Combination treatment is well-tolerated, shows antitumor effects in KRAS G12C-mutated metastatic colorectal cancer

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Combining the KRAS G12C inhibitor adagrasib with the anti-EGFR antibody cetuximab demonstrated promising anti-tumor effects in

patients with KRAS G12C-mutated metastatic colorectal cancer (CRC), according to pooled results from the Phase I/II KRYSTAL-1 trial reported by researchers from The University of Texas MD Anderson Cancer Center.

The findings were presented in a plenary session at the American Association for Cancer Research (AACR) Annual Meeting 2024 by Scott Kopetz, M.D., Ph.D., professor of Gastrointestinal Medical Oncology and associate vice president of Translational Integration, and published in *Cancer Discovery*.

The targeted therapy combination achieved a disease control rate of 85.1%, an overall response rate of 34%, and a median duration of tumor response of 5.8 months. Median progression-free survival (PFS) was 6.9 months and median overall survival (OS) was 15.9 months.

Based on preliminary results from the Phase I trial, the Food and Drug Administration (FDA) granted Breakthrough Therapy designation to this combination.

"This population of patients with KRAS-mutated colorectal cancer faces a poor prognosis, and there currently are no effective targeted therapies," Kopetz said. "Therefore, it's promising to see that this combination shows clinically meaningful benefit both in response rates and duration of disease control along with a very encouraging safety profile."

KRYSTAL-1 is a multi-center Phase I/II trial testing the safety and efficacy of adagrasib alone or in combination with other anticancer therapies in patients with KRAS G12C-mutated metastatic solid tumors. In these two cohorts presented at AACR, the combination of adagrasib plus cetuximab showed antitumor activity and was well tolerated in previously treated patients with KRAS G12C-mutated metastatic CRC, meeting its primary endpoints of safety and objective response rate.

KRAS G12C mutations occur in approximately 3–4% of patients with CRC and are associated with shorter PFS and OS when treated with standard of care chemotherapy, highlighting a critical unmet need.

Adagrasib is a selective and irreversible KRAS G12C inhibitor which can penetrate through the central nervous system, and it previously was shown to be effective for patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC) and untreated brain metastasis as part of the same trial.

The FDA granted accelerated approval to adagrasib for the treatment of certain patients with advanced KRAS G12C-mutant NSCLC, with continued approval contingent on verifying clinical benefit in a confirmatory trial.

Adagrasib monotherapy has shown limited activity in patients with KRAS G12C-mutated CRC, and some CRC patients develop resistance to KRAS G12C inhibitor treatment via epidermal growth factor receptor (EGFR)-mediated reactivation of the MAPK signaling pathway. Preclinical data suggested that dual blockade of KRAS G12C with an EGFR inhibitor could help overcome that resistance, leading to evaluation of adagrasib and cetuximab.

The study included 94 heavily pretreated patients with unresectable or metastatic KRAS G12C-mutated CRC with limited treatment options. Participants had a median age of 57 years and 53% were female.

All patients experienced side effects consistent with previous reports on the safety profile of both drugs, with 72.3% of patients experiencing low-grade and 27.7% of patients experiencing more moderate adverse events. Dose reductions of adagrasib and cetuximab occurred in 28 (29.8%) and six (6.4%) of patients, respectively. Eight patients (8.5%) discontinued the use of cetuximab due to side effects, but none led to adagrasib

discontinuation.

Further exploratory analysis showed that baseline KRAS G12C mutations were detected in the circulating tumor DNA (ctDNA) of 69 out of 83 patients, with 83% concordance between paired tumor samples. This highlights the potential future use of liquid biopsies as a means of stratifying patients most likely to respond well to the combination regimen.

"These results suggest this combination treatment should be considered as a late-line treatment for patients with unresectable or metastatic KRAS G12C-mutated CRC," Kopetz said.

Kopetz noted that the combination now is recommended by the National Comprehensive Cancer Network (NCCN) Guidelines, and that Phase III trials are currently ongoing.

More information: ABSTRACT CT013: www.abstractsonline.com/pp8/

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