without bevacizumab. Baseline characteristics were well balanced between the 2 arms, with approximately 64% and 27.5% of patients having received prior treatment by bevacizumab and anti-PD-(L)1, respectively. The primary endpoint OS, was improved with a mOS of 11.5 months in the TV *vs.* 9.5 months in the chemotherapy arms (HR 0.70; 95% CI 0.54-0.89). The ORR was 17.8% and 5.2% in the TV and chemotherapy groups, respectively.[11] AEs were consistent with the safety profile observed in the phase II study, including ocular events, peripheral neuropathy, and bleeding (epistaxis). The FDA granted full approval for this indication on the 29th of April 2024. This drug has not yet received EMA approval and is thus currently not available in Belgium.

The phase I/II **INNOVA-TV-205** study included dose-escalation and expansion arms; this later evaluated TV antitumour efficacy and safety at the recommended dose in combination with carboplatin as first-line (1L) treatment (arm D) or with pembrolizumab as 1L (arm E) or second-/third-line (2L/3L) treatment (arm F). In the dose-expansion population (n = 101), the ORR was 54.5% in the arm D [median duration of response (mDOR) of 8.6 months], 40.6% in the arm E (mDOR not reached), and 35.3% in the arm F (mDOR of 14.1 months). Therapy combinations with TV demonstrated an acceptable safety profile and promising antitumour efficacy.[12]

OTHER IMMUNOTHERAPY APPROACHES:

1) ICIs COMBINATIONS

New strategies have combined different ICIs, such as PD-1 and cytotoxic t-lymphocyte associated protein 4 (CTLA-4), to act at various stages of the immune response (preventing T cell exhaustion and promoting the initial activation of T cells) and thus trying to improve efficacy.

A phase II **NCT03495882** trial evaluated the combination of balstilimab (anti-PD-1) and zalifrelimab (anti-CTLA-4) in 155 patients. The confirmed ORR was 25.6% (10 CR and 22 PR). Of note, ORRs were 32.8% and 9.1% in patients with PD-L1-positive and -negative tumours, respectively.[13]

The **CheckMate 358** study assessed the efficacy of nivolumab either as monotherapy or in combination with ipilimumab in 193 patients with M/R CC. Objective response rates were 26% with nivolumab, 31% with NIVO3 plus IPI1 (nivolumab 3 mg/kg every two weeks plus ipilimumab 1 mg/kg every six weeks) and 40% in the NIVO1 plus IPI3 arm (nivolumab 1 mg/kg every three weeks and ipilimumab 3 mg/kg

every three weeks for four cycles). Serious AEs were reported in 16%, 27%, and 42% of patients in the nivolumab monotherapy, NIVO3 plus IPI1 and in the NIVO1 plus IPI3 groups, respectively. One treatment-related death due to immune-mediated colitis was reported in the NIVO1 plus IPI3 group.[14]

The efficacy of cadonilimab (AK104), a tetravalent bispecific antibody targeting both PD-1 and CTLA-4, has been evaluated in the randomised (1:1) phase III **Compassion-16** trial. This trial involved 445 Chinese women recruited between September 2021 and June 2022, diagnosed with persistent, recurrent, or metastatic CC and who have not received prior treatment. Participants were randomised to receive either cadonilimab (10 mg/kg) or placebo, in combination with platinum-based chemotherapy with or without bevacizumab, every three weeks for six cycles, followed by maintenance therapy for up to two years. Addition of cadonilimab improved PFS (HR 0.62; 95% CI 0.49–0.80) and OS (HR 0.64; 95% CI 0.48–0.86).[15]

A non-randomised phase II study evaluated bintrafusp alpha, a bifunctional protein consisting of an anti-PD-L1 antibody and two TGF-β receptors, in 146 R/M CC patients with disease progression during or after platinum-based chemotherapy. An ORR of 21.9% was demonstrated. However, over 72.6% of patients reported treatment-related AEs.[16]

