Role of Immunotherapy in the Management of Advanced Cervical Cancer

Amna sharif[1] and Rabab Mahmoud[2]
[1] *Oncology Registrar*
[2] *Obstetrics& Gynaecology Resident*

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Abstract
Despite continued preventive efforts with progressive human papilloma virus vaccination programs in affluent nations, cervical cancer remains fourth most frequent malignancy in women worldwide. Immunotherapy helps the body's immune system become more capable of identifying & eliminating cancer cells. To improve immune response, immunotherapy frequently targets immune system proteins. They differ from chemotherapy in that their adverse impacts can occasionally be less severe. Given viral etiology of cervical cancer, immune checkpoint inhibitors are viewed as desirable option, even though majority of studied cases do not benefit from their treatment. This review summarized state-of-the-art regarding immune checkpoint blockade's use in treating cervical cancer & discussed difficulties encountered in its clinical application, including use of biomarker-driven ICI, potential mechanisms of resistance, methods to combat like resistance, & additional immunotherapy options beyond ICI.
Keywords: cervical cancer, immunotherapy, immune checkpoint inhibitor

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Introduction

Despite continued preventive efforts with progressive human papilloma virus vaccination programs in affluent nations, cervical cancer remains4th most frequent malignancy in women worldwide. most of early-stage cervical cancer cases have been treated with decisive chemoradiotherapy; yet, 5 years after receiving this curative intent therapy, relapse rates are still above twenty percent. Beyond 1st-line chemotherapy plus bevacizumab, there are few alternative choices for treating metastatic & recurring cervical cancer; 2nd-line single-agent chemotherapy has response rates in range of fifteen to twenty percent & median survival periods are still under 2 years **(1)**.

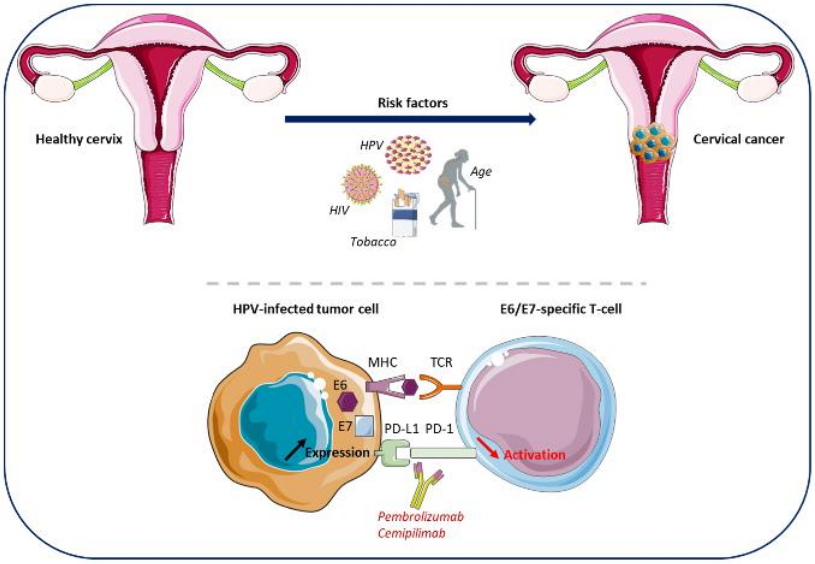

Figure (1): Role of Immunotherapy in Management of Advanced Cervical Cancer **(2)**

Immunomodulation of Cervical Cancer

Production of E6 & E7proteins, which inhibit important tumour suppressor genes p53 & Rb, occurs because of HPV infection with carcinogenic strains. These proteins can aid in capability of infected cells to avoid being recognized & eliminated by the immune system in addition to oncogenesis. For instance, E7is well known to be 'tolerogenic'; it will be ingested by local dendritic cells & presented to immune system in manner like non-inflammatory self-antigen, resulting in tolerance rather than adaptive immune response. Malignant & precancerous cells can potentially alter cytokine balance in tumour microenvironment, suppressing immune system. Last but not least, as shown in Figure 2, most cervical tumours express programed cell death ligand1, that aids in suppressing host immune response **(3)**.

