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New Colorectal Cancer Targeted Therapy Combination Shows Promise

PORTLAND, OR – New SWOG study results show significantly better outcomes for patients with a treatment-resistant form of metastatic colorectal cancer when the *BRAF* inhibitor vemurafenib is added to a standard treatment. The findings, for the first time, point at an effective treatment for this deadly type of cancer.

SWOG investigator Dr. Scott Kopetz will present the research Saturday, Jan. 21 at the 2017 Gastrointestinal Cancers Symposium in San Francisco. The symposium showcases the latest science and is sponsored by the field's leading specialty societies: the American Gastroenterological Association (AGA) Institute, the American Society of Clinical Oncology (ASCO), the American Society for Radiation Oncology (ASTRO), and the Society of Surgical Oncology (SSO).

An associate professor at the University of Texas MD Anderson Cancer Center and a member of SWOG's gastrointestinal research committee, Kopetz has spent nearly a decade studying *BRAF*-mutant metastatic colorectal cancer – how it works and how to shut it down. Mutation of the *BRAF* gene is implicated in many cancers and works by fueling cancer cell growth.

Kopetz became interested in therapies to target *BRAF* mutations years ago, and conducted early research to determine the safety and efficacy of vemurafenib, an inhibitor that targets the mutated form of the *BRAF* protein. The U.S. Food and Drug Administration in 2011 approved its use for the treatment of patients with inoperable or metastatic melanoma with a *BRAF* V600E mutation, and Genentech now sells it under the name Zelboraf. However, studies testing vemurafenib alone in metastatic colorectal cancer patients failed to show a benefit. But what if vemurafenib was combined with not one but two other cancer drugs?

Kopetz tested the idea in an earlier trial and, because of promising results, launched a randomized study, S1406, managed by SWOG, a group of cancer clinical trial specialists funded by the National Cancer Institute (NCI) under its National Clinical Trials network. The 106 patients enrolled in S1406 had *BRAF* V600E metastatic colorectal cancer, a late-stage condition in which the cancer has spread to other organs and resisted prior treatment. Roughly half the patients received an investigational regimen consisting of vemurafenib with the combination of irinotecan, a traditional chemotherapy drug, and cetuximab, a therapy targeting the epidermal growth factor receptor (EGFR), which can

cause cancer cells to grow. Other patients received irinotecan and cetuximab alone, a standard treatment for metastatic colorectal cancer. If cancer progressed for patients getting standard treatment, they were given the option to try the vemurafenib regimen.

Results showed that patients who got the treatment with vemurafenib had better progression-free survival rates. Patients who got the typical two-drug combination saw their cancer grow or spread, on average, two months after beginning treatment. That length of time more than doubled for patients who also got vemurafenib, with a median progression time of 4.4 months. The three-drug combination was also much more effective in controlling the disease. Study results showed that 67 percent of patients who got vemurafenib responded to treatment and their tumors stopped growing or shrank. Only 22 percent of patients who got standard treatment had this response.

“This looks like the one-two punch this cancer needs,” Kopetz said. “Vemurafenib inhibits the action of the mutant *BRAF* gene. But that can activate the EFGR cancer signaling pathway. Cetuximab shuts those signals down. So this combination hits not one cancer pathway, but two.”

Dr. Howard Hochster, associate director of the Yale Cancer Center, chair of SWOG’s gastrointestinal research committee, and senior member of the S1406 study team, said in the coming months, researchers will analyze overall survival data – data that can show whether the vemurafenib combination helps people live longer.

“If those findings are positive, this will set a new standard of care,” Hochster said. “That’s big news. About 60,000 people are diagnosed in the U.S. with metastatic colorectal cancer each year, and about 7 percent have a *BRAF* mutation. So each year, this could help thousands of people who have no effective course of treatment.”

Along with Kopetz and Hochster, the S1406 team includes: Shannon McDonough of Fred Hutchinson Cancer Research Center; Dr. Van Karlyle Morris of MD Anderson Cancer Center; Dr. Heinz-Josef Lenz of USC Norris Comprehensive Cancer Center; Dr. Anthony Magliocco of Moffitt Cancer Center; Dr. Chloe Evelyn Atreya of UCSF Helen Diller Comprehensive Cancer Center; Dr. Luis A. Diaz of Johns Hopkins Kimmel Cancer Center; Dr. Stephen E. Wang of Kaiser Permanente and UC Davis Medical Center; Dr. Christopher Hanyoung Lieu of University of Colorado School of Medicine; Dr. S. Gail Eckhardt of University of Colorado School of Medicine; Dr. Thomas John Semrad of UC Davis Health System; Dr. Katherine Guthrie of Fred Hutchinson Cancer Research Center; and SWOG protocol coordinator Kimberly Kaberle.

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