

# Current and Emerging Immunotherapies for Recurrent Cervical Cancer

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**Abstract:** Approximately 4290 women in the United States and 311,000 women worldwide died of cervical cancer in 2021. The management of advanced, recurrent, and/or metastatic cervical cancer has been a difficult and frustrating task owing to the paucity of available treatments. The year 2021 proved to be a boon for oncologists and their patients with cervical cancer, however, thanks to the release of data from KEYNOTE-826, which led to the approval of pembrolizumab in combination with chemotherapy, as well as the full approval of pembrolizumab alone, in the first-line setting. By January of 2022, it is likely that cemiplimab will be approved for recurrent or metastatic cervical cancer. With the availability of programmed death 1 (PD-1) inhibition in the first-line setting, it becomes important to discuss the future of second-line treatment, given that combination immunotherapy treatment that includes a PD-1 inhibitor after initial PD-1 treatment has been proved effective in the melanoma setting. Proposed and trialed combinations in immunotherapy include PD-1 inhibition with anti-T-cell immunoreceptor with Ig and ITIM domains (TIGIT) agents, anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) agents, and long-peptide vaccine. This review discusses the KEYNOTE-158 and KEYNOTE-826 trials of pembrolizumab, along with the EMPOWER CERVICAL 1 (R2810-ONC-1676/GOG 3016/ENGOT cx9) trial of cemiplimab and a phase 3 trial of balstilimab in cervical cancer. It also discusses the rationale for the use of immunotherapy in the cervical cancer setting, the mechanisms of action of available and currently studied immunotherapies, biomarkers for predicting and assessing response to treatment, and mechanisms of secondary tumoral escape or resistance to immunotherapy.

## Introduction

Despite the availability of adequate screening protocols and prevention techniques, cervical cancer remains a driver of morbidity and mortality among women. In 2021, cervical cancer was diagnosed in an estimated 14,480 US women, and 4290 women died of the

### Keywords

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disease.<sup>1</sup> The annual cost of cervical cancer care in the United States is \$1.6 billion, with the mean average cost of care in the last year of life being approximately \$118,000.<sup>2</sup> As the implementation of screening and vaccination has continued in the United States, so too has the development of treatment for patients with cervical cancer. In the last decade, immunotherapy has offered an exciting advancement in our treatment of this devastating and preventable disease. With the addition of pembrolizumab (Keytruda, Merck) to the oncologist's armamentarium, as well as the recent introduction of cemiplimab (Libtayo, Regeneron/Sanofi-Aventis), the outlook for patients with advanced cervical cancer is significantly brighter.

## Rationale for Immunotherapy in Cervical Cancer

### *Immune Checkpoint Blockade*

Immune checkpoint proteins and signals regulate self-tolerance, preventing the body from attacking itself. By appropriating checkpoint pathways, cancer cells take advantage of this natural system to escape detection by T cells that have tumor antigen recognition capabilities. Thus far, a number of these checkpoint pathways have been identified as targets for immunotherapy development, including programmed death 1 (PD-1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), lymphocyte-activating 3 (LAG3), T-cell immunoreceptor with Ig and ITIM domains (TIGIT), T-cell immunoglobulin and mucin domain-containing 3 (TIM3), and B- and T-lymphocyte attenuator (BTLA). Blockade of these pathways inhibits the ability of cancer cells to evade the immune system response.

Successful targeting and blockade of checkpoint pathways such as PD-1 depend not only on ligand expression but also on multiple intracellular and extracellular mechanisms that are poorly understood. The PD-1 receptor is expressed mostly on mature cytotoxic T lymphocytes, as well as within the tumor microenvironment. Cancer cells express the programmed death ligand 1 (PD-L1) or PD-L2. The PD-1 pathway is initiated by contact with PD-L1 or PD-L2 ligands.<sup>3</sup> Functionally, this causes an "off" signal for apoptotic or killing pathways. When the pathway is inhibited or blocked, the cancerous cells can be destroyed.

