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NEWSLETTER

Clinician Update: Esophageal Cancer

Checkpoint Inhibitors for Esophageal Cancer

This emerging form of immunotherapy is changing the paradigm for treating esophageal cancer, though proper patient selection is key.

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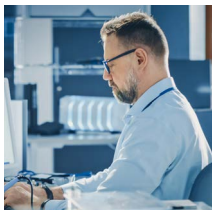

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Checkpoint Inhibitors for Esophageal Cancer

The arrival of immune checkpoint inhibitors has been a game changer in the management of advanced esophageal cancer. But which patients will benefit?

Immunotherapy with checkpoint inhibitors is changing the approach to treating a number of common malignancies, including esophageal cancer. But questions remain about which patients with this challenging cancer are most likely to benefit from these innovative drugs. A recent meta-analysis may help provide some clarity.

Esophageal cancer is the seventh most common malignancy around the world and the sixth most common cause of cancer-related death. While it has historically been a disease that primarily afflicts the elderly, recent research suggests that this aggressive cancer may be rising in younger populations in some countries, including the United States (see Research News on page 5). However, over the longer term, trends in survival have been more favorable. As recently as the 1970s, five-year survival for all patients with esophageal cancer was just 5 percent. Today, that figure has quadrupled, to 20 percent.

Several factors have contributed to improved survival with esophageal cancer, including superior treatments for some patients. One of the most exciting recent developments in the management of advanced esophageal squamous cell carcinoma (ESCC, which accounts for 85 percent of all cases worldwide) has been the arrival of immune checkpoint inhibitors. These drugs work by targeting proteins (such as PD-1, PD-L1, and CTLA-4) that inhibit the immune response, restoring T cells' ability to identify and kill cancer cells.

Several randomized clinical trials have found a significant improvement in overall survival with the combination of chemotherapy and immune checkpoint inhibitors versus chemotherapy alone in this patient population. The phase 3 KEYNOTE 590 trial led to the approval of pembrolizumab (Keytruda) plus chemotherapy for the first-line treatment of advanced ESCC. The study included patients with previously untreated, locally advanced, unresectable, or metastatic esophageal cancer or Siewert type 1 gastroesophageal junction cancer who received chemotherapy plus pembrolizumab or placebo. At median follow-up of 22.6 months, patients given pembrolizumab plus chemotherapy had superior overall survival

compared to placebo in all subgroups, regardless of the presence of tumor biomarkers. However, the greatest response occurred in patients whose tumors had PD-L1 CPS of 10 or higher, who had a median overall survival of 13.9 months versus 8.8 months in the placebo arm. (At the 2022 ASCO Gastrointestinal Cancers Symposium, researchers reported that these trends toward improved responses with combined chemotherapy and pembrolizumab persisted at median follow-up of 34.8 months.)

Interestingly, regulators have adopted different stances on the importance of biomarker status with regard to immune checkpoint inhibitors in treating esophageal cancer. The European Medicines Agency (EMA) approved pembrolizumab in combination with chemotherapy only for patients with advanced ESCC whose tumors expressed PD-L1 CPS of 10 or higher, while the U.S. Food and Drug Administration (FDA) gave it the greenlight to be used with chemotherapy regardless of the patient's PD-L1 status (though it can be offered as monotherapy to patients whose tumors overexpress PD-L1 and have failed other lines of therapy).

What's more, the CheckMate-648 trial found that the checkpoint inhibitor nivolumab (Opdivo) plus chemotherapy was superior to chemotherapy alone in all subgroups of patients with previously untreated, unresectable advanced, recurrent, or metastatic ESCC. However, at 13-month minimum follow-up, overall survival was significantly longer in nivolumab recipients with PD-L1 tumor portion score (TPS) of 1 percent or greater compared to the placebo arm (median, 15.4 months versus 9.1 months). Overall survival was also significantly longer with nivolumab plus ipilimumab (Yervoy) compared to chemotherapy alone in patients whose tumors overexpressed PD-L1 (median, 13.7 months versus 9.1 months). And here again, the EMA approved nivolumab for patients whose tumors have TPS of 1 percent or greater, while the FDA approved both ipilimumab-nivolumab dual immunotherapy and nivolumab plus chemotherapy without regard to PD-L1 status.