TIGIT (T-cell immunoreceptor with immunoglobulin and ITIM domains) regulates the activation of the T and natural killer (NK) cells to prevent excessive activation of the immune system. Moreover, TIGIT can inhibit an effective immune response against tumour cells. The phase II **SKYSCRAPER-04** study evaluated the efficacy of the combination of tiragolumab (anti-TIGIT) and atezolizumab, after 1 to 2 lines of chemotherapy, in patients with PD-L1 positive recurrent/persistent CC. The results revealed an ORR of 19% for the combination, compared to 15.6% with atezolizumab alone, not reaching statistical significance. The PFS was 2.8 months for the combination, compared to 1.9 months for atezolizumab alone, and the mOS was 11.1 months with the combination, slightly higher than 10.6 months with atezolizumab alone. Adverse events were similar between the two groups, with few patients discontinuing treatment due to serious AEs.[17]

2) THERAPEUTIC VACCINATIONS

The phase II single-arm **NCT03444376** study evaluated the combination of GX-188E, a vaccine which encodes antigens for HPV16 and HPV18 oncoproteins, and pembrolizumab in 65 patients with HPV-positive CC who had relapsed or progressed after standard treatments. The ORR was 35.0%, with 8.3% achieving a CR and 26.7% a PR. The mOS was 23.8 months, and the mPFS was 4.4 months. The combination was well tolerated, with 33.8% of patients experiencing treatment-related AEs, and no treatment-related deaths occurred.[18]

The single-arm phase II **VB-C-02** study assessed the efficacy of VB10.16 in combination with atezolizumab in 47 patients with advanced or recurrent HPV-positive CC. The VB10.16 vaccine is a gene therapy targeting HPV-positive lesions. It combines the HPV E6 and E7 antigens with the human chemokine (C-C motif) ligand 3-like 1 (CCL3L1), enabling the direct targeting of these antigens to antigen-presenting cells (APCs) and activating an effective cellular immune response. In the overall population, the mOS was 16.9 months, with a mPFS of 4.1 months. Among the PD-L1-positive population (n=24), mOS was not reached, mPFS was 6.3 months and the ORR was 29% [with 8% of CR and a disease control rate (DCR) of 75%]. The trial demonstrated promising efficacy and safety, with AEs primarily of grade 1/2.

3) TUMOUR-INFILTRATING LYMPHOCYTES (TIL) TRANSFER

The phase II **C-145-04** trial evaluated the efficacy and safety of autologous TIL transfer (LN-145) in 27 patients with recurrent, metastatic, or persistent CC. Patients were infused with a mean of 28 x 10^9 TIL cells and received a median of 6 doses of IL-2. The results from the immune-naïve patients cohort showed an ORR of 44%, including 1 CR and 9 PR and a DCR of 89%. The AE profile was generally consistent with the advanced stage of the disease and the expected effects of the lymphodepletion regimen and IL-2 treatment.[19]

THERAPIES TARGETING THE HUMAN EPITHELIAL GROWTH FACTOR 2 (HER2):

The HER2 protein is transmembrane and induces tyrosine kinase signalling involved in cell proliferation, differentiation, and survival. HER2 overexpression is observed in numerous solid tumours and is associated with poor prognosis, higher risk of recurrence, and limited effectiveness of chemotherapy. Activating HER2 somatic mutations have been identified in 3 to 6% of CCs.

