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Role of Antibody Therapy in Recurrent and Metastatic Cervical Cancer Treatment: A Review of the Literature

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Abstract: Recurrent and metastatic cervical cancer (R/M CC) presents a significant clinical challenge, with limited efficacy from conventional therapies such as chemotherapy and radiation. In recent years, antibody-based therapies have emerged as a promising frontier in oncology, offering targeted and personalized treatment strategies. This review explores the evolving role of antibody therapeutics in the management of R/M CC, focusing on immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), and targeted monoclonal antibodies. ICIs such as pembrolizumab and ipilimumab have demonstrated potential in restoring anti-tumor immunity, although their use is often complicated by immune-related adverse events. ADCs like tisotumab vedotin offer precision delivery of cytotoxic agents, minimizing systemic toxicity. Additionally, anti-angiogenic agents such as bevacizumab and novel antibody formats—including bispecific antibodies and antibody fragments—are expanding the therapeutic landscape. While these approaches show promise, variability in patient response and safety profiles underscores the need for further clinical investigation. This review highlights current advancements, challenges, and future directions in antibody-based therapies for R/M CC, emphasizing the importance of biomarker-driven strategies and combination regimens to optimize clinical outcomes.

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I. INTRODUCTION

Cancer of the cervix uteri is a common cancer-related death globally, with an estimated 342,00 deaths recorded in the year 2020 (Sung et al., 2021). Despite numerous efforts in treatment using chemotherapy and surgical interventions, a low survival rate is alarming. However, the recent strategy of antibody-based therapy in cancer is gaining popularity, and the novel antibody formats are studied extensively, including but not limited to immune checkpoint inhibitors (ICIs), antibody-drug conjugates, antibody fragments and multi-specific antibodies (Jin et al., 2022; Scott et al., 2012).

The antibody-based drugs continue to receive Food and Drug Administration (FDA) approval, with a majority in the clinical trial phase. Therefore, it is imperative to understand the mechanism of action of these therapeutic antibodies so that future strategies will create opportunities for precise cancer treatment. This essay will highlight the role of antibody-based treatment in patients with recurrent and metastatic cervical cancer (R/M CC), emphasising immune checkpoint inhibitors, antibody-drug conjugates, and targeted antibody therapy.

II. METHODS AND METHODOLOGY

This review was conducted using a structured and integrative approach to synthesize current evidence on antibody-based therapies in the treatment of recurrent and metastatic cervical cancer (R/M CC). The methodology involved the following key steps:

➢ *Literature Search Strategy*

A comprehensive literature search was performed across multiple scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search included peer-reviewed articles published in English up to September 2025. Keywords and Boolean operators used in the search included:

- *"cervical cancer" AND "antibody therapy"*
- *"immune checkpoint inhibitors" OR "PD-1" OR "CTLA-4"*
- *"antibody-drug conjugates" OR "tisotumab vedotin"*
- *"targeted therapy" AND "VEGF" OR "bevacizumab"*
- *"bispecific antibodies" OR "novel antibody formats"*

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➢ *Inclusion and Exclusion Criteria*

Studies were included if they:

- Focused on antibody-based therapies in cervical cancer, particularly in recurrent or metastatic stages.
- Reported clinical trial data, preclinical findings, or mechanistic insights.
- Were published in peer-reviewed journals.

➢ *Studies were Excluded if they:*

- Were editorials, commentaries, or lacked sufficient methodological detail.

➢ *Data Extraction and Synthesis*

Relevant data were extracted from selected studies, including:

- Type of antibody therapy (e.g., ICIs, ADCs, targeted mAbs)
- Mechanism of action and clinical outcomes (e.g., objective response rate, progression-free survival)
- Adverse effects, particularly immune-related adverse events (irAEs)
- FDA approval status and ongoing clinical trials

The extracted data were thematically organized and synthesized to provide a comprehensive overview of current therapeutic strategies, their efficacy, limitations, and future directions.