The findings of these and other trials, and the conflicting recommendations from regulators, may leave a clinician questioning whether offering a checkpoint inhibitor to a patient lacking PD-L1 overexpression makes sense. A recent report in *JAMA Oncology* may help to clarify the matter.

A team led by researchers at the Yong Loo Lin School of Medicine at National University of Singapore performed a meta-analysis of nine trials, including KEYNOTE-590 and CheckMate-648, as well as ESCORT-1st, ORIENT-15, KEYNOTE-181, ESCORT, RATIONALE-302, ATTRACTION-3, and ORIENT-2. Outcomes for 4,752 patients with advanced ESCC were

analyzed. Importantly, the team scrutinized the results for patients with low expression of PD-L1 and found that, for this population, adding a checkpoint inhibitor to chemotherapy did not improve outcomes compared to chemotherapy alone. For patients with ESCC whose tumors don't overexpress PD-L1, the authors note, "the number…who experience meaningful benefit from immunotherapy may be extremely limited." They recommend using a TPS cutoff of 1 percent or higher to identify patients who may be appropriate candidates for immunotherapy. To identify the small number of patients with low PD-L1 expression who may benefit from checkpoint inhibitors, the authors suggest that additional predictive biomarkers may help to select potential responders, such as tumor mutational burden, immune signatures, and gut microbiota.

There remains much more to be understood about the proper role for immunotherapy and potential benefits of novel checkpoint inhibitors in management of advanced esophageal cancer. Many trials are ongoing, including:

• The KEYNOTE-975 study is a randomized phase 3 study assessing the role of pembrolizumab in combination with definitive chemoradiation in patients with locally advanced esophageal or gastroesophageal junction cancer. Estimated study completion date is 2026.

• The SKYSCRAPER-07 study is a randomized phase 3 study that is evaluating a combination of the anti-PD-L1 antibody atezolizumab (Tecentriq) and tiragolumab, an anti-TIGIT antibody, compared to atezolizumab monotherapy or placebo in patients with unresectable ESCC whose cancers have not progressed after definitive chemoradiation. Blocking the TIGIT pathway may enhance the effects of chemoradiation and atezolizumab. Estimated study completion date is 2025.

• KUNLUN is a randomized, placebo-controlled, phase 3 study that is assessing the efficacy of durvalumab (Imfinzi) along with and after definitive chemoradiation in locally advanced, unresectable ESCC patients. Estimated study completion date is 2025.

Massive Bio collaborates with developers of new therapies for esophageal cancer, as well as investigational treatments for many other malignancies. If you have a patient who you believe is a candidate for a clinical trial, contact Massive Bio at (646) 867-7200 or referrals@massivebio.com.

Research News

Novel Checkpoint Inhibitor Shows Promise in Interim Phase 3 Analysis

The investigational checkpoint inhibitor tislelizumab improved overall and event-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) in an interim analysis of the phase 3 RATIONALE-306 trial, as was reported at the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancers 2022 last June. Tislelizumab is an anti-PD-1 antibody that has been investigated for use in hematological cancers and advanced solid tumors. The drug is approved for locally advanced or metastatic ESCC in patients who have disease progression or are intolerant of first-line chemotherapy in China.

RATIONALE-306 randomly assigned 649 patients with advanced ESCC to receive tislelizumab plus chemotherapy or placebo plus chemotherapy. The interim analysis found that the median overall survival in patients treated with tislelizumab was 17.2 months compared to 10.6 months in the placebo arm. At one year, 65.0 percent and 44.9 percent were alive, respectively. Interestingly, PD-L1 expression status didn't appear to influence survival. (See main article, "Checkpoint Inhibitors for Esophageal Cancer.")

