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Authors

García, Eduardo

Ayoub, Natalie

Tewari, Krishnansu

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Review Article

Recent breakthroughs in the management of locally advanced and recurrent/metastatic cervical cancer

Eduardo García [1], **Natalie Ayoub** [2], **Krishnansu S. Tewari** [1]

[1]University California, Irvine, Medical Center, Orange, CA, USA
[2]Adventist Health White Memorial, Medical Center, Los Angeles, CA, USA

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Correspondence to
Eduardo García
University California, Irvine, 3800 W. Chapman Ave, Suite 3400, Orange, CA 92868, USA.
Email: egarci17@hs.uci.edu

ORCID iDs
Eduardo García
https://orcid.org/0000-0002-8334-1382
Natalie Ayoub
https://orcid.org/0000-0003-2931-5834
Krishnansu S. Tewari
https://orcid.org/0000-0002-8417-7000

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ABSTRACT

Cervical cancer continues to be a global threat affecting individuals in resource poor communities disproportionately. The treatment paradigm for this disease is ever evolving with recent innovations propelling oncologic outcomes to a new frontier offering survival benefits for patients struggling with locally advanced disease and metastatic/recurrent carcinoma. Immunologic checkpoint inhibitors and anti-body drug conjugates represent two novel drug classes that have demonstrable activity in this disease, particularly in the first-line and second-line treatment paradigm for recurrence. The tolerability of these novel medicines and associated durable responses underscore regulatory approval by the U.S. Food and Drug Administrations and their implementation in clinic.

Keywords: Cervical Cancer; Chemoradiation; Immune Checkpoint Inhibitor; Antibody Drug Conjugate; Immunotherapy

INTRODUCTION

Cervical cancer remains a significant global health concern, particularly in low- and middle-income countries where access to radiation therapy or immunotherapy is limited. The landscape of cervical cancer treatment is constantly evolving, yet the improvement in overall survival (OS) has not been as dynamic. For the first time in over two decades an intervention for managing locally advanced disease has led to a statistically significant and clinically meaningful improvement in OS [1]. Additionally, the incorporation of immunologic checkpoint inhibitors (ICIs) has made a significant impact in both locally advanced and recurrent/metastatic cervical carcinoma (rmCC) [2]. Finally, antibody-drug conjugates (ADCs) represent a new class of drugs that have improved OS in patients with recurrent disease who have progressed on platinum-based therapy [2-5]. In this review we will focus on the most notable clinical trials that have revolutionized the treatment paradigm for locally advanced and recurrent/metastatic cervical cancer in the last two years.

LOCALLY ADVANCED CERVICAL CANCER

Chemoradiation (CRT) is the standard of care for locally advanced cervical cancer [6-11]. To improve oncologic outcomes, the role of chemotherapy in the neoadjuvant and adjuvant setting continues to be investigated. The OUTBACK trial (ANZGOG 0902, RTOG 1174, NRG 0274) studied the use of chemotherapy in the adjuvant setting by randomizing participants to receive four cycles of adjuvant carboplatin and paclitaxel after cisplatin-based CRT versus CRT alone [12]. OS at 5 years was not significantly different between the patients assigned to adjuvant chemotherapy versus the CRT alone group (OS 72% vs. 71% [95% confidence interval (CI) −6 to +7; p=0.91]) [12]. Thus, the role of adjuvant chemotherapy in locally advanced cervical cancer did not prove to be an effective adjunct.

In contrast, the use of upfront, induction chemotherapy was examined by the INTERLACE trial (NCT 01566240) with a significant improvement in OS and progression free survival (PFS). This study randomized participants to induction chemotherapy with weekly paclitaxel 80 mg/m^2 and carboplatin area under the curve of 2 for 6 weeks followed by conventional CRT versus CRT alone. Those in the experimental arm had a 9% improvement in their PFS and an 8% improvement in OS at 5 years [1]. This marks the first time in over twenty years since an OS survival has been reported in the treatment of locally advanced cervical cancer.

Timing of chemotherapy is the key for the survival outcomes seen in these two studies. Induction chemotherapy has the benefit of reducing the cycle length by dosing chemotherapy on a weekly basis and increasing its tolerability. Additionally, it reduces tumor volume and helps control micro-metastatic disease [13,14]. This reduction in tumor volume aids with radiation dosimetry by permitting delivery of ionizing radiation to a smaller bulk of disease thus making the treatment more effective. With regards to adjuvant chemotherapy, its use on the back end is perhaps too late. At this point, resistant clonal cells that have survived the effects of CRT are no longer susceptible to additional chemotherapy and additional benefit is not observed.