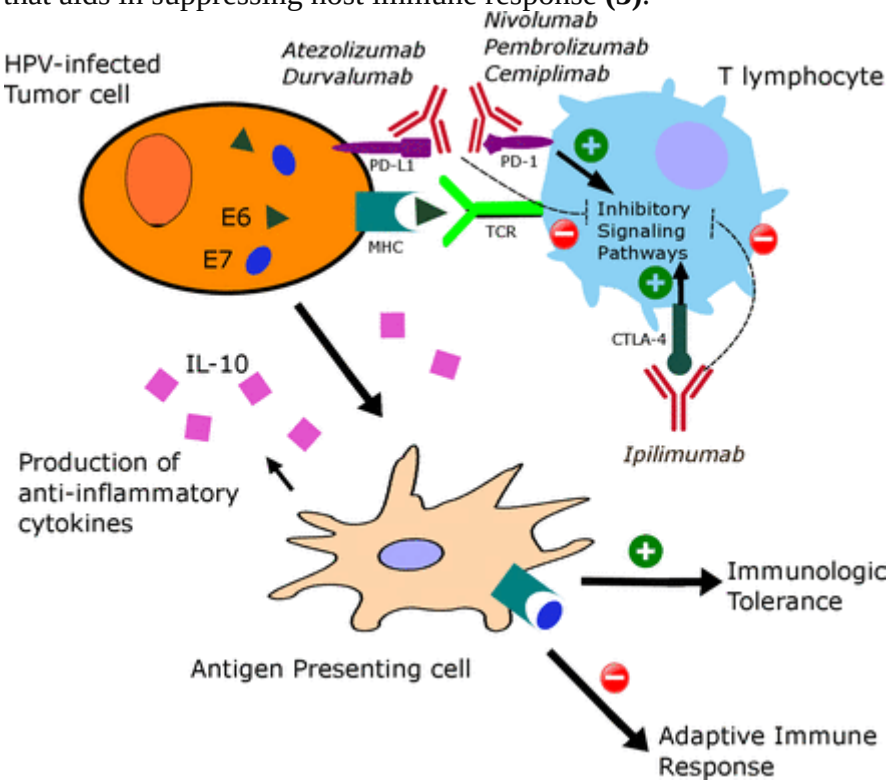

Figure (2): Immune escape mechanisms in cervical cancer. Through a variety of processes, such as development of immunological tolerance, modifications to tumour microenvironment, & expression of PD-L1, cervical cancer cells can evade immune monitoring. PD-1 & CTLA-4 axes have been targets of checkpoint inhibitors, & their mechanisms are displayed. Human papillomavirus, cytotoxic T-cell lymphocyte-associated antigen-4, interleukin-10, major histocompatibility comples, programmed cell death protein (PD-1) (PD-L1), & T-cell receptor **(4)**

These pathways not only contribute significantly to cervical cancer formation but also likely affect how well patient responds to treatment. Immune system activation is another side effect of treatment, and alterations in T-cell subsets within tumour can already be seen one week after start of chemoradiation. Results can be improved by further boosting immune response with checkpoint blockade immunotherapy targeting PD-1or cytotoxic T-lymphocyte antigen-4pathways, or other immune activators **(4)**.

Role of ICIs in locally advanced cervical cancer setting

About fifty percent of newly diagnosed instances of cervical cancer (FIGO2018 stagesIB3 & IIA2-IVA) have locally advanced cervical cancer. conventional treatment for LACC continues to be weekly cisplatin concomitant with external beam radiotherapy (average dose of45 Gy), followed by brachytherapy, & hasn't changed in past 20 years **(5)**.

Role of adjuvant treatment is investigated in numerous significant trials in response to intriguing findings presented by Peters et al. in GOG109 research. In phase III randomized trial, Duenas-González et al. evaluated double strategy, adding gemcitabine to cisplatin as concomitant with radiation followed by gemcitabine monotherapy as maintenance, in LACC studied cases with FIGO 1997stage IIB to IVA. Although the experiment had been successful, it is still challenging to determine if survival advantage had been caused by concurrent administration of platinum-doublet with radiotherapy, adjuvant chemotherapy, or both. This characteristic, together with higher toxicity, has contributed to the scientific community's resistance to it **(2)**.