III. 4.0 FINDINGS/DISCUSSION

A. Immune Checkpoint Inhibitors (ICI)

Immune checkpoints control the balance between immune activation and self-tolerance. The immune T cells involved in adaptive immune response express proteins such as programmed cell death (PD-1) and cytotoxic T lymphocyte antigen (CLTA-4). When activated, these proteins bind to their ligand PDL-1 and molecules such as CD80, CD28 and B7 present on antigen-presenting cells' surface to suppress the immune response (Alsaab et al., 2017). However, the cancer cells exploit these regulatory pathways by overexpressing checkpoint proteins such as PDL-1, CD28, and CD80, initiating decreased anti-tumour response. A study by Karpathiou et al. (2020) confirmed that patients with advanced CC expressed CTLA-4 and PDL-1 in 61.5% and 26.9%, respectively. However, the antibody blockades to these checkpoint proteins prevented tumour cell proliferation (Grau-Bejar et al., 2023; Karpathiou et al., 2020; Xie et al., 2022).

Moreover, pembrolizumab is an FDA-approved drug used for the treatment of patients with advanced CC. The KEYNOTE-158 study determined the efficacy of pembrolizumab in 98 patients, indicating promising results where twelve out of eighty- four PDL-1 positive patients showed partial or complete response to the drug. In addition, ipilimumab, an anti-CTLA-4 drug, blocks the interaction between CTLA-4 and B7-CD28 receptors on CC cells, upregulating the immune response (Azarov et al., 2022; Sobhani et al., 2021). However, in the early phase of clinical trials, ipilimumab monotherapy showed no promising results in patients with CC, thus warrants further investigation to enhance its effectiveness (Lheureux et al., 2018).

➢ *Enhancing the Efficacy of ICIs*

Combination therapy with other ICIs and chemotherapy has effectively treated cancers (Xie et al., 2022). However, various clinical trials have reported that combination therapy increases the risk of immune-related adverse events (irAEs). For instance, Oaknin et al. (2022) identified that combination therapy with ipilimumab and nivolumab drugs improved the patient objective response rate (ORR) but increased irAEs. irAEs is an unintended immune response due to the therapy, affecting various body tissues, usually confined to the skin, gastrointestinal tract, and endocrine disorders (Urwyler et al., 2020). Still, the mechanism of irAEs is not fully understood and is likely associated with overactivation of the immune response, off-target effects or loss of self-tolerance (Urwyler et al., 2020).

In contrast, studies have suggested that combination therapy provided better clinical outcomes with reduced risk of immune-related adverse events (Monk et al., 2023; Tewari et al., 2014; Xie et al., 2022). These rather contradictory results may be because antibody therapy response varies between individuals and tumour type. However, identifying the specific immune targets and evaluating the safety profiles of therapy will minimise irAEs (O'Malley David & Calo, 2021; Ventola, 2017). Therefore, further research is warranted to understand the mechanism of irAEs.

Table 1 Summary of the Current Immune Checkpoint Inhibitors in Recurrent or Metastatic Cervical Cancer

Antibody Format/ Specific target	Drug	Approved/phase of trial /	Findings	Author/Year
Immune Checkpoint Inhibitor Anti-PD-1 (humanised monoclonal Ab)	Pembrolizumab	**FDA Approved** Phase II KEYNOTE 158 KEYNOTE 826 Phase III trial.	Monotherapy with pembrolizumab showed reasonable anti-tumour effects. - ORR- 12.2% (CI-95% -6.5% -20.4%) - irAEs in 65.3% of patients. Pembrolizumab, in combination with chemotherapy, showed better results than monotherapy. - ORR 68% (95% CI- 62%-74%) Limitation: Individual therapies were discontinued in 15% of patients in KEYNOTE 826	(Chung et al., 2019) (Monk et al., 2023)