Surgery has also been evaluated in this population with the use of neoadjuvant chemotherapy to shrink tumor to a size that permits for radical surgery and has previously been found to be effective [15,16]. With this knowledge in mind, EORTC-55994 (NCT 00039338) randomized participants to receiving neoadjuvant chemotherapy with a platinum-based regimen followed by radical surgery versus chemoradiotherapy with weekly cisplatin for those with Stage IB2-IIB cervical cancer [17]. The use of radiation (with chemotherapy) in the surgery arm was reserved only for individuals with proven lymph node metastases, parametrial infiltration or positive surgical margin. Radical surgery was not aided by the addition of neoadjuvant chemotherapy.

This study reaffirms the crucial role that CRT plays in the treatment of locally advanced cervical cancer with a reported OS similar to that of other published studies [10].

The addition of ICIs to CRT offers a new treatment option with an acceptable toxicity profile though survival benefit has been variable. The CALLA trial (NCT 03830866) randomized patients to receiving the programmed death-ligand 1 (PD-L1) inhibitor, durvalumab, in combination with CRT followed by a maintenance phase versus CRT alone [18]. A statistically significant improvement in PFS was not identified in patients receiving durvalumab and CRT compared to patients receiving CRT alone (65.9% vs. 62.1% at 24 months, respectively), however safety profiles were comparable between the 2 groups [18]. In contrast,

KEYNOTE-A18 (NCT 04221945), used the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab with concurrent CRT and as part of maintenance therapy in comparison with CRT alone. The primary endpoint, PFS, was reached with a PFS of 67.8% versus 57.3% at 24 months in the CRT plus pembrolizumab arm versus CRT alone, respectively (hazard ratio [HR]=0.70; 95% CI=0.55–0.89) [2]. OS has not yet matured.

These observed differences in PFS between Keynote-A18 and CALLA are likely attributed to the differences in the study populations and the ICI used. The Keynote-A18 inclusion criteria specified 2 or more involved lymph nodes 1.5 cm in short axis whereas CALLA only required 1 or more nodes 1 cm in short axis. This selection criteria suggests the possibility that the addition of ICI to CRT is most beneficial for a higher risk population and the effects are blunted in the lower risk population where CRT alone may be enough. Additionally, in the lower risk (CALLA) population, disease progression and death events will take a longer time to occur so the full effect of the intervention may not be captured in the study period. With regards to the different type of ICI used, understanding their mechanism of action is important. PD-1 is expressed on cytotoxic T lymphocytes and PD-L1 is upregulated on the surface of tumor cells [19]. Blocking the PD-L1/PD-1 pathway is known to strengthen antitumor response by preventing T cell anergy [19-21]. Perhaps since pembrolizumab targets a receptor that is intrinsic to the immune system, PD1 on T cells, its response is more reliable and robust compared to durvalumab whose effect is on PD-L1 which relies on the tumor microenvironment which can be highly variable from patient to patient (**Table 1**).

FIRST LINE THERAPY FOR RECURRENT/METASTATIC CERVICAL CANCER

In GOG-240 (NCT 00803062), the addition of antiangiogenetic therapy to conventional chemotherapy addressed a high, unmet, clinical need in the management of rmCC. Median OS had been 13.3 months in this population but was extended to 16.8 months by incorporating bevacizumab to a platinum doublet (HR=0.77; 95% CI=0.62–0.95) making this the standard of care in 2014 [22]. Running in parallel with GOG-240 was the Japan Clinical Oncology Group study (JCOG0505) that demonstrated a non-inferior outcome in patients who received carboplatin and paclitaxel versus cisplatin and paclitaxel in stage IVB, persistent or recurrent cervical cancer [23]. However, upon performing subgroup analysis it was determined that in

Table 1. Randomized trials in locally advanced cervical cancer, their intervention, and associated outcomes