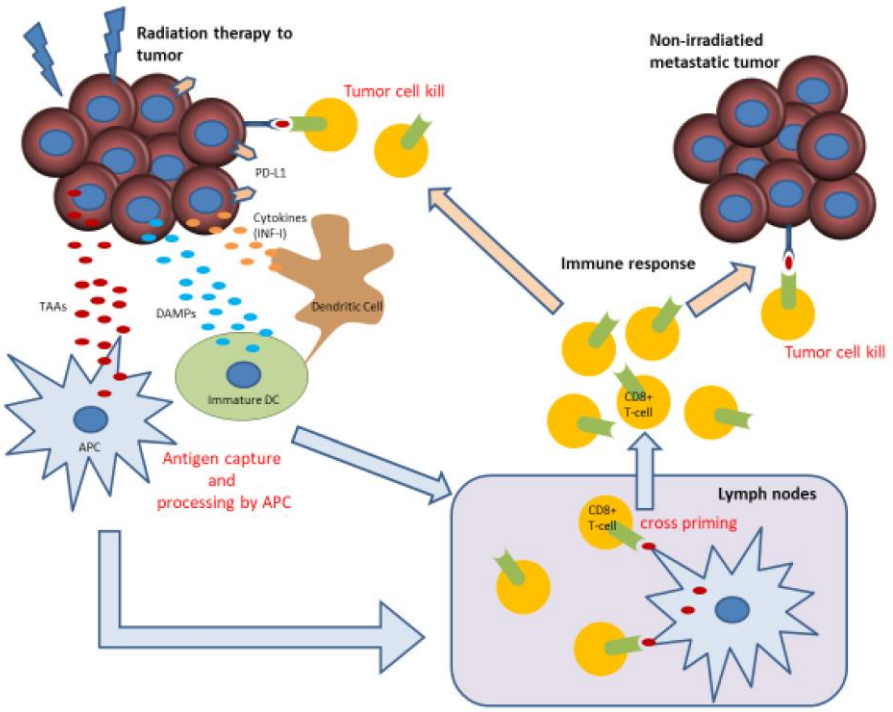

Figure (3): Role of Immunotherapy in Management of Advanced Cervical Cancer **(6)**

Based on strong biological justification & rapidly mounting evidence supporting its use in both advanced/recurrent & frontline settings, immunotherapy has started to gain prominence as viable treatment to enhance clinical results of LACC studied cases. In fact, combining immunotherapy with concurrent CRT appears to be 1 of best options since it makes use of more advantageous immunological tumour microenvironment brought on by radiation & cytotoxic drugs. Additionally, cisplatin exhibits immunomodulatory qualities because it raises MHC class I expression, encourages proliferation & recruitment of effector cells, & inhibits immunosuppressive elements in tumour microenvironment. New methods of combining cisplatin with immunotherapy, including ICIs, can thus favor synergistic impact **(7)**.

Novel immunotherapy approaches in cervical cancer

In context of advanced cervical cancer, various immunotherapy strategies are being researched in addition to ICIs. most promising methods include cell-based treatment & cancer therapeutic vaccines. neutralizing antibody response is intended to be produced by prophylactic HPV vaccinations using capsid proteins from a variety of high-risk HPV strains to prevent further HPV infection **(8)**.

target antigen is expressed by genetically modified live, attenuated, or inactive viral or bacterial vectors in vector-based vaccinations. Their primary interest in vaccine technology stems from its simplicity, scalability, & capacity to manufacture significant quantities of antigens in vivo, inducing potent immune response. unfortunately, FDA's investigation into manufacturing practices caused trial to be delayed, & it had been finally discontinued in2019 based on funding company priorities & before full accrual had been attained **(9).**

Introduction & biological rationale for immunotherapy in cervical cancer

Importantly, cervical cancer positions 2nd in both incidence & mortality between women in low- to middle-income countries, where over seventy percent of fatalities from the disease occur. In addition to high frequency of human papillomavirus infection, striking geographic variance in cervical cancer may be attributed to unequal access to organized screening programs & preventative vaccination. Consequently, cervical cancer has been widely regarded as condition that may be prevented **(10)**.

bulk of cervical cancer cases are caused by HPVs, withHPV-16 & HPV-18 accounting for about seventy percent of cases. It is generally known how cervical cancer develops naturally. In more detail, keratinocytes in basal layers of stratified epithelia are infected by HPV, & integration of HPV genome into host chromosome has been crucial step in development of HPV-induced cancer. It is critical to stress that, through a process known as "immunoediting," dynamics & make-up of immune milieu have significant impact on carcinogenesis **(11)**.