Cervical cancer demonstrates a number of features that make it a good candidate tumor for immunotherapy, including viral pathogenesis (human papillomavirus [HPV] antigens), high tumor mutational burden (TMB), frequent neoantigen formation, high-grade tumor infiltration (particularly CD8+ cytotoxic T lymphocytes and macrophages), and amplification in multiple checkpoint-controlling targets, including PD-L1.<sup>4,5</sup>

### *Expression of PD-L1*

The expression of PD-L1 and PD-L2 ligands on tumor cells is assessed with immunohistochemical testing; the sample is then given a combined positive score (CPS). Currently, only one companion diagnostic test has been approved in the setting of cervical cancer for the identification of PD-L1 expression.<sup>6</sup> The CPS is the number of PD-L1-staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen is considered to express PD-L1 if the CPS is 1 or higher.

The PD-1 pathway has also been implicated as a route by which infectious agents can evade immune system detection. Cervical cancer proves to be an interesting model because it is initiated by the HPV, which can lead to expression of PD-L1 in certain circumstances. An early study completed in 2015 by Mezache and colleagues determined that normal cervical epithelial cells do not express PD-L1; however, expression is noted in those cells affected by HPV in both cervical intraepithelial neoplasia (CIN) and cervical cancer.<sup>7</sup> In this study, PD-L1 expression was found in 95% of cases of CIN and 80% of cases of cervical squamous cell carcinoma.

Cervical adenocarcinoma has a worse prognosis than squamous cell carcinoma of the cervix. In analyses of PD-1 expression and other markers for a possible response to PD-1 inhibition, adenocarcinoma demonstrates less expression. In one study of cervical tumors, the rate of PD-1 positivity was 37.8% in squamous cell carcinoma, 28.6% in adenosquamous carcinoma, and 16.7% in endocervical adenocarcinoma.<sup>8</sup>

Data are increasingly demonstrating that a higher level of PD-L1 expression does not necessarily correspond to a better response to blockade. Data regarding the prognostic value of PD-1 expression are conflicting as well. Other methods of assessment that have been explored are tumor-infiltrating lymphocyte and CD8+ expression of PD-L1 and mRNA. Interestingly, an in vitro study demonstrated an increase in PD-1 expression following treatment with platinum-based neoadjuvant therapy.<sup>9</sup> Thus far, not enough is known about the degree of PD-1 expression beyond positivity or negativity to guide treatment with PD-1 inhibition in the clinical setting.

### *Genomic Biomarkers for PD-1 Checkpoint Inhibition*

Numerous molecular predictors besides PD-L1 expression have been examined as possible markers for patient response to PD-1 inhibition. A study published in 2018 examined the genomic signatures of participants in the KEYNOTE study series, specifically a high TMB and a "hot" T-cell-inflamed microenvironment or T-cell-inflamed gene expression profile (GEP).<sup>10</sup> When used in conjunction, TMB, GEP, and PD-L1 expression served as

a tumor molecular signature that could be used to determine clinical response to pembrolizumab.

Mismatch repair deficiency (dMMR) and its resulting microsatellite instability (MSI) are also markers of potential response to PD-1 inhibition. Germline mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* are most commonly seen in Lynch syndrome. Detection of dMMR and MSI has proved most useful in the colon cancer and endometrial cancer settings. These maladaptive functions of cancer cells cause somatic mutations that can lead to the expression of neoantigens, thereby upregulating checkpoint inhibition proteins such as PD-1 and CTLA-4. Approximately 2% to 4% of all cancer types exhibit dMMR and MSI, with reported rates of occurrence in cervical cancer of up to 25%.<sup>11,12</sup> Immunohistochemical staining or polymerase chain reaction can be used to detect dMMR and MSI.<sup>13</sup>

The DNA polymerase epsilon (*POLE*) and DNA polymerase delta 1 (*POLD1*) gene mutations have also been associated with the successful use of immunotherapy. These genes code for proofreading and fidelity proteins in DNA replication. In an evaluation of *POLE* and *POLD1* mutations as possible biomarkers for immunotherapy, overall survival (OS) was significantly longer in patients who had either or both mutations than in those without the mutations, at 34 vs 18 months, across all tumor types.<sup>14</sup> Approximately 5% of the patients with cervical cancer were found to have mutations in *POLE*, *POLD1*, or both.<sup>14</sup>

## Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody that has been demonstrated to have efficacy in the treatment of numerous PD-L1–positive tumor types and those tumors that demonstrate dMMR or MSI.