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Immune Checkpoint Inhibitor **Anti-PD-1**	Nivolumab	Phase I/II CheckMate 358 Trial (n= 19) Phase II NCT02257528 (n= 26)	Both studies showed limited anti-tumour activity; therefore, a further trial using combination therapy is warranted. The small sample size was a limitation in both studies.	(Naumann et al., 2019) (Santin et al., 2020)
Immune Checkpoint Inhibitor **Anti-PD-1**	Balstilimab-	Phase II Phase III BRAVA trial NCT04943627)	Treatment response was noted in both PDL-1 positive and negative participants. - ORR- 15%. (95% CI- 10%-21%) Phase III trial as a monotherapy was discontinued- more emphasis was put on pembrolizumab	(O'Malley et al., 2021) (Grau-Bejar et al., 2023)
Immune Checkpoint Inhibitor	Cemiplimab- Anti- PD-1	Phase III trial	The overall survival was higher (12 months) in the Cemiplimab group than in the chemotherapy group (8.5 months)	Tewari et al. (2022)
Combination Therapy Immune Checkpoint Inhibitor Anti - CTLA-4	Ipilimumab- Anti - CTLA-4 -Combined Ipilimumab and Nivolumab	Phase I/II (n=40) Phase I/II NCT02488759	When used as a monotherapy, ipilimumab did not show a promising result. Median ORR of 20% was not met. Patients in the combined therapy demonstrated more durable tumour regression than those in monotherapy.	(Lheureux et al., 2018) (Oaknin et al., 2022)

Note:

- ***ORR- Objective response rate. To determine the treatment efficacy at 95% Confidence interval***
- ***irAEs- Immune-related adverse events. To assess the safety of the drug***
- ***OS- overall survival***
- ***n- Number of participants***

B. Antibody-Drug Conjugates (ADCs)

The novel approach of ADCs and targeted therapy is moving towards personalised treatment and ensuring minimum irAEs with an augmented patient response (Karpel et al., 2023). ADCs combine highly selective monoclonal antibodies (mAbs) with an anti-cancer drug via a linker protein. The drug is delivered directly to the tumour-associated antigen site. While the target antigen is expressed highly on the tumour cells, minimal damage to the healthy tissues reduces side effects (Karpel et al., 2023). For example, the protein tissue factor (TF) is present up to 95% times more in cervical cancer tissues than in normal cells (Zhao et al., 2018). Tisotumab vedotin (TV) is an anti-tissue factor mAb, linked to an anti-cancer microtubule targeting agent, monomethyl auristatin (MMAE). The binding of the TV to TF forms a complex internalised by the tumour cells. After internalisation, the MMAE targets specifically to the tumour cells and disrupt the microtubule network preventing damage to the normal cells (Karpel et al., 2023; Kim & Al-Salama, 2022).

C. Antibody Targeted Therapy.

Induced angiogenesis is considered a hallmark of cancer, facilitated by the vascular endothelial factors (VEGF) and tyrosine kinases (TK) signalling pathways. Therefore, targeting specific intracellular pathway receptors and proteins has been a potential treatment for many cancers, including CC (Jin et al., 2022). According to Tomao et al. (2022), the human papillomavirus protein E6 is responsible for p53 degradation and overexpression of the VEGF receptor, encouraging angiogenesis activation. Bevacizumab is an FDA-approved humanised mAb that targets and binds to the VEGF, disrupting the signalling and angiogenesis.

In addition, targeting VEGF receptors using cetuximab has shown positive results in treating bowel, head, and neck cancers (Muraro et al., 2021; Xie et al., 2020). However, (Hertlein et al. 2011) found no positive effects of cetuximab in a follow-up study including five patients with CC. The authors highlighted that further research with cetuximab in treating patients with R/M CC is warranted, considering that patients respond differently to antibody-based therapies.

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Table 2 Summary of Current Antibody-Drug Conjugates and Targeted Therapy in Recurrent or Metastatic Cervical Cancer Treatment