Comparing cervical cancer to HPV-negative malignancies, cervical cancer exhibits significantly increased lymphocyte infiltration as virally driven tumour. Additionally, it is demonstrated that individuals with cervical cancer who have higher levels of CD8+ tumor-infiltrating lymphocytes had higher survival rates & better responses to standard therapy. It's interesting to note that tumour growth can continue even in presence of this T-cell infiltration since cancer cells infected with HPV have capacity to modify immune milieu to produce pro-tumorigenic state of immune evasion & suppression through a variety of mechanisms, including It is demonstrated that E7 oncoprotein inhibits STING, hence downregulating cGAS-STING pathway,

crucial innate response route to viral DNA that stimulates production of type I IFN genes **(12)**.

Immune Response to Cancer & Immune Checkpoint Inhibition: Rationale for Immunotherapy in Cervical Cancer

steps necessary for immune response to emerge against tumours are referred to as "cancer immunity cycle." Tumor-associated antigens are released because of cell death & are then phagocytosed, processed, & presented by antigen-presenting cells (APCs) using MHC. These non-self-antigens cause naive T-cell activation, which causes them to pass through & enter tumour before triggering CD8+ T-cells & natural killer cells to cause cytotoxic cell death. most researched immune checkpoints are cytotoxic T lymphocyte antigen4 & programmed death1, which act as negative regulators of this cycle. These inhibitory mechanisms are used by tumours to elude host immune monitoring **(13)**.

As immune checkpoint inhibitors, antibodies directed against targets like PD-1, its ligand programmed death ligand1, & CTLA-4aim to disrupt these pathways to promote immunological response from host against tumour. use of ICI has significantly changed landscape of treatment for numerous solid organ malignancies, such as lung, renal cell, melanoma, & colorectal cancers. Insights into possible therapeutic efficacy of ICI in this tumour may be gained by understanding role of HPV in etiology of cervical cancer. High-risk HPV (sixteen or eighteen) are linked to bulk of cervical cancer cases; these HPVs encode E5, E6, & E7proteins, which promote malignant transformation. These proteins have been connected to PD1/PDL1 pathway, which increases production of PD-L1 and may promote immune evasion **(14)**.

ICI Monotherapy & Combination in Cervical Cancer

Use of ICI monotherapy & combination in advanced cervical cancer has been examined in several studies. These involve monoclonal antibodies against PD1 (pembrolizumab, nivolumab, & cemiplimab), PDL1 (durvalumab), & CTLA4 (ipilimumab, tremelimumab) **(15)**.

Pembrolizumab

Pembrolizumab's overall response rate inKEYNOTE-028, single-arm research in studied cases with recurrent squamous cell carcinoma of cervix, was seventeen percent in twenty-four PDL1 positive studied cases. PDL1 was found to be response biomarker in KEYNOTE-158, basket research that included cohort of studied cases with advanced cervical cancer. Regardless of PDL1 status, studied cases (n = ninety-eight) had been enrolled, & ninety-four percent of them had squamous histology. They had been given pembrolizumab 200 mg three times per week for up to two years. overall ORR had been 12.2percent, however, only PDL1positive subgroup (83.7percent of study population) showed responses. PDL1positivity had been identified by combined positive score of ≥one based on 22C3assay. PDL1 positive group's ORR had been 14.6 percent, & median duration of response had not been attained. Pembrolizumab had been therefore approved by US Food & Drug Administration in2018 for treatment of PDL1-positive (CPS ≥ 1) cervical cancer **(16)**.

Nivolumab

In preliminary analysis of Checkmate-358, research of studied cases with advanced cervical cancer and less than two lines of prior therapy, anti-PD1 antibody nivolumab had optimistic OR Rof 26.3percent. Even though testing had not been required for enrollment, studied cases with known HPV-negative tumours had been excluded. Responses had been detected in bothPD-L1 positive & negative tumours when PD-L1

status had been determined using 28-8 pharm Dx test. Nivolumab had lower ORR of four percent in smaller research encompassing twenty-six studied cases with advanced cervical SCC who had already received treatment, while another four studied cases had unconfirmed response. However, median overall survival of 14.3months had been encouraging & can highlight challenge in determining therapeutic success when immunotherapy is being used **(17)**.

