A new targeted treatment shows promise for select patients with stomach cancer

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An international phase 3 clinical trial, done in participation with Weill

Cornell Medicine and NewYork-Presbyterian, has found that a new targeted treatment called zolbetuximab, given in combination with a standard chemotherapy, extended survival for patients with advanced gastric or gastroesophageal junction cancer that overexpressed a specific biomarker.

Results from the GLOW study, published July 31 in *Nature Medicine*, together with results from the parallel SPOTLIGHT study that evaluated zolbetuximab with an alternative standard chemotherapy, prompted the United States Food and Drug Administration to grant priority review to the manufacturer's biologic license application and set January 12, 2024, as the target decision date.

If approved, zolbetuximab will be the first targeted therapy in the U.S. for patients with previously untreated advanced gastric or esophageal junction cancer that is human epidermal growth factor receptor 2 (HER2)-negative and overexpresses the protein claudin-18 isoform 2 (CLDN 18.2).

Gastric cancer is the fifth most diagnosed cancer globally, and its incidence has increased markedly in the last few decades. Patients with cancer of the stomach or at the junction where the esophagus joins the stomach, known as the gastroesophageal junction, typically have few symptoms in early disease stages, so most are diagnosed after the cancer has advanced or become metastatic. According to the National Cancer Institute, the five-year survival rate for patients with metastatic disease is about 7%.

There are few targeted treatments available for patients with gastric and gastroesophageal cancers: Patients with tumors expressing the programmed cell death ligand 1 protein can be treated with immunotherapy, and those with HER2-positive tumors can be treated with trastuzumab, also known by the trade name Herceptin.

There is another group of HER2-negative patients who fit neither category, and for whom targeted therapies aren't generally used. However, these gastric cancers tend to have higher levels of CLDN 18.2, which is normally found in gastric mucosa cells and becomes more exposed as gastric cancer develops. Zolbetuximab is a monoclonal antibody, administered intravenously, that binds to CLDN18.2, killing the dividing cancer cells directly and also alerting the immune system to respond.

"Currently, standard chemotherapy regimens are the only treatment options for many patients with HER2-negative and low PD-L1 gastric and gastroesophageal cancer, and survival is about 12 months," said lead study author and trial co-principal investigator Dr. Manish Shah, the Bartlett Family Professor of Gastrointestinal Oncology and director of the Gastrointestinal Oncology Program in the Division of Hematology and Medical Oncology at Weill Cornell Medicine. "A new treatment for these patients would address a significant unmet need to extend survival."

The GLOW study was conducted between November 2018 and February 2022 at 166 sites, including NewYork-Presbyterian/Weill Cornell Medical Center, across 18 countries. A total of 507 patients with previously untreated HER2-negative locally advanced or metastatic gastric or gastroesophageal junction cancer expressing CLDN18.2 were randomized to receive zolbetuximab in combination with capecitabine plus oxaliplatin chemotherapy (CAPOX) or a placebo plus CAPOX.

Zolbetuximab plus CAPOX significantly increased progression-free survival compared with placebo plus CAPOX. Specifically, zolbetuximab plus CAPOX lowered the risk of disease progression or death by 31% compared with placebo plus CAPOX. The median progression-free survival was 8.21 months for patients in the zolbetuximab group compared with 6.8 months for those in the placebo

group. Furthermore, the addition of zolbetuximab doubled the chance of not having disease progression at 2 years (from 7% with placebo versus 14% with zolbetuximab).

Results also demonstrated that zolbetuximab plus CAPOX significantly lengthened overall survival and reduced the risk of death by 23%. The median overall survival was 14.4 months for patients in the zolbetuximab plus CAPOX group versus 12.2 months for those in the placebo plus CAPOX group. Long terms survival similarly increased significantly with the addition of zolbetuximab—29% survival at 2 years with zolbetuximab versus 17% with placebo.

Treatment-related adverse events were similar between groups, with nausea, vomiting and decreased appetite reported most frequently. "These side effects were as expected," said Dr. Shah, who is also chief of the Solid Tumor Oncology Service and co-director of the Center for Advanced Digestive Care at NewYork-Presbyterian/Weill Cornell Medical Center and a member of the Sandra and Edward Meyer Cancer Center and of the Englander Institute for Precision Medicine at Weill Cornell Medicine. "It was good to see zolbetuximab did not add significant toxicity."

Similarly, a study published in *The Lancet* on May 20, 2023 reported strong survival outcomes for the international phase 3 SPOTLIGHT trial that evaluated zolbetuximab in combination with a different chemotherapy regimen consisting of modified folinic acid or levofolinate, fluorouracil and oxaliplatin (mFOLFOX). Dr. Shah was a member of the SPOTLIGHT steering committee, co-author of *The Lancet* paper and involved in designing both the GLOW and SPOTLIGHT trials.

"We now have evidence from two large trials showing that the addition of zolbetuximab provides a meaningful survival benefit for patients with

CLDN 18.2-positive gastric cancers," he said. "If zolbetuximab is approved, patients will be able to decide with their physicians whether zolbetuximab plus CAPOX or mFOLFOX is the right regimen for them."

More information: Manish A. Shah et al, Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial, *Nature Medicine* (2023). DOI: 10.1038/s41591-023-02465-7

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