Krazati Plus Erbitux May Provide Clinical Benefit for Patients With Colorectal Cancer

The combination showed clinical activity and promising survival outcomes in patients with metastatic KRASG12C-mutated colorectal cancer.

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A combination of the KRAS-G12C inhibitor adagrasib (Krazati) and the anti-epidermal growth factor receptor (EGFR) antibody cetuximab (Erbitux) showed clinical activity and promising survival outcomes in a cohort of patients with metastatic, heavily pretreated, KRAS-G12C-mutated colorectal cancer, according to results from the phase I/II KRYSTAL-1 trial presented at the American Association for Cancer Research (AACR) Annual Meeting 2024, held April 5-10.

The study was simultaneously published in Cancer Discovery.

KRAS-G12C mutations occur in around 4% of colorectal cancers and are associated with a poor prognosis. Drugs targeting KRAS-G12C, such as adagrasib, have emerged in recent years but are currently only approved by the U.S. Food and Drug Administration (FDA) to treat non-small cell lung cancer.

“Treatment options are limited for previously treated patients with KRAS-G12C-mutated colorectal cancers,” said Scott Kopetz, MD, PhD, a professor of Gastrointestinal Medical Oncology and associate vice president of Translational Integration at The University of Texas MD Anderson Cancer Center. “Although there is some encouraging single-agent activity of adagrasib in KRAS-G12C-mutated colorectal cancer, it is important to continue finding ways to mitigate resistance.”

Preclinical evidence has shown that cancer cells can develop resistance to KRAS-G12C inhibition by upregulating EGFR activity, Kopetz explained. EGFR can drive tumor growth through the same molecular pathway that includes KRAS.

“Preclinical work combining a KRAS-G12C inhibitor with an EGFR inhibitor showed that we could mitigate adaptive resistance,” Kopetz said. “In the KRYSTAL-1 trial we sought to evaluate this in patients.”

KRYSTAL-1 is a multiple expansion cohort phase I/II trial testing the safety and efficacy of

adagrasib alone or in combination with other anticancer therapies in patients with advanced solid tumors that harbor a KRAS-G12C mutation. In the presented study, Kopetz and colleagues examined the use of adagrasib plus the EGFR inhibitor cetuximab in 94 patients with metastatic, KRAS-G12C-mutated colorectal cancer enrolled in either phase of the trial.

The objective response rate (the primary endpoint) was 34%, and the disease control rate was 85.1%; responses lasted a median of 5.8 months. The median progression-free survival was 6.9 months, and the median overall survival was 15.9 months.

While the study was not designed to compare the outcomes of patients treated with adagrasib plus cetuximab to those of patients treated with adagrasib monotherapy, Kopetz said the combination performed favorably compared to historical data. For instance, adagrasib monotherapy has been observed to have response rates around 20% in similar cohorts, compared to the 34% observed here, he explained.

The combination therapy was well tolerated, Kopetz noted, with treatment-related adverse events of grade 3 or higher occurring in 27.7% of patients. Adverse events led to adagrasib dose reduction in 29.8% of patients.

Kopetz noted that the combination is currently under priority review by the FDA for this indication. Kopetz and colleagues are exploring the efficacy of the regimen further in the phase III KRYSTAL-10 trial, which compares adagrasib plus cetuximab to standard-of-care chemotherapy in the second line of treatment for metastatic, KRASG12C-mutated colorectal cancer.

“Adagrasib plus cetuximab may be a potential new standard of care for patients with previously treated, KRAS-G12C-mutated colorectal cancer,” Kopetz said. “Our study builds upon the progress made with KRAS-G12C inhibitors and underscores the importance of ongoing research to refine and expand treatment options for patients with colorectal cancer.”

Limitations of this study include its single-arm, open-label design. This study was funded by Mirati Therapeutics. See disclosures in the link below.

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