

CERVICAL CANCER IN FOCUS

Current Developments in the Management of Cervical Cancer

Section Editor: Robert L. Coleman, MD

The Role of Immunotherapy in Recurrent or Metastatic Cervical Cancer



Leslie M. Randall, MD
Associate Professor, Obstetrics & Gynecology
University of California, Irvine
Orange, California

H&O What makes cervical cancer a good target for immunotherapy?

LR Cervical cancer is a good target for immunotherapy because its presence indicates an impairment in the immune system; most cases of cervical cancer occur in response to a failure of the immune system to clear the human papillomavirus (HPV). A second rationale for using immunotherapy in cervical cancer is that most of these cancers express programmed death ligand 1 (PD-L1), which is an optimal target for immune checkpoint inhibition.

H&O What are the shortcomings of non-immunotherapy treatment for recurrent or metastatic cervical cancer?

LR The addition of bevacizumab to chemotherapy was an important advance in the treatment of patients with recurrent or metastatic cervical cancer. Unfortunately, this combination can be associated with an increased risk for fistula formation, typically in patients who have received prior radiotherapy. In addition, an exploratory analysis by Tewari and colleagues of the Gynecologic Oncology Group (GOG) 240 registration trial of bevacizumab in this setting reported a greater magnitude of benefit from bevacizumab in patients who had not received prior pelvic radiation. Because most patients who need bevacizumab have received prior radiotherapy, this group might have

an elevated risk for severe adverse events, with a smaller magnitude of benefit. Despite this caveat, bevacizumab remains an important addition to chemotherapy in well-selected patients, even those with prior pelvic radiation.

In fact, immunotherapy is being used in addition to bevacizumab in the management of cervical cancer, rather than replacing it. Immunotherapy offers several advantages over chemotherapy. First, it seems to benefit patients with previous radiation as much as it benefits patients who are radiotherapy-naïve. In addition, it is less associated with the formation of fistulas, which can have a dramatic adverse effect on quality of life.

H&O What are the most important studies to look at immunotherapy in patients with recurrent or metastatic cervical cancer?

LR The most important immunotherapy against cervical cancer is preventative. The HPV vaccine now covers 9 serotypes of HPV. It is approved for all individuals starting at 9 years of age and extending up to 45 years of age, although it is most effective before sexual debut. The inception of HPV tumor-infiltrating lymphocyte (TIL) therapy was the beginning of treatment-intent immunotherapy; TIL therapy induced a complete and durable response in heavily pretreated patients at the National Institutes of Health and was then expanded commercially. This therapy is selective, however; a large tumor biopsy specimen is required to obtain the

tumor-specific TILs, and it takes time to expand the TILs in vitro (approximately 22 days). The risks of treatment include lymphodepletion-associated cytopenias and cytokine release syndrome. Therefore, developing more generalizable and practical immunotherapies became a high priority. The first important study of a checkpoint inhibitor was KEYNOTE-158, a phase 2 basket trial that looked at the use of the checkpoint inhibitor pembrolizumab (Keytruda, Merck) as second-line therapy in a variety of cancer types. The trial included 98 women with previously treated, advanced cervical cancer. After a median follow-up of 10.2 months, the objective response rate was 12.2% (3 complete and 9 partial responses, all in patients with PD-L1–positive tumors). The median duration of response was not reached, but some responses lasted as long as 18.6 months, which far exceeded what we expected to see in this population. The results of this study led to accelerated US Food and Drug Administration (FDA) approval of pembrolizumab for second-line or later treatment in PD-L1–positive cervical cancer.

Evidence of the benefit of checkpoint inhibition in cervical cancer was strengthened by the results of the phase 3 EMPOWER study, which looked at the use of the immune checkpoint inhibitor cemiplimab (Libtayo, Regeneron/Sanofi-Aventis). This trial, which was conducted by GOG Partners and the European Network of Gynaecological Oncological Trial Groups (ENGOT), enrolled patients whose disease had progressed after first-line chemotherapy containing platinum. A total of 608 women were randomly assigned to cemiplimab or physician's choice of single-agent chemotherapy. The trial found that both progression-free survival (PFS) and overall survival (OS) were longer in the cemiplimab group than in the chemotherapy group.