Trial	Intervention	Outcome	Citation
GOG 109	Adjuvant RT vs. CDDP-based RT	Superiority of Adjuvant ChemoRT	Peters III WA, et al. J Clin Oncol 2000;18:1606-13.
GOG 85	CDDP-based vs. HU-based RT	Superiority of ChemoRT	Whitney CW, et al. J Clin Oncol 1999;17:1339-48.
GOG 120	CDDP-based vs. HU-based RT	Superiority of ChemoRT	Rose PG, et al. N Engl J Med 1999;340:1144-53.
GOG 123	CDDP-based RT vs. RT alone	Superiority of ChemoRT	Keys HM, et al. N Engl J Med 1999;340:1154-61
RTOG 90-01	CDDP+5FU-based RT vs. RT alone	Superiority of ChemoRT	Morris M, et al. N Engl J Med 1999;340:1137-43.
GOG 191	ChemoRT±Erythropoietin	TERMINATED EARLY	-
GOG 219	ChemoRT±Tirapazimine	TERMINATED EARLY	-
AIM2CERV	ChemoRT±Axalimogene Filolisbac	TERMINATED EARLY	-
OUTBACK	ChemoRT±consolidation ChemoRx	NEGATIVE (OS)	Mileshkin, LR, et al. Lancet Oncol 2023;24:468-82.
CALLA	ChemoRT±anti-PD-L1 Durvalumab	NEGATIVE (PFS)	CALLA: Monk BJ, et al. Lancet Oncol 2023;24:1334-48, LBA#1, NCT03830866.
NRG-GY006	ChemoRT±Triapine	NEGATIVE (OS)	Leath CA, et al. ASCO 2023, Abstract #5502, NCT02466971.
KEYNOTE-A18	ChemoRT±anti-PD-1 Pembrolizmab	PFS significantly improved	Lorusso D, et al. ESMO 2023, LBA#38, NCT04221945.
INTERLACE	Induction ChemoRx followed by ChemoRT	OS & PFS significantly improved	McCormack M, et al. ESMO 2023, LBA#8, NCT01566240.

CDDP, cisplatin; HU, hydroxyurea; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression free survival; RT, radiotherapy.

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patients who had not received prior cisplatin, OS was shorter with carboplatin plus paclitaxel versus cisplatin plus paclitaxel (13.0 versus 23.2 months; HR=1.571; 95% CI=1.06–2.32) [24]. This established carboplatin plus paclitaxel as the standard platinum doublet for stage IVB or recurrent cervical cancer unless the patient is cisplatin naïve [23,24].

The PD1 inhibitor, pembrolizumab, has shown efficacy and acceptable toxicity in the treatment of cervical cancer [25-28]. Thus, in a search for more effective and durable treatment options, the addition of an ICI to standard of care chemotherapy was investigated in the Keynote-826 trial. The use of pembrolizumab in patients with rmCC and a PD-L1 combined positive score (CPS) of greater than or equal to 1 with a platinum doublet with or without bevacizumab resulted in significantly longer PFS and OS [4]. The median PFS was 10.4 months in the pembrolizumab group, and 8.2 months in the placebo group (HR=0.62; 95% CI=0.5–0.77). The median OS at 24 months was 53% in the pembrolizumab arm and 41.7% in the placebo arm (95% CI=0.5–0.81; p<0.001) [4]. This was further corroborated by the final OS analysis in the PD-L1 CPS ≥1 (HR=0.60; 95% CI=0.49–0.74), all-comer (HR=0.63; 95% CI=0.52–0.77), and CPS ≥10 (HR=0.58; 95% CI=0.44–0.78) populations. Based on these results, pembrolizumab and chemotherapy with or without bevacizumab is the new standard of care for persistent, recurrent, or metastatic cervical cancer for those with CPS ≥1 [29].

A subgroup analysis examined primary endpoints of PFS and OS based on bevacizumab use, histology, type of platinum drug used, and prior CRT [3]. The findings underscore bevacizumab's integral role resulting in nearly a 40% reduction in the risk of progression or death when incorporated into the treatment regimen. While cisplatin is associated with greater toxicity compared to carboplatin, its use was associated with a more pronounced PFS benefit compared to carboplatin-based regimens. However, though a trend towards better OS in the cisplatin group was observed, the results were not statistically significant. A statistically significant OS benefit was seen in those who used carboplatin [3]. Lastly, health-related quality of life in patients who received pembrolizumab found that the addition of pembrolizumab to chemotherapy with or without bevacizumab did not negatively affect health-related quality of life [30]. This supports the value of pembrolizumab in those with rmCC.