Antibody Format	Therapeutic drug/specific target	Approved/phase of trial	Findings	Author/Year
Antibody-Drug Conjugates -Tissue factor	Tisotumab vedotin- Tistumab vedotin + Bevacizumab + Pembrolizumab +/- chemotherapy	**Accelerated FDA approval** in 2021 after phase II trial (Innova TV 204) Phase Ib/II NCT03786081	High Efficacy- ORR 24% (CI:95%-16%-33%) TRAE in 92% of patients but very mild and manageable. An encouraging anti-tumour effect was noted when Tistumab was used as a combination therapy.	(Coleman et al., 2021) (Vergote et al., 2023)
VEGF/VEGFR targeted therapy **- Humanised Anti-VEFG monoclonal antibody**	Bevacizumab-	**FDA approval** in 2014 after phase III trial Phase III randomised trial	The use of bevacizumab in combination with chemotherapy in metastatic/recurrent CC is highly recommended. The overall survival was significant in patients with chemotherapy combined with bevacizumab; however, the toxicity level needs to be evaluated.	(Tewari et al., 2014) (Tewari et al., 2017)
IgG1 isotype Anti-EGFR monoclonal antibody	Cetuximab	Phase II trial (n=5)	The addition of cetuximab to chemotherapy did not show a positive outcome. The small sample size was a limitation. Proceeding with phase III trials at this stage is not recommended.	(Hertlein et al., 2011)
Combination Therapy scFV-Anti PDL-1 + Anti PD-1 +/- Anti-VEGF	Atezolizumab + Prolgolimab +/- Bevacizumab	Phase II trial NCT03912415 Phase III trial BEATcc NCT03556839	Phase II trial of Prloglimab in combination with bevacizumab showed promising efficacy. No Results Published for Phase III	(Fogt et al., 2023) (Grau-Bejar et al., 2023)
Bi-sepcific tetravalent antibody -Anti-PD-1/CTLA-4	Cadonilimab	**NMPA approved** Phase I/Ib- study QL1706	Showed an exceptional response rate in CC cohort n= 55 (ORR- 27.3%) Limitation- single ethnic groups were studied, thus warrants further investigation.	Zhao et al. (2023)
Bifunctional Fusion protein -Anti- TGF β - and PDL-1	Biintrafusp alfa	Phase I/II NCT02517398/ NCT03427411	Showed promising results in HPV-related cancers (cervical, anal, head and neck) ORR- 30.5% (95% CI, 19.2-43.9)	(Strauss et al., 2020)

- ***ORR- Objective response rate. To determine the treatment efficacy at 95% Confidence interval***
- ***n- Number of participants***

D. Novel Antibody Therapy Approaches in Cervical Cancer Treatment.

Advancement in recombinant DNA technology has paved the way to developing novel therapeutic antibody formats. For example, using phage display and transgenic animal technology enabled the designing of antibodies or antibody fragments directed to specific biomarkers on cancer cells. Atezolizumab is a single chain variable (scFV) currently in the phase III trials for R/M CC treatment, showing antigen specificity similar to a full-length antibody. The scFV lacks an Fc portion on the antibody, which prevents off-target binding, minimising irAEs (Lu et al., 2022; Sun et al., 2023).

In addition, bi-specific antibodies are engineered to bind two different molecules simultaneously. For example, one arm binds to the TGF β on CD3 T cells, and the other attaches to the PDL-1 tumour cells, causing T cell activation and destruction of tumour cells (Strauss et al., 2020). These unique characteristics of bi-specific antibodies increase the efficacy of antibody-based therapeutic drugs. Cadonilimab is an approved bispecific antibody that simultaneously targets PD-1 and CTLA 4 receptors, allowing a 10-fold increased binding avidity in patients with R/M CC (Pang et al., 2023; Zhao et al., 2023). However, Ordóñez-Reyes et al. (2022) highlighted that such a therapeutic approach needs evaluation regarding efficacy and safety. Nevertheless, the promising evidence of these pharmacological drugs represents groundbreaking alternatives in cervical cancer treatment.

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IV. CONCLUSION

To sum up, antibody therapy in cancer treatment is on the horizon. However, the new therapeutic target for gynaecological cancer is showing slow progress, with the majority of the drugs still in the clinical trial phase. Pembrolizumab, bevacizumab, tisotumab vedotin and cadonilimab represent four approved therapies for patients with R/M CC. However, preliminary studies and clinical trial evidence suggest potential novel treatment options. Using robust techniques and designing target-specific antibodies using phage display techniques, second-generation sequencing, and integrated bioinformatics will provide an understanding of the mechanism of tumour cells, creating an opportunity for improved outcomes. However, the issues of drug efficacy, safety, accessibility, and affordability are substantial challenges that require careful consideration to gain success in antibody-based therapy of cervical malignancies.

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