Other Anti-PD-1Agents

Cemiplimab and physician's choice chemotherapy (pemetrexed, irinotecan, topotecan, gemcitabine, vinorelbine), regardless of PD-L1 status, were compared in EMPOWER-Cervical-1 phase III research for studied cases with advanced cervical cancer after ≥1lines of therapy and who progressed within six months of platinum therapy. With median OS of12 versus 8.5 months, respectively, primary endpoint ofOS demonstrated significant advantage for cemiplimab over chemotherapy. This advantage was evident in both SCC & non-SCC histological groups. With an expected median DOR of 16.4months, response rates had been encouraging at 16.4percent. AGEN2034, monoclonal anti-PD1 antibody, demonstrated therapeutic activity in phaseI investigations of studied cases with breast, ovarian, & cervical cancer. PhaseII research in studied cases with recurrent advanced disease is currently ongoing **(18)**.

Anti-CTLA-4 Therapy

In phaseII research ofSCC & adenocarcinoma of cervix after prior exposure to platinum chemotherapy, monotherapy with anti-CTLA4 drug ipilimumab had minimal effectiveness. One studied case out of thirty-four evaluable studied cases had partial response **(19)**.

Anti-PD-1/PD-L1 & AntiCTLA-4Combinations

Despite encouraging but limited effects with single agent ICI, substantial rates of primary resistance were seen in research mentioned above. idea of immunological escape in both priming & effector phases of immune response is 1 potential mechanism behind such resistance. In addition to antigen presentation, T-cell priming in lymph nodes also necessitates interaction of B7 family molecules with CD-28 produced on T-cells. High affinity CTLA-4 binding to B7 blocks costimulatory signal. Immune activity at tumour level triggers release of interferon, which then increases PDL1 expression, limiting T-cell response. Therefore, blocking both the PD1/PDL1 & CTLA-4 checkpoints at the same time looks like sensible strategy to try & boost immune response & therapeutic effectiveness. like combination (anti-PD1/PDL1 & anti-CTLA4) is approved in 1st line advanced setting for mesothelioma, renal cell carcinoma, melanoma, & non-small cell lung cancer after it was demonstrated to be effective in various tumour groups. Advanced cervical cancer is studied using this strategy **(12)**.

Nivolumab 3mg/kg 2weekly with ipilimumab 1mg/kg 6weekly (combination A) & nivolumab 1mg/kg with ipilimumab 3mg/kg 3weekly for 4doses followed by nivolumab maintenance 2weekly (combination B) are dose combinations that Checkmate-358 reported results for. With ORRs of 41.3 & 26.7 percent, respectively, combination B had greater response rate than combination A. studied cases withPD-L1negative tumours (2/14, 14.3percent combination A; 4/11, 36.4percent

combinationB) experienced responses. With rates of83.5 & 78 percent for combinations A & B, respectively, survival at twelve months had been optimistic in both arms for studied cases who had not previously received treatment **(20)**.

Role for ICI in Small Cell Neuroendocrine Carcinoma of Cervix

Neuroendocrine carcinoma of cervix has been rare histology that accounts for 1.4 percent of all cervical malignancies. Small cell NECC is most prevalent form, & it has aggressive course & bad prognosis. Yet, case reports suggest potential role, with nivolumab producing radiologic complete response in1 studied case with metastatic PDL1negative small cell NECC, casting doubt on efficacy of ICI in absence of big research. High HPV positive rates in analysis point to viral role in etiology of NECC, like cervical SCC. This viral pathogenic component justifies additional research into ICI treatment use in this histological subgroup **(21)**.

Challenges ofICI Therapy inCervical Carcinoma

Findings of trials mentioned above show that although ICI therapy may be beneficial for studied cases with cervical cancer, responses are rare. Yet, additional confirming results from randomized studies are still necessary. Early reports of combined ICI seem to indicate better response rates. Finding new biomarkers for response and thinking about strategies to overcome immunotherapy resistance is essential for increasing ICI efficacy. Below is a discussion of current biomarkers & chosen methods for overcoming such resistance, such as combining ICI with radiation, chemotherapy, & anti-angiogenics **(22)**.