The phase II **DESTINY-Pan02** study evaluates the efficacy of trastuzumab deruxtecan, also known as T-DXd, across seven cohorts of solid tumours (cervical, ovarian, endometrial, bladder, pancreatic, biliary tract, and other tumours). This ADC recognises HER2 and is coupled with the payload

deruxtecan, an inhibitor of topoisomerase 1. It has bystander cytotoxic action, allowing it to be effective in heterogeneous tumours, regardless of the level of HER2 expression in neighbouring cells. The authors demonstrated efficacy in the global population, with an ORR of 37.1%, an mPFS of 6.9 months, and an mOS of 13.4 months. In patients with high levels of HER2 [immunohistochemistry (IHC) 3+ score], an ORR of 75% was observed, whereas in those with an IHC2+ score, the ORR is 40%.[20] Disitamab vedotin, another HER2-targeting ADC, is currently being evaluated in the phase II **RC48-C018 trial** in 22 R/M patients CC who have received at least one line of platinum-based therapy and have an HER2+ IHC score ≥1. Disitamab vedotin demonstrated an ORR of 36.4% and a median PFS of 4.37 months. The toxicity profile of this ADC is considered tolerable, with two patients experiencing serious AEs and no treatment-related deaths reported.[21]

In the phase II **SUMMIT** multi-tumour study, the efficacy of neratinib, an irreversible tyrosine kinase pan-HER inhibitor, was evaluated. Twenty-two patients with an HER2-mutation and on progression after platinum-based therapy, were enrolled. The ORR was 18.2%, with 1 CR and 3 PR. Additionally, 45.5% of patients had stable disease for ≥16 weeks. The mDoR was 7.6 months, and the mPFS was 5.1 months.[22]

ADC TARGETING THE TROPHOBLAST CELL SURFACE ANTIGEN 2 (TROP-2):

TROP-2 is a transmembrane protein that is abnormally overexpressed on the surface of tumour cells in various types of cancer, including cervical, breast, lung, ovarian, pancreatic, and bladder cancers. This TROP-2 overexpression is associated with increased cell proliferation and metastatic dissemination. Sacituzumab govitecan and sacituzumab tirumotecan are ADCs targeting TROP-2, linked to topoisomerase inhibitors payloads. The phase I/II basket **IMMU-132-01** trial evaluated the efficacy of sacituzumab govitecan as monotherapy in 495 patients with various metastatic cancers. Among treatment-related AEs, the most common include nausea, diarrhoea, fatigue, alopecia, and neutropenia.[23] The phase II **SKB264-II-06** trial assessed the efficacy of sacituzumab tirumotecan combined with pembrolizumab in 38 patients with R/M CC. The ORR was 57.9%, with 3CR and a DoR of more than six months in 82.1% of patients. The treatment combination toxicity was considered tolerable, although grade 3 or higher AEs were observed in 47.4% of patients, leading to dose reduction in 44.7% and treatment discontinuation in one patient.

The phase III ongoing **ENGOT-Cx20** study is comparing the efficacy and safety of sacituzumab tirumotecan with the treatment of the physician's choice in the context of R/M CC. This is a randomised, open-label study that aims to recruit 686 women who have failed prior chemotherapy and immunotherapy treatments. The primary endpoint is OS; the secondary endpoints include ORR, OS, PFS, DoR, safety and quality of life .

LOCALLY-ADVANCED CERVICAL CANCER (LACC):

Cisplatin-based chemoradiotherapy followed by brachytherapy has been the recommended treatment for over twenty years. The overall treatment time should be less than 55 days. The EMBRACE studies reported three-year local and pelvic control rates of more than 90% across all LACC stages. Although conformal radiotherapy techniques have improved local control and reduced toxicity, distant metastases (30%) are still responsible for most recurrences. Despite trials testing various therapeutic strategies, nothing has been proven to improve survival.

A meta-analysis including 2150 LACC patients (from eight studies), evaluated the addition of adjuvant chemotherapy with carboplatin and paclitaxel after CRT and brachytherapy. The results showed no significant improvement in OS (HR=0.78; 95% CI 0.45-1.33; p=0.36) or PFS (HR=0.85; 95% CI 0.65-1.10; p=0.22).[24]

Very recently, two phase III clinical trials have shown encouraging results that are currently reshaping the LACC landscape. The phase III randomised, double-blind, **CALLA** study evaluated the addition of durvalumab or placebo to CRT followed by brachytherapy. The trial was conducted across fifteen countries, with 770 women aged eighteen years or older with previously untreated LACC, including FIGO 2009 stages IB2-IIB lymph node positive and stage ≥III with any lymph node status. The results showed that, after a median follow-up of 18.5 months, the mPFS was not reached in either group, with an HR of 0.84 (95% CI 0.65–1.08; p=0.17). The twelve-month PFS was 76% in the durvalumab group and 73.3% in the placebo group.[25] In conclusion, the CALLA study did not achieve the primary endpoint of PFS.