A third study, KEYNOTE-826, led to full FDA approval of pembrolizumab for cervical cancer. This phase 3 trial enrolled 617 patients with recurrent or metastatic cervical cancer. Patients were randomly assigned to pembrolizumab or placebo and in addition received platinum-based chemotherapy; they were also allowed to receive bevacizumab. The study found that PFS and OS were significantly longer with pembrolizumab as first-line therapy for recurrent or metastatic cervical cancer than with placebo (KEYNOTE-158 and EMPOWER had looked at checkpoint inhibition as second-line or later treatment). This finding suggests that immunotherapy might work better when given earlier, which has been shown to be the case in other tumor types.

H&O What would you say the effect of KEYNOTE-826 has been?

LR I would say that the use of pembrolizumab as

frontline therapy in PD-L1–positive patients increased immediately; the majority of patients with recurrent or metastatic cervical cancer are PD-L1–positive, and in the KEYNOTE-826 study, nearly 90% of patients were PD-L1–positive. The addition of pembrolizumab clearly improves outcomes, leading to a median OS of 24 months in patients with metastatic cervical cancer, when we are used to seeing OS of no longer than a year. I certainly have changed my practice to incorporate pembrolizumab in frontline treatment.

H&O What would you say the effect of EMPOWER has been?

LR This is a bit tricky because EMPOWER was a positive trial that led to FDA review, but not FDA approval. Given the results of EMPOWER, there has been some confusion as to why cemiplimab was not approved. The reasoning is not completely in the public domain, but I think the failure to approve cemiplimab might stem from the fact that pembrolizumab was getting its final approval in the second-line or later setting right at the time that the FDA was reviewing cemiplimab, so at that point there was no lack of an effective therapy. Another possible reason is that the second- and third-line use of checkpoint inhibition is becoming less relevant because most patients receive it in the first-line setting.

H&O What are the disadvantages of pembrolizumab and cemiplimab?

LR Most patients tolerate checkpoint inhibitors well and do not experience serious adverse events. However, although serious adverse events are less common with checkpoint inhibitors than with other agents, they can be problematic and very difficult to manage. The most common serious adverse events I see are those that affect the endocrine system and require additional monitoring and medication. An adverse event that my patients find especially problematic is rash. Severe rashes are difficult to manage, and even mild rashes are bothersome to patients.

As we gain more experience with immunotherapy, we see just how responsive these adverse events are to treatment with a corticosteroid. We do not want to use high-dose corticosteroids without good reason, but short courses of corticosteroids are helpful if they allow patients to stay on effective immunotherapy. They are especially helpful in treating rashes—they are almost like an eraser in some cases! Fatigue associated with checkpoint inhibitors also responds very well to both dose delay and corticosteroids, which can dramatically improve patients' quality of life. Transient elevations in liver function tests are typically mild and can be addressed with dose interruption or

corticosteroid treatment, although some are of a higher grade and require permanent treatment discontinuation.

One interesting thing about corticosteroids and immunotherapy is that unlike with chemotherapy, where we have to resume treatment at a lower dose after an adverse event has resolved, we are often able to resume immunotherapy at the prior dose without inducing the same adverse event. If an adverse event does recur, it can be milder than it was before. Interrupting the adverse event with the course of corticosteroids seems to reset the clock. The key is to address the adverse event promptly.

H&O What other studies are investigating the use of immunotherapy in cervical cancer?

LR Right now, the 2 highest-profile studies of immunotherapy are in the locally advanced cervical cancer space: CALLA (NCT03830866) and KEYNOTE-A18 (NCT04221945). The standard treatment for these patients is chemoradiation. Patients whose disease progresses after chemoradiation account for most of those who need systemic therapy in the future.

