Increased Detection Sensitivity for KRAS Mutations Enhances the Prediction of Anti-EGFR Monoclonal Antibody Resistance in Metastatic Colorectal Cancer

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Abstract

Purpose: KRAS mutations represent the main cause of resistance to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (MoAbs) in metastatic colorectal cancer (mCRC). We evaluated whether highly sensitive methods for KRAS investigation improve the accuracy of predictions of anti-EGFR MoAbs efficacy.

Experimental Design: We retrospectively evaluated objective tumor responses in mCRC patients treated with cetuximab or panitumumab. KRAS codons 12 and 13 were examined by direct sequencing, MALDI-TOF MS, mutant-enriched PCR, and engineered mutant-enriched PCR, which have a sensitivity of 20%, 10%, 0.1%, and 0.1%, respectively. In addition, we analyzed KRAS codon 61, BRAF, and PIK3CA by direct sequencing and PTEN expression by immunohistochemistry.

Results: In total, 111 patients were considered. Direct sequencing revealed mutations in codons 12 and 13 of KRAS in 43/111 patients (39%) and BRAF mutations in 9/111 (8%), with almost all of these occurring in nonresponder patients. Using highly sensitive methods, we identified up to 13 additional KRAS mutations compared with direct sequencing, all occurring in nonresponders. By analyzing PIK3CA and PTEN, we found that of these 13 patients, 7 did not show any additional alteration in the PI3K pathway.

Conclusions: The application of highly sensitive methods for the detection of KRAS mutations significantly improves the identification of mCRC patients resistant to anti-EGFR MoAbs. Clin Cancer Res; 17(14); 4901–14. ©2011 AACR.