### KEYNOTE-158

In the phase 2 basket trial KEYNOTE-158, patients with previously treated advanced cervical cancer received 200 mg of pembrolizumab every 3 weeks for 2 years or until progression, intolerable toxicity, or physician/patient decision.<sup>15</sup> Interim study results were reported in 2019 and again in 2021. It is important to recognize that squamous cell carcinoma was the most frequent histologic type among the participants. Only 5 patients had adenocarcinoma histology, and 1 had adenosquamous histology; all tumors with an adeno-type histology tested positive for PD-L1. The primary endpoint was objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST). A total of 98 patients underwent treatment; 83.7% of these patients had a CPS above 1. The ORR was 12.2% (95% CI, 6.5%-20.3%) in the overall population,

0.0% in those with PD-L1–negative tumors, and 14.6% (95% CI, 7.4%-24.1%) in those with PD-L1–positive tumors. Median OS was 9.2 months in the total population and 11 months in the PD-L1–positive patients. On the basis of the findings reported from this study, the US Food and Drug Administration (FDA) in 2018 granted accelerated approval for pembrolizumab in the treatment of recurrent or metastatic cervical cancer. Interim results from KEYNOTE-158 were presented at the Society of Gynecologic Oncology 2021 Annual Meeting. The ORR was 14.3% (95% CI, 8.0%-22.8%), and the disease control rate was 30.6%. The ORR was 17.1% in the PD-L1–positive cohort and 0.0% in the PD-L1–negative cohort. Median progression-free survival (PFS) and OS were 2.1 months and 9.3 months, respectively. Durable activity and continued manageable safety were confirmed in this 17-month additional follow-up report.<sup>16</sup>

### KEYNOTE-826

Results from the double-blind, phase 3 KEYNOTE-826 trial were published online in *The New England Journal of Medicine* in September of 2021.<sup>17</sup> This trial studied the addition of a PD-1 inhibitor to first-line treatment for advanced cervical cancer. It examined the use of pembrolizumab plus concurrent chemotherapy (paclitaxel and carboplatin or cisplatin) with or without bevacizumab at the treating physician's discretion. Eligible patients had persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous cell carcinoma of the cervix that was not amenable to curative treatment, and they had not received systemic chemotherapy.

Patients who had received radiation were eligible but had to have completed radiation at least 2 weeks before the start of the trial. A total of 617 patients were randomly assigned to receive either pembrolizumab plus chemotherapy with or without bevacizumab or placebo plus chemotherapy with or without bevacizumab. At trial entry, baseline characteristics in the pembrolizumab group vs the placebo group were as follows: adenocarcinoma (18.2% vs 27.2%); adenosquamous carcinoma (4.9% vs 4.5%); squamous cell carcinoma (76.3% vs 68.3%); PD-L1–positive score of less than 1 (11.4% vs 11.0%); PD-L1–positive score of 1 to less than 10 (37.3% vs 37.5%); PD-L1–positive score of 10 or greater than 10 (51.3% vs 51.5%); and bevacizumab use (63.6% vs 62.5%). The dual primary endpoints examined were OS and PFS according to RECIST determined by investigator review. In the patients with a CPS greater than 1, PFS was 10.4 months in the pembrolizumab group and 8.2 months in the placebo group (hazard ratio [HR] for disease progression or death, 0.62; 95% CI, 0.50-0.77;  $P < .001$ ). In the intention-to-treat group, PFS was 10.4 months in the pembrolizumab group and