CALLA is a phase 3 trial that is comparing durvalumab (Imfinzi, AstraZeneca) vs placebo during and after chemoradiation therapy in 770 patients with locally advanced cervical cancer. Although we are still waiting for the data from this study to be presented at a meeting, a press release from AstraZeneca announced that the trial did not meet its primary endpoint of improved PFS. Although KEYNOTE-A18 is a similar study that is looking at pembrolizumab, its population is at higher risk than the CALLA population. The findings of these trials will be very important in determining the role of checkpoint inhibitors in locally advanced cervical cancer.

H&O What additional questions would you like to see answered regarding immunotherapy in cervical cancer?

LR We have preliminary phase 2 data that show good responses with the addition of a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor to a programmed death 1 (PD-1) or PD-L1 inhibitor. Drs Oaknin and Naumann, at the 2019 Congress of the European Society for Medical Oncology (ESMO), presented data on nivolumab (Opdivo, Bristol-Myers Squibb) plus ipilimumab (Yervoy, Bristol-Myers Squibb) in recurrent or metastatic cervical cancer, and Dr O'Malley presented data at the 2021 ESMO Congress on balstilimab plus zalifrelimab in advanced cervical cancer, which were later

published in the *Journal of Clinical Oncology*. It would be useful to see how these combinations perform relative to single-agent checkpoint inhibitors.

I would also like to see more research on additional combinations, such as agents that target the vascular endothelial growth factor pathway plus immunotherapy. Although more than half of the patients in KEYNOTE-826 received bevacizumab, that was up to the physician's discretion. An ongoing phase 3 trial called BEATcc, which is led by the Spanish Ovarian Cancer Research Group (GEICO), is comparing atezolizumab (Tecentriq, Genentech) vs placebo in combination with bevacizumab and chemotherapy in metastatic cervical cancer (NCT03556839).

Disclosures

Dr Randall has received honoraria from Blueprint Oncology, Physicians' Education Resource, Curio Science, and Products in Knowledge; has served in a consulting or advisory role for AstraZeneca, Clovis Oncology, the GOG Foundation, Merck, Mersana Therapeutics, Agenus, Rubius Therapeutics, Myriad Genetics, EMD Serono, Genentech/Roche, Seagen, Novartis, and Eisai; has served on the speakers' bureau of AstraZeneca, Tesaro, and Merck; and has received institutional research funding from Genentech/Roche, On Target Laboratories, Pfizer, AIVITA Biomedical, Tesaro, AstraZeneca, Merck, Akeso Biopharma, and GEICO.

Suggested Readings

Chung HC, Ros W, Delord JP, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol*. 2019;37(17):1470-1478.

Colombo N, Dubor C, Lorusso D, et al; KEYNOTE-826 Investigators. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med*. 2021;385(20):1856-1867.

Naumann RW, Oaknin A, Meyer T, et al. Efficacy and safety of nivolumab (nivo) + ipilimumab (ipi) in patients (pts) with recurrent/metastatic (R/M) cervical cancer: results from CheckMate 358 [ESMO abstract 5630]. *Ann Oncol*. 2019;30(5) (suppl).

O'Malley DM, Neffa M, Monk BJ, et al. Dual PD-1 and CTLA-4 checkpoint blockade using balstilimab and zalifrelimab combination as second-line treatment for advanced cervical cancer: an open-label phase II study. *J Clin Oncol*. 2022;40(7):762-771.

Tewari KS, Monk BJ, Vergote I, et al; Investigators for GOG Protocol 3016 and ENGOT Protocol En-Cx9. Survival with cemiplimab in recurrent cervical cancer. *N Engl J Med*. 2022;386(6):544-555.

Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*. 2017;390(10103):1654-1663.

Update on CALLA phase III trial of concurrent use of Imfinzi and chemoradiotherapy in locally advanced cervical cancer [press release]. <https://www.astrazeneca.com/media-centre/press-releases/2022/update-on-calla-phase-iii-trial-for-imfinzi.html>. Published March 24, 2022. Accessed June 2, 2022.