The phase III randomised **GCIC INTERLACE** trial assessed the addition of induction chemotherapy before CRT followed by brachytherapy in 500 patients with LACC recruited between 2012 and 2022. The induction chemotherapy consisted of weekly carboplatin (AUC 2) and paclitaxel (80 mg/m^2) for six weeks with CRT starting at week seven. Among the 500 patients included, 86% (n=431) had stage I

or II according to the 2008 FIGO classification, and 43% (n=215) had positive pelvic lymph nodes. Adherence to treatment was high in both groups: 85% of patients in the induction chemotherapy group received at least four cycles of cisplatin, and 98% received external beam radiotherapy and brachytherapy. The median radiation treatment time was 45 days, with 96% of patients completing radiotherapy within 56 days or less. Nearly 60% of patients in both groups received external beam radiotherapy using 3D-CRT, and approximately 40% were treated with IMRT. Regarding brachytherapy, 21% used 2D imaging , 49% 3D imaging, and 30% 3D Image-guided adaptive brachytherapy (IGABT) . After five-years of follow-up, OS was improved, with 80% of patients alive in the experimental group *versus* 72% in the control group (HR 0.60; 95% CI 0.40-0.91). Induction chemotherapy reduced the risk of recurrence or metastatic progression by 45% (HR 0.65; 95% CI 0.46-0.91), but also the distant-only relapses (7% *vs* 12%; p=0.015).[26]

The phase 3 randomised **ENGOT-Cx11/GOG-3047/KEYNOTE-A18** trial evaluated the impact on OS and PFS of adding pembrolizumab to CRT followed by brachytherapy in 1060 patients with high-risk LACC, defined as stages IB2-IIB with positive lymph nodes or stage III-IV, according to the 2014 FIGO classification. This two-arm study was conducted from June 2020 to December 2022 with 529 patients assigned to the pembrolizumab arm (200 mg, 5 cycles every three weeks, administered concomitantly with CRT, followed by 15 cycles of pembrolizumab 400 mg every six weeks) and 531 patients were assigned to the placebo + CRT arm. Baseline demographic and disease characteristics were homogeneous between the two arms. Of note, 95% had a CPS (PD-L1) score greater than 1, and 85% had positive lymph nodes. The majority of patients (89%) were treated with conformal radiation techniques (Intensity-Modulated Radiation Therapy [IMRT] or Volumetric Modulated Arc Therapy [VMAT]), with a median total equivalent dose of 87 Gy in 2 Gy fractions, delivered over a median treatment time of 52 days.

The first interim analysis (median follow-up of 17.9 months) showed that the addition of pembrolizumab improved two-year PFS (HR 0.70; 95% CI 0.55-0.89).[27] With a median follow-up of 29.9 months (second interim analysis), the 36-month OS was 82.6% in the experimental group compared to 74.8% in the placebo group (HR 0.67; 95% CI 0.50-0.90). Median OS was not reached in either group. The combination of pembrolizumab and CRT demonstrated a satisfactory safety profile, with 75% and 69% of patients experiencing grade ≥3 AEs in the pembrolizumab and placebo arms, respectively.[28] The **KEYNOTE-A18** trial presents several strengths, making it a key trial in the evaluation of ICIs for patients with LACC. First, its robust design as a randomised, double-blind, multicentric study with 1,060 patients enrolled across Asia, Australia, Europe, North America, and South America ensures methodological rigour. Second, the rapid recruitment and well-balanced assignment of participants into two groups minimises potential biases, ensuring reliable conclusions. Third, the study achieved their primary endpoints, with HR favourable for PFS and OS.