8.2 months in the placebo group (HR, 0.65; 95% CI, 0.53-0.79;  $P < .001$ ). In the patients with a CPS score of 10 or higher, PFS was 10.4 months with pembrolizumab and 8.1 months with placebo (HR, 0.58; 95% CI, 0.44-0.77;  $P < .001$ ). Median OS with pembrolizumab was not reached in the PD-L1–positive population. OS in the intention-to-treat population was 24.4 months with pembrolizumab and ranged from 16.3 to 16.5 months with placebo. The most common adverse events in all groups were anemia, alopecia, and nausea. The risks were greater with pembrolizumab than with placebo for hypothyroidism (18.2% vs 9.1%) and decreased white blood cell count (12.1% vs 7.1%). The subgroup of patients with a CPS of less than 1 was too small for the investigators to conclude benefit from treatment with pembrolizumab. In a subgroup analysis of PFS in the intention-to-treat population, the HR for disease progression or death was 0.61 (95% CI, 0.47-0.79) with bevacizumab vs 0.74 with placebo (95% CI, 0.54-1.01).

## Cemiplimab

Cemiplimab is a monoclonal antibody that binds to the PD-1 receptor found on T cells, inhibiting interaction with PD-L1 and PD-L2 antigens and enabling immune system detection of cancer.

### EMPOWER

In the phase 3 EMPOWER CERVICAL 1/GOG 3016/ENGOT cx9 trial, cemiplimab was given to patients with recurrent or metastatic cervical cancer who had disease progression after chemotherapy.<sup>18</sup> Patients were randomly assigned to receive 350 mg of intravenous (IV) cemiplimab or physician's choice of chemotherapy. The primary endpoint was OS, analyzed hierarchically in the patients with squamous cell carcinoma, then in the total population. Patients were enrolled regardless of PD-L1 status. A total of 608 patients were enrolled; 477 had a squamous cell history, and 131 had an adenocarcinoma or adenosquamous carcinoma history. In the total population, OS was 12.0 months in those who received cemiplimab and 8.5 months in those who received chemotherapy. Analysis for PD-L1 status was completed in 254 patients who had valid baseline samples. The HR for death was 0.69 (95% CI, 0.56-0.84;  $P < .001$ ). In those with PD-L1 expression of 1 or greater, median OS was 13.9 months (95% CI, 9.6 to not evaluable) with cemiplimab vs 9.3 months (95% CI, 7.0-11.4) with chemotherapy (HR, 0.70; 95% CI, 0.46-1.05). In the subset of patients with PD-L1 expression of less than 1, the median OS was 7.7 months with cemiplimab (95% CI, 4.3-12.3) vs 6.7 months (95% CI, 3.9-9.5) with chemotherapy (HR, 0.98; 95% CI, 0.59-1.62). The

median PFS was 2.8 months (95% CI, 2.6-3.9) in all patients who received cemiplimab vs 2.9 months (95% CI, 2.7-3.4) in those who received chemotherapy (HR, 0.75; 95% CI, 0.63-0.89). In the subset of patients without PD-L1 expression, the median PFS was 2.8 months (95% CI, 2.7-4.0) in the investigative arm and 2.8 months (95% CI, 2.6-3.5) in the control arm (HR, 0.71; 95% CI, 0.56-0.90). In those with PD-L1 expression, the median PFS was 2.8 months (95% CI, 1.7-4.0) in the investigative arm vs 2.9 months (95% CI, 2.6-4.0) in the control arm (HR, 0.82; 95% CI, 0.62-1.08). The most common adverse events were anemia, nausea, and vomiting. Approximately 8% of patients in the cemiplimab group vs 5% in the chemotherapy group discontinued therapy owing to adverse events. At the end of September 2021, the FDA announced that priority review would be granted to cemiplimab in this setting. The target action date is January 30, 2022 for cemiplimab monotherapy in the second line and beyond. At this time, it is unknown whether approval will occur and if so, whether it will be granted to all comers or only to PD-L1–positive patients.

