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Evaluation of tumor gene expression and *K-Ras* mutations in FFPE tumor tissue as predictors of response to cetuximab in metastatic colorectal cancer

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Abstract: Background: The anti-EGFR monoclonal antibody cetuximab shows activity in a subset of patients with metastatic colorectal cancer (mCRC). This study was conducted to discover and validate markers that are found to be associated with disease control and improved progression-free survival (PFS) time in patients treated with cetuximab.

Methods: Formalin-fixed paraffin-embedded primary tumors of 226 patients from three studies of cetuximab monotherapy in advanced mCRC were retrospectively assayed for *K-Ras* mutations and for expression of candidate genes. The expression of *K-Ras* sequences (7 mutations and 1 wild-type) and 102 candidate genes were measured by quantitative RT-PCR. Statistical associations of mutation and gene expression with disease control (CR+PR+SD) or PFS were determined.

Results: 82 (36%) of the 226 analyzed samples had *K-Ras* mutations. Patients whose tumors did not have *K- Ras* mutations had a significantly higher disease control rate (60%) than those with *K-Ras* mutations (23%) ($p << 0.001$). Among all 226 patients, quantitative expression of 40 genes was significantly associated with disease control ($p<0.05$) after adjusting for multiplicity. Among 144 patients without *K-Ras* mutation, 31 genes were significantly associated with disease control ($p<0.05$) after adjusting for multiplicity. Genes that were strongly associated with disease control in both analyses included genes encoding the EGFR ligands epiregulin (EREG) and amphiregulin (AREG). Based on these results, we have developed multi-gene predictors that incorporate EREG and AREG, which when used in conjunction with *K-Ras* mutation status increase the ability to predict who might benefit from cetuximab treatment over *K-Ras* mutation status alone.

Conclusions: A multi-parameter marker test comprising of *K-Ras* mutation status in combination with the expression levels of a small number of genes could be developed further to select patients for cetuximab therapy. Applicability of this test to cetuximab combination therapy should be explored.

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