GYNECOLOGIC CANCER IN FOCUS

Current Developments in the Management of Gynecologic Cancer

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Update on Immune Checkpoint Inhibition for Cervical Cancer

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H&O What is it about the biology of cervical cancer that makes it an attractive target for immune checkpoint inhibition?

LD More than 98% of cases of cervical cancer are caused by the human papillomavirus (HPV), meaning that the development of disease is integrally connected to the immune system. As a result, it is logical to treat cervical cancer with agents that act on the immune system.

Additionally, HPV causes malignant changes by inserting its DNA into cervical cells, a process that ultimately makes these cells more visible to the immune system and therefore more susceptible to actions of the immune system.

H&O Which patients with cervical cancer are currently eligible for treatment with checkpoint inhibition?

LD Patients may be eligible for treatment with checkpoint inhibition in multiple clinical settings. The first is locally advanced cervical cancer (LACC). In this setting, the combination of the checkpoint inhibitor pembrolizumab (Keytruda, Merck) plus chemoradiotherapy is currently approved for use in stage III and IV disease according to the International Federation of Gynaecology and Obstetrics (FIGO) 2014 staging criteria. The approval is based on results of the phase 3 KEYNOTE-A18 trial.

The second setting is metastatic or recurrent disease, in which checkpoint inhibitors are approved for use as single agents and in combination with chemotherapy and bevacizumab. In most but not all cases, the tumor must test positive for programmed death ligand 1 (PD-L1) expression on the basis of a predetermined score. It is important to note that most cervical cancers will express PD-L1 by immunohistochemical staining.

H&O What are the key studies that established the role of checkpoint inhibition in metastatic cervical cancer?

LD Pembrolizumab received US Food and Drug Administration (FDA) approval as a single agent in the recurrent setting on the basis of the results of KEYNOTE-158, which was a "basket trial" for patients with any recurrent solid tumor that had progressed after standard-of-care chemotherapy. In this study, 12 patients responded to pembrolizumab; all of them had PD-L1–positive tumors with a combined positive score of 1 or higher, which led to the FDA approval of single-agent pembrolizumab in this setting.

EMPOWER showed that cemiplimab (Libtayo, Sanofi-Aventis/Regeneron) improved overall survival (OS) in comparison with single-agent chemotherapy in patients with recurrent cervical cancer after first-line platinum-containing chemotherapy, regardless of the PD-L1 status. Although EMPOWER was a great trial and cemiplimab is approved for cervical cancer in many countries, it has never received FDA approval for this use.

Two important phase 3 studies established the first-line use of PD-L1 inhibitors in recurrent or metastatic cervical cancer after chemotherapy plus radiation therapy: KEYNOTE-826 with pembrolizumab (Keytruda, Merck)[1] and BEATcc with atezolizumab (Tecentriq,

Genentech).[2] KEYNOTE-826 demonstrated the value of adding pembrolizumab to frontline chemotherapy with or without the bevacizumab backbone established by the GOG 240 trial. A subset analysis of KEYNOTE-826 supported the importance of adding bevacizumab to this 4-drug regimen. BEATcc demonstrated that incorporating atezolizumab into first-line treatment with chemotherapy and bevacizumab improved both progression-free survival (PFS) and OS in patients with metastatic, persistent, or recurrent cervical cancer. The BEATcc trial did not report PD-L1 status, and the improvements in PFS and OS were seen in the overall trial group.

H&O Could you discuss the design and results of your KEYNOTE-A18 trial?

LD In KEYNOTE-A18, we randomized 1060 patients with newly diagnosed, locally advanced, high-risk cervical cancer to receive pembrolizumab plus chemoradiotherapy followed by pembrolizumab or placebo plus chemoradiotherapy followed by placebo. All patients had high-risk disease, which was defined as FIGO 2014 stage IB2 to IIB with lymph node positivity or stage III to IVA with any nodal status.

This study was conducted from 2020 to 2022, during the COVID pandemic; it is amazing we were able accomplish accrual in 2 years during a pandemic. The fact that the trial was an international collaboration is what made this possible. One shortcoming of the trial is that we had a limited representation of Black and Hispanic women, groups that are disproportionately affected by cervical cancer.

The overall survival data for KEYNOTE-A18 were published in *The Lancet* in 2024.[3] At a median follow-up of 29.9 months, the 3-year median OS rates were 82.6% in the pembrolizumab group vs 74.8% in the control group; this difference was statistically significant, with a hazard ratio for death of 0.66 in the subset of patients whose tumor expressed PD-L1. The rates of grade 3 or higher treatment-related adverse events were 69% in the pembrolizumab group and 61% in the placebo group. The final analysis, presented at the 2025 ASCO Annual Meeting, confirmed the robustness of the OS data, with a median follow-up of more than 41 months.[4]

A study similar to KEYNOTE-A18 is CALLA, which looked at a different checkpoint inhibitor, durvalumab (Imfinzi, AstraZeneca), in a similar population of patients.[5] The patients in this study had FIGO 2009 stage IB2 to IIB disease with lymph node positivity or stage III or higher disease with any nodal status. A total of 900 patients were randomly assigned to either durvalumab or placebo during and following chemoradiotherapy. At a median follow-up of 18.4 to 18.5 months, the 12-month PFS was not significantly higher in the durvalumab group than in the placebo group.