VEGF inhibitors and ICIs are not only relevant but important in the first line treatment of rmCC. In Keynote-826 the use of bevacizumab was left at the discretion of the investigator making it difficult to form definitive conclusions about its effect on survival. BEATcc (NCT 03556839) enrolled and randomized individuals with rmCC to treatment with cisplatin/ paclitaxel and mandatory bevacizumab with or without the PDL1 inhibitor atezolizumab. The addition of atezolizumab resulted in significantly higher PFS and OS with a 38% reduction in the risk of progression and 32% reduction in the risk of death respectively [31]. Notably, overall response rate (ORR) and duration of response were higher in the experimental arm versus placebo with an ORR of 84% versus 72% and a complete response rate of 32% vs 20% respectively [31]. Toxicity profile was acceptable.

When comparing Keynote-826 to BEATcc, ORR was more pronounced in the BEATcc cohort (84%) compared to Keynote-826 (69%) [4,29,31]. Complete response was also more common in BEATcc (32%) versus Keynote-826 (26%). It is likely that these observed differences are a result of the uniform use of bevacizumab in BEATcc (100% compared to 63% in Keynote-826) and the synergistic effect that exists between platinum doublets, VEGF inhibitors and ICIs. Additional studies looking at the effect of the different ICIs are needed to assess for the optimal treatment regimen (**Table 2**).

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Table 2. Evolution of first line treatment for recurrent/metastatic cervical cancer

	First line therapy		
	GOG-204	GOG-240	Keynote-826
Treatment	CDDP+Paclitaxel	Doublet+Bevacizumab	ChemoRx+Pembrolizumab with or without Bevacizumab
Median OS	12.0 mo	17.0 mo, HR 0.71	24.4 mo, HR 0.64
ORR	29.1%	48.0%	68.1% in PD-L1+≥1%
Citaion	Monk BJ, et al. J Clin Oncol 2009;27:4649-55.	Tewari KS, et al. N Engl J Med 2014;370:734-43.	Colombo N, et al. N Engl J Med 2021;385:1856-67.

HR, hazard ratio; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1.

SECOND LINE THERAPY FOR RECURRENT CERVICAL CANCER

When managing recurrent cervical cancer, a very small number of patients can be salvaged with a pelvic exenteration. However, in the era of CRT for locally advanced disease, pelvic exenteration is often not an option because most patients that fail locally, also fail at distant sites. The EMPOWER trial (NCT 03257267) examined whether single-agent cemiplimab, a PD-1-blocking antibody, demonstrated improvement in OS in patients who had disease progression after first-line platinum-containing chemotherapy [32]. Cemiplimab was initially approved to treat skin and lung cancer but has shown potential for clinical efficacy in this patient population. Patients were randomized to receive cemiplimab as 350 mg every 3 weeks or the investigator's choice of single-agent chemotherapy [32]. The median OS was longer in the cohort that received cemiplimab versus chemotherapy (12 vs. 8.5 months) (HR=0.69; 95% CI=0.56–0.84). The survival benefit was seen regardless of histological subtype. This study is the largest randomized study to date in which a meaningful survival benefit was seen in rmCC following progression after failing first-line platinum-containing chemotherapy.

Highly targeted and unconventional anti-tumor agents named ADCs have also emerged as second-line options for patients with recurrent or metastatic cervical cancer. ADCs are composed of a monoclonal antibody that is attached to a cytotoxic drug via a chemical linker [33]. The monoclonal antibody recognizes and binds to the cancer cell's antigen which allows for precise and potent elimination of cancer cells, sparing healthy cells. A phase III randomized trial, innovaTV 301 (NCT04697628), examined the utility of the ADC, tisotumab vedotin (TV), in the treatment of recurrent or metastatic cervical cancer with disease progression on or after chemotherapy [5]. Patients were randomized to TV monotherapy or investigator's choice of topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed. Sixty-four percent and 27.5% of patients had prior bevacizumab or prior ICI therapy, respectively. Those in the TV arm had a 30% reduction in risk of death versus the chemotherapy arm (HR=0.70; 95% CI=0.54–0.89) along with a statistically significant longer median PFS and OS [5]. Thus, TV quickly became a viable option for those with rmCC that have failed first line treatment options (**Table 3**).