## Balstilimab

Balstilimab is an anti-PD-1 monoclonal antibody. Results from the phase 2 trial of balstilimab were published in August of 2021. This study enrolled 161 patients with recurrent and/or metastatic cervical cancer, who received IV balstilimab at 3 mg/kg every 2 weeks for up to 24 months. A total of 62.7% of patients had squamous cell carcinoma, 32.3% had adenocarcinoma, and 4.3% had adenosquamous histology. The ORR was 15% (95% CI, 10.0%-21.8%) overall, 20% in patients with PD-L1–positive tumors, and 7.9% in patients with PD-L1–negative tumors. The ORR was 12.5% in patients with adenocarcinoma vs 17.6% in those with squamous cell carcinoma. A complete response occurred in 5 patients. The incidence of grade 3 adverse events was 11.8%, the most common being immune-mediated enterocolitis in 3.1%.<sup>19</sup> As a result of these findings, the FDA granted priority review for balstilimab as a single agent, with a target action date of December 16, 2021. The application was withdrawn, however, following the approval of pembrolizumab in the first-line setting with chemotherapy with or without bevacizumab for PD-L1–positive tumors based on results from KEYNOTE-826. Following this, the accelerated approval of pembrolizumab in the second line based on KEYNOTE-158 was converted to full approval. Based on these approvals, a high unmet need was fulfilled and the regulatory path for balstilimab under the accelerated approval pathway as second-line monotherapy was closed. Two other promising therapies have also had this pathway close as

a result of pembrolizumab's approval, bintrafusp alfa (a transforming growth factor beta neutralizer and PD-L1 binder) and lifileucel (a tumor-infiltrating lymphocyte therapy).

### Combination Immunotherapy

We are likely to see approval of cemiplimab in the second line by January of 2022. With the use of PD-1 inhibition in the first-line setting and the possible use of 2 PD-1 inhibitors as monotherapy in the second-line setting, it becomes important to address that fact that after first-line PD-1 treatment, second-line treatment has so far proved to be effective only in combination with another agent. The following studies describe the use of combination immunotherapy in the recurrent or metastatic setting; combination immunotherapy likely represents the future of second-line treatment for cervical cancer.

#### *Balstilimab and Zalifrelimab*

Zalifrelimab is an anti-CTLA-4 antibody. In prior studies that examined the combination of CTLA-4 blockade (ipilimumab; Yervoy, Bristol Myers Squibb) with PD-1 inhibition (nivolumab; Opdivo, Bristol Myers Squibb) for the treatment of melanoma, toxicities proved to be limiting and necessitated dose reduction.<sup>20</sup> CTLA-4 blockade results in the increased activation of CD8-positive cells as well as an increased number of CD8 cells within the tumor environment, so that more immune cells can reach the tumor. In contrast, the PD-1 pathway does not induce antitumor immunity.<sup>21</sup> Final results from a phase 2 trial of the anti-PD-1 agent balstilimab in combination with zalifrelimab in patients with recurrent or metastatic cervical cancer were presented at the European Society for Medical Oncology (ESMO) Congress 2021 in September.<sup>22</sup> Enrolled patients had advanced, recurrent, or metastatic cervical cancer and had previously received chemotherapy. A total of 160 patients received balstilimab at 3 mg/kg every 2 weeks, and 143 patients received both balstilimab and zalifrelimab at 1 mg/kg every 6 weeks. The ORR was 14% in the balstilimab group and 22% in the combination group. Immune-related adverse events affected 30% of patients in the balstilimab group and 35% of those in the balstilimab/zalifrelimab group. Grade 3 or higher adverse events were noted in 8% of patients in the balstilimab group and 10% of those in the balstilimab/zalifrelimab group. Overall, the treatment was well tolerated.

#### *Ipilimumab and Nivolumab*

Ipilimumab is an anti-CTLA-4 antibody and nivolumab is an anti-PD-1 monoclonal antibody. The combination is approved for use in numerous cancers, including metastatic

non-small cell lung cancer, gastric and esophageal cancers, squamous cell carcinoma of the head and neck, renal cell carcinoma, melanoma, and mesothelioma. In addition, the combination is being studied for use in colorectal cancer, urothelial cancer, and other types of cancer.