H&O What other recent studies have looked at improving the outcome of patients with LACC?

LD Another recent study is the phase 3 INTERLACE study.[6] Patients were eligible if they had LACC, defined as FIGO 2008 stage IB1 disease with nodal involvement or stage IB2, IIA, IIB, IIIB, or IVA disease. A total of 500 patients were randomly assigned to induction chemotherapy followed by standard cisplatin-based chemoradiotherapy or to chemoradiotherapy alone. After a median follow-up of 67 months, the 5-year OS rates were 80% in the combination group and 72% in the control group. Grade 3 or higher adverse events occurred in 59% of 250 individuals in the combination group and in 48% of those in the control group.

Treating providers should bear in mind that the patients in INTERLACE had much lower-risk disease than those in KEYNOTE-A18, making it difficult to compare the results of these trials. The INTERLACE regimen would not be appropriate for someone with stage IIIB disease and hydronephrosis, whereas the KEYNOTE-A18 regimen would not be appropriate for someone with stage II disease and negative periaortic nodes. The choice of treatment needs to reflect the reality of the patient in front of us.

One question brought up by these trials is whether we can combine the use of induction chemotherapy as in INTERLACE with the addition of pembrolizumab as in KEYNOTE-A18. To answer this question, the phase 3 NRG-GY037 study is currently looking at whether combining the 2 regimens can further improve outcomes (NCT07061977). In the meantime, no evidence is available to support the idea of combining these approaches.

H&O What agents are being studied in combination with checkpoint inhibition for use in cervical cancer?

LD When we are looking at a tumor that does not respond well to a checkpoint inhibitor alone, we want to see if we can make the checkpoint inhibitor work better by adding a second agent, such as a tyrosine kinase inhibitor (TKI), antiangiogenesis agent, chemotherapy agent, or radiation. The goal is to increase the antigen load in the tumor, which in turn can make the checkpoint inhibitor work better. We already know the value of adding bevacizumab to a chemotherapy backbone plus immunotherapy, as discussed earlier. Other modalities can be added to immunotherapy to improve response rates: radiation therapies, other immunotherapies (eg,

cytotoxic T-lymphocyte–associated antigen 4 inhibitors added to PD-L1 inhibitors), antibody-drug conjugates (ADCs) such as tisotumab vedotin (Tivdak, Seagen), poly(ADP-ribose) polymerase inhibitors, and other targeted therapies and novel agents. Of note, the phase 3 GOG-3123 study is looking at the experimental ADC sacituzumab tirumotecan in combination with pembrolizumab as first-line maintenance treatment for cervical cancer (NCT07216703).

> The idea of checkpoint inhibition as neoadjuvant therapy in locally advanced cervical cancer is a fascinating idea.

H&O What do we know about the sequencing of checkpoint inhibition in the setting of LACC?

LD The best sequencing of radiation and checkpoint inhibition in LACC is a very interesting and understudied question. I worked on a small phase 2 study several years ago in which we compared the use of pembrolizumab both concurrently with and following chemoradiation.[7,8] This was the first time anyone had combined pembrolizumab with pelvic radiation, and we found that both approaches were safe and feasible. We are still analyzing the data to better understand the biological effects of concurrent vs sequential therapy in this setting.

The idea of checkpoint inhibition as neoadjuvant therapy in LACC is a fascinating idea. The phase 1 NRG-GY017 study showed that induction atezolizumab is a safe approach that is associated with immunologically and clinically favorable outcomes.[9] The question of sequencing is extremely important, and I would like to see the research moved beyond small phase 1 and 2 studies.

H&O Is there anything you would like to add?

LD Cervical cancer is almost completely preventable with vaccination against HPV, which also cuts the number of head and neck cancers in half and reduces the number of anal cancers. It is important that we educate people about the efficacy and safety of this vaccine. Whenever I see a woman in my office with cervical cancer, I ask her if her kids have been vaccinated.

Patients should also be made aware that we have FDA-approved options for at-home HPV test sample collection. This is especially important for patients in rural areas, where reaching a doctor's office may be difficult.

Disclosures

Dr Duska has served on the scientific advisory board of Daiichi Sankyo; has been a member of the data and safety monitoring committee for Inovio (fees to institution) and NX Development Corp; has received speaker fees from Merck; and has worked with UpToDate, ASCO Connection, CEA Group, Clinical Care Options, Wiley, and Advance Medical. Multiple companies have sponsored clinical trials at her institution.

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