Patients with metastatic colorectal cancer harboring certain BRAF mutations may respond to anti-EGFR

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Patients with metastatic colorectal cancer harboring a subset of non-V600 mutations in the BRAF gene, known as class 3 BRAF mutations, were more likely to respond to anti-EGFR treatment.

The study is published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research. Senior author is Hiromichi Ebi, MD, Ph.D., chief of the Division of Molecular Therapeutics at the Aichi Cancer Center Research Institute in Nagoya, Japan; and first author is Rona Yaeger, MD, medical oncologist at Memorial Sloan Kettering Cancer Center.

"Cancer genomic profiling is rapidly transforming the clinical management of cancer patients," said Ebi. "Results from our study indicate that metastatic colorectal cancer patients with certain BRAF mutations should be considered for anti-EGFR treatment, a new indication for this population of patients."

Alterations to the RAS signaling pathway, which controls key functions such as cellular proliferation and survival, is a known driver of oncogenesis. Mutations to BRAF, a kinase that interacts with RAS, can result in activation or amplification of the RAS signaling pathway. Roughly 10 percent of metastatic colorectal cancer tumors harbor mutations in the BRAF gene, noted Ebi.

BRAF mutations belong to one of three functional classes. Class 1 comprises BRAF V600 mutations. Non-V600 BRAF mutations are divided into two classes: class 2 mutations are RAS-independent, and class 3 mutations have enhanced binding to RAS and the kinase CRAF, resulting in increased RAS-dependent signaling.

While tumors with V600 BRAF mutations are often susceptible to RAF inhibitors, this therapeutic strategy is not predicted to be successful in tumors with non-V600 BRAF mutations, explained Yaeger. Prior smaller studies have shown that some patients with non-V600 BRAF-mutant colorectal cancer may respond to anti-EGFR treatment, she noted.

To determine if different functional classes of non-V600 BRAF mutations affected responses to anti-EGFR therapy, Ebi and colleagues retrospectively analyzed data from 40 patients with metastatic colorectal cancer whose treatment included an anti-EGFR therapy through an international multicenter collaboration. Using biochemical assays, the researchers classified the patients' tumors as having one of the two classes of non-V600 BRAF mutations: 12 patients had class 2 BRAF mutations and 28 patients had class 3 BRAF mutations. Patients from both groups had comparable clinical characteristics.

Eight percent of patients with tumors harboring class 2 BRAF mutations responded to anti-EGFR treatment regimens, compared with 50 percent of those with class 3 BRAF mutations.

The researchers also analyzed responses to anti-EGFR regimens based on treatment line. In the first- or second-line setting, 17 percent of patients with tumors harboring class 2 BRAF mutations responded to treatment, compared with 78 percent of those with class 3 BRAF mutations. In the third-line setting or later, no patients with class 2 BRAF mutations responded to treatment, compared with 37 percent of

those with class 3 BRAF mutations.

"Through the analysis of colorectal cancer tumors with specific BRAF mutations, we identified a potential new indication for anti-EGFR treatment, highlighting the power of precision oncology," noted Ebi.

Limitations of the study include the small number of patients with metastatic colorectal cancer harboring class 2 or class 3 BRAF mutations. Additionally, because most of the patients analyzed in this study were also treated with chemotherapy, the researchers could not assess the efficacy of anti-EGFR monotherapy based on the functional class of non-V600 BRAF mutations, Ebi noted.

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