CheckMate 358, a phase 1/2 study, examined the use of nivolumab and ipilimumab in patients with various recurrent or metastatic virus-associated cancers, regardless of PD-L1 expression. Patients in the first arm, called Combo A, received nivolumab at 3 mg/kg every 2 weeks and ipilimumab at 1 mg/kg every 6 weeks until progression or unacceptable toxicity. Patients in the second arm, called Combo B, received nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab at 240 mg every 2 weeks until progression or unacceptable toxicity. Interim results in patients with cervical, vulvar, and vaginal cancer, presented at ESMO Congress 2019, demonstrated a higher ORR in the patients in Combo B without prior systemic therapy (46% vs 32%) and with prior systemic therapy (36% vs 23%). A complete response was observed in 4 patients in each arm. The ORR among patients in Combo A with PD-L1 expression greater than 1% was 30.8% in those who had not received prior systemic therapy and 40.0% in those who had received prior systemic therapy. The ORR among patients in Combo A with PD-L1 expression below 1% was 33.3% in those who had not received prior systemic therapy and 9.1% in those who had received prior therapy. The ORR among patients in Combo B with PD-L1 expression greater than 1% was 36.4% in those who had not received prior systemic therapy and 16.7% in those who had received prior systemic therapy. The ORR among patients in Combo B with PD-L1 expression below 1% was 0% in those who had not received prior systemic therapy and 57.1% in those who had received prior therapy. The incidence of grade 3 or 4 adverse events was 28.9% in Combo A and 37.0% in Combo B.<sup>23</sup>

### PD-1 Inhibition After PD-1 Treatment

Given that cemiplimab is now undergoing priority review for the same indication as that for pembrolizumab in patients with advanced, recurrent, and/or metastatic cervical cancer following treatment with chemotherapy, it is reasonable to conjecture that physicians who treat cervical cancer will now be faced with some of the same treatment decisions that physicians who treat renal cell carcinoma, non-small cell lung cancer, and melanoma must make. Some of the questions relate to concurrent treatment, sequential treatment, and treatment with a PD-1 inhibitor after prior treatment with another PD-1 inhibitor. Numerous clinical trials of PD-1 inhibitors in non-small

cell lung cell cancer, renal cell carcinoma, and melanoma are now open that allow prior treatment with a PD-1 inhibitor. Plausible rationales include treatment following prior discontinuation for a reason other than progression, treatment in combination with another immunotherapeutic agent, and perhaps treatment with a PD-L1 inhibitor. Structural and crystallization studies, however, have demonstrated that pembrolizumab and nivolumab share epitopes as well as act on the same pathway. As a result, these agents may not exhibit a synergistic effect, or they may not be effective when given in succession.<sup>24</sup> Future studies may demonstrate that immunotherapies that act on the same pathway but do not share epitopes will work synergistically or be effective when used sequentially.

Ongoing studies in the melanoma setting are investigating treatment of those patients whose disease progressed on a PD-1 inhibitor or on combination PD-1 inhibition and CTLA-4 inhibition. In August of 2021, Olson and colleagues reported results from a trial that examined the treatment of patients with melanoma whose disease had progressed on PD-1 inhibition with pembrolizumab and the anti-CTLA-4 antibody ipilimumab.<sup>25</sup> Prior data had demonstrated an ORR of 13% with an anti-CTLA-4 antibody alone following failure of a PD-1 inhibitor. The trial demonstrated an ORR of 29% in the entire population. Interestingly, the responders in this trial tended to be PD-L1–negative.

No current studies have demonstrated the efficacy of sequential treatment with PD-1 inhibitor therapies in the cervical cancer setting.