Fourth, the high-quality radiotherapy delivery being a sign of a high local control rate (although not mentioned) in both groups has allowed an assessment of the true benefits of the combination strategy. Finally, the safety profile remained largely consistent across both interim analyses and was in line with the safety profile of each individual component, thereby excluding cumulative toxic effects.[29] The FDA has approved the addition of pembrolizumab to CRT for patients with LACC at stage III-IVA according to the 2014 FIGO classification. On the 24th of October 2024, pembrolizumab received EMA approval for the same indication. However, lymph node involvement is a poor prognostic risk factor, and there is no scientific rationale for patients with stage IB2–IIB and positive lymph nodes to respond differently to treatment. Moreover, OS HR in this subgroup has improved between the first (HR= 1.62) and secondary (HR= 0.89) interim analyses, postulating further improvement with additional events. Approval based on the 2018 FIGO classification would have been more coherent for integration into our daily clinical practice.

However, questions also arise when considering how to integrate negative results from the randomised phase 3 CALLA study. Although the study design was globally similar, some differences were observed between the two studies such as sample size, choice of ICI (anti-PD-L1 *vs* anti-PD-1), outperformance of the placebo group in the CALLA trial (better PFS), and the higher-risk population in the KEYNOTE-A18 trial (84% *vs*. 74% positive lymph nodes, 22% *vs* 11% para-aortic lymph node involvement). Regarding the integration of the positive results from the INTERLACE trial, there are also several differences, leading to challenging comparisons. Indeed, 195 (77%) of the 250 patients had stage II disease according to the 2008 FIGO classification, and 146 (58%) were lymph node-negative in the INTERLACE trial, representing a lower-risk population compared to ENGOT-cx11 (44% of FIGO 2014 stages IB2–IIB and 16% lymph node-negative). Furthermore, the recruitment for the INTERLACE study spanned a long period of ten

years, during which significant advancements were made in external beam radiotherapy and brachytherapy techniques.[30] Therefore, it is crucial to consider the quality of radiotherapy administered throughout the study in order to accurately interpret the clinical outcomes. Of note, access to immunotherapy in developing countries remains a major obstacle.[29]

CONCLUSION AND KEY MESSAGES FOR CLINICAL PRACTICE

First-line treatments for primarily **metastatic/recurrent CC include** chemotherapy (platinum+ paclitaxel) with bevacizumab (if no contra-indication). When the CPS score is ≥1, pembrolizumab is added during CT and in maintenance. In the second line, chemotherapy other than the standard regimen (carboplatin/paclitaxel) or inclusion in clinical trials is suggested. If the patient has not yet received immunotherapy in the first line, cemiplimab can be used regardless of the CPS status. EMA approval and Belgian reimbursement for tisotumab vedotin is still awaited. Promising results from current and ongoing clinical trials provide considerable hope for patients, particularly through the combination of CTLA-4 and PD-1 inhibitors, the combination of different drugs with TV, the use of ADCs targeting HER2 and TROP2...

The treatment of **LACC (FIGO 2018 IB3-IVA)** involves a multidisciplinary approach including exhaustive workup (local, lymph node and distant), concurrent cisplatin-based chemoradiotherapy and brachytherapy (image-guided). This combination achieves local and pelvic control in over 90% of patients but has a distant recurrence rate of around 30%. Pembrolizumab availability for FIGO 2014 stages III-IVA represents a significant advancement in CC treatment. However, patients in FIGO 2014 stages IB2-II with positive lymph nodes are not eligible, despite the lack of a scientific rationale for such a restriction. The INTERLACE study raised concerns regarding radiotherapy quality, given the extended ten year recruitment period during which substantial advancements were made in external beam radiotherapy and brachytherapy techniques. The precise place of this induction chemotherapy regimen in our daily practice is not really clear.

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