Role of Biomarkers

PDL1has not been expressed in healthy cervical tissue, but it has been present in malignant & pre-malignant lesions. Cervical intraepithelial neoplasia & cervical SCC have high PDL1 expression rates of ninety-five percent & eighty percent, respectively. However, cervical SCC has low PDL1expression rate of 24.9percent. Due in part to use of several assays & cut-offs for positive, reported expression levels vary. In 1 research, PDL1 tumour cell positivity was found in fourteen percent of cervical adenocarcinoma samples compared to fifty-four percent of SCC, indicating that cervical adenocarcinoma exhibits lower rates of expression than SCC. Based on findings of KEYNOTE-158, which was previously mentioned, PDL1 isFDA-approved biomarker for cervical cancer, making patients with positive tumours who advance after receiving 1st-line treatment eligible for pembrolizumab monotherapy. Using IHC 22C3 pharmDx test, PDL1 positivity had been assessed by CPS $\geq$ one, where CPS is total number ofPDL1-stained cells divided by total number of viable tumour cells, multiplied by 100 **(23)**.

Thus, it would appear appropriate to use CPS positivity to determine malignancies that can benefit from PD1/PDL1 blocking. Yet, other trials, notably Checkmate-358, which used IHC28-8 pharmDx test, have observed responses in PDL1 negative tumours. PDL1 is poor choice since reports of copy number analysis suggest that rate of amplification is modest, occurring in just 0.7 percent of cohort of different solid tumour types & and two percent of cases of cervical SCC. PDL1 mRNA may be detected using RNAish, and fifty-six percent of cancer cells were found to express it **(24)**.

TMB, indicator for tumour neoantigen load & possible immunogenicity, is determined by counting the number of non-synonymous somatic mutations per

megabase. research of 284cervical SCC specimens revealed median TMB of5.4 mutations/mb, with TMB > twenty mutations/mb seen in 6.7percent of cases. Pembrolizumab had been approved for use in studied cases with highTMB (≥ten mutations/mb) based on research in lung cancer that demonstrated enhanced efficacy of ICI with greater TMB & and biomarker analyses of basket of KEYNOTE158. In this investigation, sixteen studied cases with cervical SCC and ORR of thirty-one percent were included. While this is encouraging & gives studied cases another way to get ICI, response rates are still quite low **(25)**.

Resistance Mechanisms & Treatment Strategies

mechanisms underlying resistance to ICI treatment in cervical cancer have been poorly understood. Work in lung cancer & melanoma has started to uncover important host & and tumour variables in such immunotherapy resistance **(26)**.

Immunosuppressive Microenvironment

immunosuppressive, "cold," & non-inflamed tumour may be produced through microenvironment dysregulation. In research involving Forty individuals, pre-malignant lesions that wereCIN-1 to CIN-3moved from Th1to immunosuppressive Th2 state. On the other hand, 'hot' inflammatory tumours are linked to T cell infiltration and tumour infiltrating lymphocytes, which are connected to increased survival. In addition to having a significant number of TILs, intra-epithelial M1 macrophages were linked to increased survival, according to analysis of surgical specimens from eighty-six studied cases with FIGO I-II cervical SCC **(27)**.

When compared to lymph nodes free of cancer, lymph nodes draining cervical carcinoma showed immunosuppressive milieu with larger proportion of CD4 & CD8positive Tregs & elevated expression of the coinhibitory molecules PDL1 & B7-H4. While IFN release had been high in cells from tumour-free lymph nodes, in vitro research revealed immunosuppressive cytokine profile in tumor-involved lymph nodes with greater levels ofIL6, IL10, & TNF released under stimulation. In phase 1 DURVIT research, primary secondary objectives examine impact of durvalumab on microenvironment of tumour & draining lymph nodes in studied cases with cervical cancer who are scheduled for hysterectomy & lymph node dissection **(28)**.

In prospective investigation of cervical cancer cases who had not yet received treatment, mutations in the PIK3CA gene that are linked to immunosuppressive microenvironment had been found in forty percent of studied cases. PIK3CA mutations had considerably shorter PFS when they had been combined with loss of function mutations in epigenetic pathway regulators (thirty-four percent of cases). In mouse models of PTEN null melanoma, PI3K inhibition & anti-PD1 therapy combined to achieve improved tumour control over either agent alone. Tumours with PTEN loss indicated an inferior reduction in tumour size compared to those with retained expression **(29)**.