### Acquired Resistance to Checkpoint Inhibition

Disease progression following a period of response to treatment with immune checkpoint inhibition is common. This type of acquired resistance is known as secondary tumoral escape. Understanding the pathways that lead to resistance is relevant to understanding whether resistance develops to a single agent or to an entire class of drugs. Mechanisms thought to contribute to secondary tumoral escape include loss of T-cell function, lack of antigen recognition with drug-responsive downregulation of tumor antigen presentation, expression of multiple or additive checkpoints, the presence of immunosuppressive cells, and the development of escape mutation variants.<sup>26,27</sup> Genomic and tumor microenvironment analyses are currently being done in those patients whose disease progresses on immunotherapy to determine what adaptations occur to allow acquired resistance. On the basis of these mechanisms, dual or triple immunotherapy treatments administered concurrently and targeting different pathways are being examined as a method to avoid acquired resistance.

### Upcoming Studies: Frontline PD-1 Inhibition

#### *CALLA*

Among patients with locally advanced cervical cancer, the CALLA study will examine standard-of-care chemoradiation therapy with and without the anti-PD-L1 inhibitor durvalumab (Imfinzi, AstraZeneca). The trial, which has a planned enrollment of 714 patients, has completed accrual. The primary endpoint is PFS.<sup>28</sup> Treatment with concurrent radiation therapy and immunotherapy in this setting is exciting because immunotherapy may enhance radiation therapy. Treatment with radiation has been demonstrated to upregulate the expression of PD-L1 on tumor cells, facilitating the ability of a tumor to evade the immune system. With simultaneous blockage of PD-1, it is surmised that the therapeutic efficacy of radiation and durability of the response may be increased. An abscopal effect is also possible, in which tumor outside the radiated field shrinks without direct treatment.

#### *BEATcc (ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030)*

The phase 3 BEATcc trial of frontline treatment in patients with advanced, recurrent, or metastatic cervical cancer is currently under way, with researchers awaiting maturity of the primary endpoint of OS.<sup>29</sup> Patients are randomly assigned to standard cisplatin and paclitaxel chemotherapy plus bevacizumab with or without the anti-PD-L1 antibody atezolizumab (Tecentriq, Genentech). Examined arms will be balanced with respect to disease histology: squamous cell carcinoma vs adenocarcinoma, prior radiosensitization with cisplatin vs radiation alone, and cisplatin vs carboplatin. This study takes the backbone of GOG-240, which demonstrated increased OS (17.0 vs 13.4 months) and improved ORR (48% vs 36%) with the addition of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab to standard chemotherapy, and it adds the anti-PD-L1 antibody atezolizumab.<sup>30</sup> Anti-angiogenesis treatment may decrease secondary tumoral escape and facilitate response by normalizing vessels, allowing greater access to T cells in the tumor environment and creating an immunosupportive milieu.<sup>31</sup>

#### *KEYNOTE-A18 (164 ENGOT-cx11/GOG 3047/KEYNOTE-A18)*

KEYNOTE-A18 will examine the use of pembrolizumab in patients with locally advanced high-risk cervical cancer (NCT04221945). Enrollment of 980 patients who have not received prior therapy is planned; they will be randomly assigned in a 1:1 ratio to receive 5 cycles of pembrolizumab with cisplatin and external beam radiotherapy followed by brachytherapy, with a subsequent 15

cycles of pembrolizumab vs placebo. Primary endpoints to be examined are PFS per RECIST and OS. Enrollment began in May 2020.

### Upcoming Studies: Advanced, Recurrent, and Metastatic Disease

#### **SKYSCRAPER-04**

The phase 2 SKYSCRAPER-04 study will examine the use of the anti-PD-L1 antibody atezolizumab with or without tiragolumab, an anti-T-cell immunoreceptor with Ig and ITIM domains (TIGIT) monoclonal antibody. The study will enroll patients with recurrent or persistent cervical cancer after 1 to 2 lines of prior systemic chemotherapy that is not amenable to curative treatment. With a planned enrollment of 160 participants, patients will receive atezolizumab (1200 mg every 3 weeks) with tiragolumab (600 mg IV every 3 weeks) or placebo. The primary endpoint to be examined is overall response rate. The anticipated study completion date is in the summer of 2023.<sup>32</sup> TIGIT is expressed on tumor-infiltrating lymphocytes, natural killer cells, helper T cells, and regulatory T cells. In preclinical trials, anti-TIGIT therapies did not work as a single agent, but a synergistic effect was demonstrated when they were combined with checkpoint blockade. TIGIT is unique in that the numerous types of cells express it. Therefore, TIGIT inhibition in combination with PD-1 or checkpoint inhibition initiates a number of antitumor effects by upregulating the effector T-cell and natural killer cell response and reducing the suppressive effects of regulatory T cells.<sup>33</sup>

