People With Esophageal and Stomach Cancer Can Benefit From Immunotherapy

Opdivo and Keytruda are potential alternatives to current first-line therapies.

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Three different studies with different study populations that used either Opdivo (nivolumab) or Keytruda (pembrolizumab) as first-line treatment found that immunotherapy improves survival in people with gastric and esophageal cancers. Findings from these clinical trials were presented at the ESMO Virtual Congress 2020.

Gastric (stomach) and esophageal cancers, of which squamous cell carcinoma and adenocarcinoma are the most common, are the third and sixth leading causes of cancer death around the world. Current first-line treatments have remained mostly unchanged for years and have a limited impact on survival. Chemotherapy makes cancer more susceptible to an immune attack, so combining chemotherapy and immunotherapy could prove more effective. But immunotherapy is currently not considered standard first-line treatment.

Opdivo and Keytruda are monoclonal antibodies that block PD-1, a receptor on T cells that regulates immune function. PD-1 can sometimes be commandeered by a tumor to turn off immune responses. Drugs that block PD-1 or its binding partner, PD-L1, can release the brakes and restore T-cell activity to help fight cancer. Tumors with higher PD-L1 levels tend to respond better to this type of immunotherapy. Yervoy (ipilimumab) blocks CTLA-4, a different immune checkpoint that turns off immune responses by suppressing T-cell multiplication.

At the virtual conference, the three clinical trials showcased the use of a combination of either Opdivo or Keytruda plus chemotherapy as the first choice of treatment for people with gastric or esophageal cancers.

Opdivo Studies

In the CheckMate 649 trial (ClinicalTrials.gov CT02872116), researchers assessed the effectiveness of Opdivo in combination with chemotherapy compared with chemotherapy alone as first-line therapy in people with HER2-negative unresectable advanced or metastatic gastric

cancer, esophageal cancer or gastroesophageal junction adenocarcinoma.

“While it has been an important treatment option for these patients, chemotherapy alone is associated with a marginal survival benefit of often less than one year from the time a patient’s treatment is initiated,” presenter Markus Moehler, MD, PhD, of the Johannes-Gutenberg University Clinic, in Mainz, Germany, said in a press release. “Innovative treatments are urgently needed for patients around the world who are living with these advanced or metastatic upper gastrointestinal cancers, as there are currently no approved immunotherapy options in the first-line setting.”

The Phase III study included more than 1,500 people who were randomized to receive Opdivo plus chemotherapy, Opdivo plus Yervoy or chemotherapy alone.

The researchers found that Opdivo plus chemotherapy delayed disease progression and improved overall survival in people with tumors having a PD-L1 combined positive score (CPS, the proportion of PD-L1-positive tumor cells) of five or more. The median progression-free survival (PFS) time with Opdivo was 7.7 months compared with 6.0 months in the chemotherapy group. The median overall survival for the Opdivo group was 14.4 months compared with 11.1 months with chemotherapy alone. They also noted improvements in overall survival among people who had tumors with a CPS of one or more (14.0 months versus 11.3 months) and in the randomized population as a whole (13.8 months versus 11.6 months).

Treatment discontinuation due to treatment-related adverse events occurred in 36% of the Opdivo group and 24% of the chemotherapy group.

Based on this trial, for patients with HER2-negative gastric, esophageal or gastroesophageal junctional adenocarcinoma with tumor PD-L1 scores of 5 or more, “the addition of nivolumab to chemotherapy will become the standard of care for first-line treatment,” Salah-Eddin Al-Batran, MD, of the Krankenhaus Nordwest-University Cancer Centre, in Frankfurt, Germany, said in a press release. He added that the effect for patients with a CPS below 5 remains an “open question.”

The ATTRACTION 4 trial (NCT02746796) was similar to CheckMate 649, but this study included only Asian participants with gastric or gastroesophageal junction cancer, and the main analysis was not limited to those with a specific PD-L1 score. A total of 742 people were randomly assigned to receive Opdivo plus chemotherapy or a placebo plus chemotherapy.

Narikazu Boku, MD, PhD, of the National Cancer Center Hospital, in Tokyo, Japan, and colleagues found that the combination therapy significantly improved progression-free survival but had no impact on overall survival. People taking the combination had a higher objective response rate, meaning complete or partial reduction in tumor size.

“The improvement in progression-free survival was clinically relevant and the trial strongly supports the results of CheckMate 649,” said Al-Batran. “Overall survival was not improved, possibly because all comers were treated or because patients in Asia receive more subsequent therapies than Western populations.”

The occurrence of treatment-related severe adverse events and deaths was higher with Opdivo plus chemotherapy (58%) than with the placebo plus chemotherapy (49%).

Keytruda Study

In the KEYNOTE 590 study (NCT03189719), researchers compared Keytruda with or without chemotherapy as a first-line treatment for people with unresectable locally advanced or metastatic esophageal adenocarcinoma or esophageal squamous cell carcinoma (ESCC) or Siewert type 1 esophagogastric junction cancer.

Ken Kato, MD, PhD, of the National Cancer Center Hospital in Tokyo, Japan, and colleagues included 749 participants (83% men), half of whom were randomly selected to receive Keytruda plus chemotherapy.

The study demonstrated an improvement in overall survival in the study population as a whole, in those with ESCC (73% of the population) and in those with a CPS or 10 or more. In the full population, the median overall survival was 12.4 months in the Keytruda group versus 9.8 months in the chemotherapy group, a 27% improvement.

In participants with tumors having a CPS of 10 or more, the median overall survival was 13.5 months in the Keytruda group versus 9.4 months in the chemotherapy group. In people with ESCC with a CPS of 10 or more, the median overall survival was 13.9 months versus 8.8 months, respectively.

Keytruda plus chemotherapy also significantly improved progression-free survival by 35% in the population as a whole. Across the study and in the subgroup with ESCC, the median PFS was 6.3 months in the combination arm compared with 5.8 months in the chemotherapy arm. Among those whose tumors had a CPS of 10 or more, median PFS was 7.5 months and 5.5 months, respectively.

“In KEYNOTE-590, with a 27% reduction in the risk of death, the results show Keytruda has the potential to change the current treatment paradigm for the first-line treatment of patients with locally advanced and unresectable or metastatic esophageal or esophagogastric junction cancer,” Kato said in a press release.

“Pembrolizumab plus chemotherapy should be a new standard of care as first-line therapy in patients with locally advanced unresectable or metastatic esophageal cancer,” study coauthor Peter Enzinger, MD, of the Dana-Farber Cancer Institute in Boston, said at a press conference.

Discontinuation due to treatment-related adverse events occurred in 20% of people on combination therapy and 12% of those on chemotherapy alone. There were nine treatment-related deaths in the Keytruda arm and five in the chemotherapy arm.

In conclusion, “The results of these trials offer oncologists new treatment options,“ said Al-Batran. ”In the first-line setting, there is a clear change of our standard of care, in which patients with high

PD-L1 expression will be candidates for immune checkpoint inhibitors plus chemotherapy."

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