Role ofVEGF Signalling

In many cancers, vascular endothelial growth factor has been linked to immunosuppressive microenvironment & decreased lymphocyte inflow. Dendritic cell maturation is observed to be inhibited, while tumor-associated macrophages & inhibitory Treg levels are observed to increase. Furthermore, in vitro, VEGF-Aseems to boost expression of PD-1on CD-8 T cells, amplifying immunosuppressive signals. 'normalization' of tumour vasculature & CD8+ T cell response is linked to VEGF signaling suppression, making combination of ICI & VEGF inhibition appealing approach to test in clinical trials. In NSCLC, hepatocellular carcinoma, & renal cell carcinoma, such combination methods have improved

survival rates. Due to upregulation of VEGF-A & VEGF receptor1 in cases of recurrent disease, anti-VEGF treatment has been appealing in cervical cancer, & addition of bevacizumab (anti-VEGF-A) to chemotherapy has been presently 1st line standard of care for recurrent/metastatic cervical cancer due to reported survival benefit over chemotherapy alone **(5)**.

In studied cases with previously treated advanced cervical cancer, CLAP research, single arm phase II trial of anti-PD1camrelizumab combined with apatinib, demonstrated remarkable OR Rof 55.6 percent. response was observed in both PDL1 positive & negative instances, with thirty-three percent of studied cases being PDL1 negative or unknown. Ongoing phase III trials will provide information about these combinations' use in 1st-line settings. In 1st-line BEATcc research, chemotherapy is combined with bevacizumab with or without atezolizumab, whereas 1st-line KEYNOTE 826 research evaluates addition of pembrolizumab or placebo to combination of chemotherapy with or without bevacizumab (investigators' option) **(5)**.

Tumour Antigen Presentation

Multiple cancer types exhibit disruption of antigen presentation pathway as immune evasion and ICI resistance mechanism. The functioning of MHC is impacted by 2-microglobulin mutations, which are also linked to ICI resistance in melanoma & NSCLC. With ongoing trials in locally advanced context, such asKEYNOTE-A18, phase III trial investigating addition of pembrolizumab to standard of care concurrent chemoradiotherapy, combining ICI with chemoradiotherapy is promising approach **(3)**.

Immunotherapy beyond ICI

In addition to ICI, many other immunotherapy approaches are being researched, including some in context of advanced cervical cancer that are covered below **(8)**.

Cancer Vaccines

Since HPV & cervical SCC are associated, HPV-related proteins are appealing targets for vaccine-based treatment. Listeria monocytogenes vector vaccineADXS11-001 has been live, attenuated strain that encodes E7 oncoprotein. With twelve-monthOS rate of 38.5percent in studied cases with pre-treated recurrent or metastatic cervical cancer (squamous & non-squamous), initial findings of GOG/NRG0265 investigation with ADXS11-001 are encouraging. In phase II research with ADXS11-001with & without cisplatin in studied cases with advanced cervical cancer, combined twelve-month OS rate of 34.9percent had been observed **(5)**.

Genome Editing Tools

fast expanding field of study involves the use of CRISPR-associated protein 9 & clustered regularly interspaced palindromic repeats to carry out genetic editing. In vitro studies have shown that TALENs, which target the oncoprotein E7, suppress E7 production & cause cell death. These nucleases are also used as gene editing tools. studied cases with CIN will participate in phase I research to compare TALEN-HPV E6/E7 & CRISPR/Cas9-HPV E6/E7 **(5)**.

Cell Based Therapy—Engineered T-Cells

phase II study involving studied cases who received lymphodepletion with cyclophosphamide & fludarabine followed by infusion of TILs (LN-145) & up to six doses ofIL-2 demonstrated impressive OR Rof forty-four percent in studied cases with advanced cervical cancer progressing on prior chemotherapy. Adoptive cell transfer has been promising field **(3)**.

Conclusions

Our efforts to enhance ICI responses in cervical cancer face significant obstacles. absence of more reliable biomarkers than PD-L1expression, high TMB, or MSI-high continues to be 1 of fundamental shortcomings. Response rates are still modest in malignancies with these well-established indicators, but crucially long-lasting in minority of responders. To fully understand many mechanisms of ICI resistance that occur in cervical cancer, rationally designed clinical trials merging biomarker discovery with combination tactics, such as addition of PARP inhibitors, therapeutic vaccines, & radiation to ICI, will be essential. More importantly, solutions to these problems will be necessary to increase effectiveness of ICIs in treating cervical cancer **(8)**.

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