#### **Cemiplimab and ISA101b Vaccine**

This phase 2 trial will examine the use of cemiplimab with the ISA101b vaccine in patients with recurrent or metastatic HPV16-positive cervical cancer that progressed after first-line chemotherapy. The planned enrollment is 103 patients, with patients receiving cemiplimab every 3 weeks and the ISA101b subcutaneous vaccine on days 1, 29, and 50. The HPV16 vaccine is used to augment the HPV-specific T-cell population, which increases the infiltration of HPV-specific T-cells into a tumor. In combination with PD-1 inhibition, the HPV16 vaccine theoretically increases the response to PD-1 blockade.<sup>34</sup> Alone, HPV16-specific vaccines have been unable to elicit effective responses to invasive cancer. The estimated study completion date is October 22, 2024.<sup>35</sup>

#### **Pembrolizumab/Vibostolimab**

Vibostolimab is an anti-TIGIT monoclonal antibody. In 2021, a phase 2 basket trial opened to investigate the use of a co-formulation of pembrolizumab/vibostolimab in patients with advanced solid tumors (NCT04738487).

The primary hypothesis is that the co-formulation is superior to pembrolizumab alone. Numerous arms of the study will include disease-specific advanced cancer therapy. Participants must have PD-L1 expression with a CPS of greater than 1. The primary endpoints will be ORR and PFS per RECIST 1.1.

### Conclusion

Following a brief pause in the introduction of new therapeutics for cervical cancer following bevacizumab, several new immunotherapeutic drugs have been brought forward to treat this devastating disease. With the possibility of 2 PD-1 inhibitors available to treat advanced and/or recurrent cervical cancer in early 2022 and the use of pembrolizumab in the first-line setting, oncologists will have multiple choices for this previously treatment option-poor scenario. However, with new options come more questions to be answered. The future will be likely be combination therapy for continued immunotherapy following first-line immunotherapy failure. Immunotherapy offers an exciting opportunity to harness the body's own immune system to treat cancer. The mechanisms behind eliciting the immune system response remain elusive, however, and are not well understood. The introduction of PD-1 and PD-L1 blockade brings new opportunities in the treatment of cervical cancer, but many questions have arisen as a result. Stronger PD-L1 expression as measured with the CPS does not necessarily directly correspond to a more robust response, as demonstrated in KEYNOTE-826. PD-L1 inhibition combined with anti-CTLA-4 therapy following prior treatment with PD-1 inhibition in the melanoma setting demonstrated that response was better in those patients who were PD-L1-negative than in those who were PD-L1-positive. A multitude of factors, including synergistic effect and pathways in secondary tumoral escape, are currently being examined to explain these questions. Additionally, toxicities from combinations of immunotherapeutics will need to be closely examined and followed because the toxic effects appear to demonstrate synergy as well. With the advancement and combination of chemotherapy, immunotherapy and anti-VEGF treatment, molecular signatures with multiple biomarkers and information about the tumor microenvironment for individual patients will likely dictate therapeutic options.

#### **Disclosures**

*Drs Liu has no disclosures to report. Dr Tewari has served on the speaker's bureau and advisory board of Clovis, Astra-Zeneca, Merck, Eisai, and Seagen; has served on the advisory board of Regeneron, Genentech, AbbVie, and GSK/Tesaro; and has received research grants from Seagen, Merck, Clovis, Regeneron, Genentech, AbbVie, and Morphotek.*

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