TIGIT Inhibitor Shows Promise for Esophageal Cancer

Dual checkpoint inhibitors tiragolumab and Tecentriq improved survival when added to chemotherapy.

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Tiragolumab, a new type of checkpoint inhibitor that promotes T-cell activity, plus Tecentriq (atezolizumab) led to modestly improved survival for people with advanced esophageal cancer when combined with chemotherapy, according to a report at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. However, the contribution of the new drug remains unclear.

"Esophageal squamous cell carcinoma accounts for most esophageal cancer cases worldwide," ASCO expert Pamela Kunz, MD, of Yale School of Medicine, said in a news release. "This Phase III trial demonstrates that dual immunotherapy plus chemotherapy with the novel checkpoint inhibitor, tiragolumab, improves progression free and overall survival without compromising safety."

Cancer of the esophagus and gastroesophageal junction (where the esophagus meets the stomach) is often detected late and can be difficult to treat. Around 22,000 people in the United States will be diagnosed with esophageal cancer this year, and it is the eighth most common cancer worldwide. Treatment may include surgery, radiation, chemotherapy, targeted therapy and immunotherapy that helps the immune system fight cancer.

TIGIT is an immune checkpoint that suppressed T-cell and natural killer cell activity; blocking the checkpoint can restore immune responses against tumors. Tiragolumab, a monoclonal antibody from Roche/Genentech, is among the TIGIT inhibitors furthest along in development. Currently available checkpoint inhibitors work in different ways, restoring T-cell activity by blocking the PD-1/PD-L1, CTLA4 or LAG-3 checkpoints. Early research suggests that combining these medications may have a synergistic effect.

Chih-Hung Hsu, MD, PhD, of the National Taiwan University Hospital in Taipei, and colleagues assessed the safety and efficacy of tiragolumab plus Tecentriq—an approved PD-L1 checkpoint inhibitor—in combination with chemotherapy for people with unresectable locally advanced, recurrent or metastatic esophageal cancer.

The SKYSCRAPER-08 trial enrolled 461 previously untreated patients from five Asian countries, including China, which accounts for about half of the global burden of esophageal cancer. Neary 90% were men, and the median age was 63 years.

The participants were randomly assigned to received tiragolumab plus Tecentriq or a placebo along with platinum-based chemotherapy for six cycles, followed by tiragolumab plus Tecentriq or placebo maintenance therapy until they experienced disease progression or unacceptable toxicity.

Combining the PD-L1and TIGIT checkpoint inhibitors with chemotherapy led to prolonged survival, Hsu reported. After a minimum follow-up of 6.5 months, the median progression-free survival (PFS) time was 6.2 months in the tirogolumab plus Tecentriq group compared with 5.4 months in the placebo group. After a minimum follow-up of 14.5 months, the median overall survival was 15.7 versus 11.1 months, respectively. Among those with longer follow-up, the 12-month PFS rates were 24% and 6%, respectively, and the overall survival rates were 61% versus 46%. The overall response rate, indicating tumor shrinkage, was 60% with tirogolumab plus Tecentriq versus 46% with the placebo.

Treatment was generally safe, but more than half of participants in both groups experienced severe effects. While most adverse events were associated with the chemotherapy, people in the tirogolumab plus Tecentriq group experienced immune-mediated side effects, including rash (39%), hepatitis (35%), hypothyroidism (18%) and pneumonitis (8%). About 18% experienced infusion-related reactions. Most of these effects were mild to moderate and manageable, according to Hsu, but about twice as many people in the combination therapy group discontinued treatment (11% versus 5%).

Based on these findings, Hsu suggested that tiragolumab plus Tecentriq and chemotherapy "may represent an alternative first-line treatment option" for inoperable advanced esophageal cancer.

However, a limitation of the study is that chemotherapy alone is no longer the standard of care for advanced esophageal cancer. Standard treatment in the United States involves an approved PD-1/PD-L1 checkpoint inhibitor plus chemotherapy. Further controlled studies will need to determine whether tiragolumab adds any benefit over Tecentriq alone.

Some recent data have cast doubt on the TIGIT approach. In 2022, Roche/Genentech reported that tiragolumab plus Tecentriq did not work better than Tecentriq alone in the first interim analysis from the SKYSCRAPER-01 trial for non-small-cell lung cancer (NSCLC), although the combination looked better in a later—though still immature—analysis. Merck has seen unimpressive results for its experimental TIGIT inhibitor vibostolimab plus its PD-1 checkpoint inhibitor Keytruda (pembrolizumab) added to chemotherapy for NSCLC.

The new results from SKYSCAPER-08 are therefore welcome, suggesting that the TIGIT approach still holds promise for some types of cancer.

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