Esophageal Cancer Rates Rise in Middle-Aged People

Esophageal cancer is most commonly diagnosed in people aged 65 to 74. However, the portion of people aged 45 to 64 diagnosed with this malignancy in the United States nearly doubled between 2012 and 2019, from 49 per 100,000 population to 94 per 100,000, according to an analysis of five million patient records presented at Digestive Disease Week 2022, held in San Diego last May. Meanwhile, diagnoses of pre-

cancerous Barrett's esophagus rose 50 percent in this demographic group during the same period. The study ruled out better screening as the cause of this increase in diagnoses, noted lead author Bashar J. Qumseya, MD, an associate professor of medicine and chief of endoscopy at the University of Florida, Gainesville, in comments to *The ASCO Post*. Qumseya added that middle-aged patients with risk factors for esophageal cancer should be considered candidates for early and frequent screening.

Genes May Explain Race Differences in Esophageal Cancer

It is well established that white people have a higher risk for esophageal adenocarcinoma (EA) than other races, but the reason why was unclear. A study published in *JCI Insight* in September offers important clues to why Black people in the United States are four to five times less likely to develop EA than white Americans.

In the study, a team led by researchers at University of California San Diego School of Medicine used artificial intelligence and machine learning tools to understand how precancerous cells in Barrett's esophagus progress to cancer, confirming their findings in organoids, biopsies, and a cross-sectional study of 113 patients with Barrett's esophagus and EA. They demonstrated that white blood cells called neutrophils drive an inflammatory response that spurs the progression from Barrett's esophagus to EA. However, they also discovered that a single nucleotide polymorphism, or SNP—a variation in a single base pair in a DNA sequence—appears to protect Blacks from this progression. The authors suggest that targeting neutrophils with therapeutics may be an option in treating EA.

Study Details Risks of Delaying Surgery for Esophageal Cancer

Putting off surgery for advanced esophageal cancer can dramatically reduce survival in some patients, according to a 2022 study published in the *Journal of the American College of Surgeons*. Researchers at Massachusetts General Hospital and Harvard University analyzed medical records from the National Cancer Database (NCDB) to understand the effects of delaying surgery following a diagnosis of esophageal cancer. Among patients diagnosed with stage I cancer, there was no apparent benefit to undergoing surgery promptly (within four weeks of diagnosis) versus waiting (within 12 to 16 weeks)—five-year survival in both groups was nearly identical, at 65.0 and 65.1 percent, respectively.

However, the analysis of patients with stage II and III esophageal cancer told a different story. After undergoing up to four weeks of chemoradiation, patients who had prompt surgery (within nine to 17 weeks of diagnosis) had a five-year survival rate of 41.6 percent, compared to 22.9 percent among patients who delayed surgery (21 to 29 weeks after diagnosis)—a difference of 45 percent. That's concerning, especially given that many hospitals delayed surgeries for esophageal cancer at the height of the COVID-19 pandemic—a policy that may need to be reconsidered. Moreover, the authors of the study emphasized in an interview with *The ASCO Post* that all patients diagnosed with operable esophageal cancer at any stage should undergo surgery as soon as possible.

For Your Patients:

Where To Turn for Support

The Esophageal Cancer Action Network

The Esophageal Cancer Action Network (ECAN) provides information and support to patients with esophageal cancer. ECAN traces its roots to a 2008 awareness-raising event called Dance for a Cure, staged by the family of John "Monte" Mordecai, who died of esophageal cancer earlier that year. An organization took shape and was eventually renamed the Esophageal Cancer Action Network.

One of ECAN's earliest goals was to bring awareness to two primary—and largely preventable—risk factors for esophageal cancer, heartburn and gastroesophageal reflux disease, or GERD. The organization has blossomed into an important resource for patients, offering a range of information, sponsoring fundraisers, and hosting an online community, where members can seek out advice from others who are living with esophageal cancer. Learn more at ecan.org.