Adding vemurafenib doubles progression-free survival in BRAF metastatic colorectal cancer

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Christoper Lieu, M.D., and colleagues show increased survival with addition of vemurafenib to common therapy for metastatic colorectal cancer. Credit: University of Colorado Cancer Center

Clinical trial results presented in an oral abstract session 3:00pm Monday, June 5 at the American Society for Clinical Oncology (ASCO) Annual Meeting 2017 shows promising results for the addition of vemurafenib (anti-BRAF) to treatment with cetuximab and irinotecan (anti-EGFR) in patients with metastatic colorectal cancer that have a BRAF V600E mutation. In the randomized trial, 49 patients who received vemurafenib in combination with cetuximab and irinotecan

showed median 4.3 months progression-free survival (PFS), compared with 2.0 months median PFS for 50 patients given cetuximab and irinotecan alone. Disease control rate was 67 percent for the combination including vemurafenib versus 22 percent for the two-drug combination. Overall survival was median 5.9 months for the two-drug combination and 9.6 months with the addition of vemurafenib. The study implies that inhibiting BRAF along with EGFR in this population may be more potent than inhibiting either of these targets alone.

"The 5-10 percent of patients with metastatic colorectal cancer that have a BRAF V600E mutation tend to have a significantly worse prognosis than patients who do not have this mutation," explains Chris Lieu, MD, director of the University of Colorado Cancer Center Colorectal Medical Oncology Program. "This is a group of patients that clearly need better treatment options, and this study is a very positive step in the right direction."

The discovery takes place in a mutational landscape that can be seen as a musical mixing board. Alone, vemurafenib turns down BRAF but often at the expense of turning up the gene EGFR, which is involved in controlling the rate of cell replication (a hallmark of cancer). Preclinical work by Lieu and colleagues shows that this upregulation of EGFR in response to BRAF inhibition may be one reason that BRAF inhibitors alone have not been especially successful in treating colorectal tumors.

"This laboratory research showing that EGFR upregulation is a resistance mechanism of colorectal cancer to BRAF targeted therapy led to the development of this trial," says Lieu. "This is truly a success of what we consider bench-to-bedside research."

In the study, 99 patients were given the common colorectal cancer treatment of the chemotherapy irinotecan with the anti-EGFR therapy cetuximab, with half adding the BRAF inhibitor vemurafenib. This study

allowed crossover in which patients who were not randomized to receive vemurafenib were allowed to receive the combination of all three drugs at the time that their tumor grew. Fifty percent of patients who were enrolled onto the trial crossed over and received the three-drug study regimen.

"These results and others demonstrate that recent successes in genetically targeted therapies may be only a first step toward the best clinical use of these therapies," Lieu says. "Now, the challenge is to combine, sequence and prescribe these therapies with the most rational strategies to the patient populations most likely to benefit."

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