FUTURE DIRECTIONS

To further integrate the use of ADCs in the treatment of rmCC, investigators explored combinations of TV plus chemotherapeutics with known activity in cervical cancer. The phase 1b/2 trial, innovaTV 205 (NCT 03786081), assessed TV in doublet combinations with bevacizumab, pembrolizumab or carboplatin for treatment naïve and previously treated rmCC [34]. These doublet combinations demonstrated tolerable safety outcomes and

Table 3. Evolution of second line treatment for recurrent cervical cancer

	First line therapy			Second line therapy	
	GOG-204	GOG-240	Keynote-826	EMPOWER	Innova TV 301
Treatment	CDDP+Paclitaxel	Doublet+ Bevacizumab	ChemoRx+Pembrolizumab with or without Bevacizumab	Cemiplimab	Tisotumab Vedotin
Median OS	12.0 mo	17.0 mo, HR 0.71	24.4 mo, HR 0.64	12.0 mo, HR 0.69	11.5 mo, HR 0.70
ORR	29.1%	48.0%	68.1% in PD-L1+≥1%	18.0% in PD-L1+≥1%	17.8%
Citation	Monk BJ, et al. J Clin Oncol 2009;27:4649-55.	Tewari KS, et al. N Engl J Med 2014;370:734-43.	Colombo N, et al. N Engl J Med 2021;385:1856-67.	Tewari KS, et al. N Engl J Med 2022;386:544-55.	Vergote I, et al. ESMO 2023 LBA#9, NCT04697628.

CDDP, cisplatin; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1.

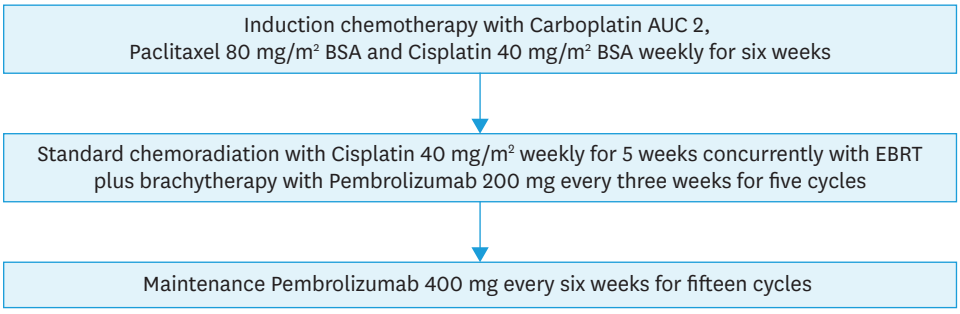

Fig. 1. Proposed treatment regimen for locally advanced cervical cancer combining treatment approaches described in the INTERLACE and Keynote-A18 trials.
AUC, area under the curve; BSA, body surface area; EBRT, external beam radiation therapy.

favorable antitumor activity with ORRs similar to the current standard of care treatments, and in some subgroups, more pronounced than previously reported treatment regimens. These encouraging results further support the assessment of triplet/quadruplet combinations of TV, carboplatin, pembrolizumab with or without bevacizumab, potentially replacing paclitaxel in the treatment of rmCC [34]. This study highlights the important role of novel therapeutics such as ADCs in redefining the treatment paradigm for rmCC to improve clinical outcomes.

Similarly, once the OS endpoint from Keynote-A18 is reached, this will have the potential to change the standard treatment approach for locally advanced cervical cancer. This could prompt the U.S. Food and Drug Administrations (FDA) to move pembrolizumab to frontline therapy for locally advanced disease, fundamentally establishing its role as a first-line therapy. This, in conjunction with the results from the INTERLACE trial, would offer a completely new approach to the treatment of locally advanced cancer (**Fig. 1**). Furthermore, this would also shape the first line treatment of rmCC leaving the combinations studied in GOG-240 and innovaTV301 or 205 as the new treatment frontier underscoring the need for new therapeutic options.

CONCLUSION

The landscape of cervical cancer treatment has seen significant advancements in recent years, particularly in the management of locally advanced, recurrent, and metastatic disease. The addition of ICIs, such as pembrolizumab, to CRT in locally advanced cervical cancer and to conventional chemotherapy in rmCC has modernized first-line treatment options [2-4,29].

Even more surprising, the addition of induction chemotherapy in the treatment of locally advanced cervical cancer, as indicated by the INTERLACE trial, has made crucial headway in improving OS [1]. These improvements provide patients, and practitioners alike, with the hope that research efforts continue to push the boundaries of cervical cancer treatment and will improve outcomes in years to come.

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