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Clinical Cancer Research

Predictive Biomarkers and Personalized Medicine

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

Francesca Molinari[1], Lara Felicioni[3], Michela Buscarino[4], Sara De Dosso[5], Fiamma Buttitta[3], Sara Malatesta[3], Alessandra Movilia[6], Marco Luoni[7], Renzo Boldorini[8], Oscar Alabiso[9], Salvatore Girlando[10], Barbara Soini[11], Alessandra Spitale[2], Federica Di Nicolantonio[4,12], Piercarlo Saletti[5], Stefano Crippa[1], Luca Mazzucchelli[1], Antonio Marchetti[3], Alberto Bardelli[4,12], and Milo Frattini[1]

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.*