

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## IN FOCUS: Colorectal Cancer

### *K-Ras* and Sensitivity to EGFR Inhibitors in Metastatic Colorectal Cancer

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**H&O** What is the background of research on *K-Ras* as a predictor of sensitivity to epidermal growth factor receptor inhibitors?

**CE** Two monoclonal antibodies that inhibit the epidermal growth factor receptor (EGFR) are currently approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer: cetuximab (Erbix, Bristol-Myers Squibb/ImClone) and panitumumab (Vectibix, Amgen). Cetuximab is a chimeric monoclonal antibody indicated for use in patients who have progressed on irinotecan-based therapy or are intolerant of irinotecan-based therapy. Panitumumab is a fully human monoclonal antibody indicated for use as a single agent in patients who have progressed on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapeutic regimens. Previously, it was required that patients' tumors overexpress EGFR in order to receive these therapies. It was originally believed that there was a correlation between degree of EGFR expression and clinical response to anti-EGFR therapy. However, it is now known that there is no correlation between the degree of EGFR expression and response to these agents. As a result, researchers began to look into other potential predictive and prognostic markers of anti-EGFR agents. Identification of a predictive marker to anti-EGFR therapy would not only guide efficacy of therapy but also protect patients from exposure to the potential toxicities associated with this class of agents,

including dermatologic toxicities and infusion reactions. Normally, ligand binding of the extracellular EGFR receptor results in phosphorylation of the intracellular tyrosine kinase domain and subsequent downstream activation of the Ras/MAPK pathway, resulting in cellular proliferation and impaired apoptosis. Therefore, competitively inhibiting ligand binding with an anti-EGFR monoclonal antibody should result in inactivation of these downstream pathways. Researchers thus began to test the hypothesis that the presence of a mutation in the *K-Ras* oncogene may be associated with resistance to anti-EGFR agents. Pivotal data on *K-Ras* were presented at the European Cancer Organisation (ECCO) meeting in Barcelona, Spain, in September 2007.

**H&O** What were the findings of this research?

**CE** Although there were some earlier, smaller studies, the data presented at the 2007 ECCO meeting represent the largest population of patients in whom *K-Ras* was assessed as a predictive marker for anti-EGFR therapy. In this study, Dr. Amado and colleagues analyzed tumor samples from patients treated with panitumumab versus best supportive care (BSC) in metastatic colorectal cancer to distinguish patients with mutant or wild-type (WT) *K-Ras* and their clinical outcome. In general, approximately 30–40% of patients with colorectal cancer are considered to have mutant *K-Ras*. Presence of the *K-Ras* mutation was tested by using a *K-Ras* identification kit which is able to detect 7 somatic mutations in codons 12 and 13. Of the 463 patients, 92% were evaluated for the presence of a *K-Ras* mutation, of whom 184 (43%) harbored the mutation. Of the *K-Ras* mutant patients, the median progression-free survival was 7.4 versus 7.3 weeks for the panitumumab versus BSC arms, respectively. Hence, none of these patients responded to therapy with panitumumab. In comparison, of the WT *K-Ras* population, 17% had a partial response to panitumumab; the median progression-free survival was 12.3 versus 7.3 weeks for the panitumumab versus BSC arms, respectively. Of those patients treated with panitumumab, the median overall survival was superior in those with WT versus mutant *K-Ras*, resulting in a median overall survival of 8.1 months versus 4.9 months, respectively.

The investigators concluded that their findings of the correlation between mutant *K-Ras* and a lack of efficacy for panitumumab warrants further investigation and that *K-Ras* genotyping should be considered in all metastatic colorectal patients who are to be treated with panitumumab. It is important to note that these data were based on single-agent panitumumab, and additional ongoing research is assessing the utility of *K-Ras* as a predictive marker based on combinations of anti-EGFR therapy and chemotherapy. Furthermore, researchers are retrospectively evaluating data from completed combination-therapy trials.

### H&O Is *K-Ras* mutation status being used as an eligibility criterion in planned studies?

**CE** Yes. Some investigators believe that *K-Ras* mutation status should be used to determine whether or not a patient is a candidate to receive anti-EGFR therapy in clinical trials. Other trials are substratifying based on *K-Ras* status. Researchers are also assessing the utility of other predictive markers of response to therapy with cetuximab, such as the ligands amphiregulin and epiregulin. Data from one small study by Dr. Khambata-Ford and colleagues of patients treated with single-agent cetuximab suggest that epiregulin and amphiregulin expression may help to predict for outcome. The investigators concluded that cetuximab confers significantly better disease control in patients whose tumors do not harbor *K-Ras* mutations ( $P=.0003$ ) and that patients with tumors that express high levels of the EGFR ligands epiregulin and amphiregulin are also more likely to achieve disease control with cetuximab ( $P=.000015$  and  $P=.000025$ , respectively). Identification of these ligands is not as far along in development as that of *K-Ras*. However, there is a good deal of interest in these ligand markers, and I believe additional data will soon become available. Research will likely continue to assess the ligands in conjunction with *K-Ras*.

### H&O How do these findings affect the clinical treatment picture for patients with colorectal cancer?

**CE** Patients whose tumors do have mutant *K-Ras* are less likely to be offered anti-EGFR therapy going forward because of the correlation between WT *K-Ras* and improved response and progression-free and overall survival. Beyond the avoidance of toxicities associated with EGFR inhibitors, knowing whether patients will respond to these agents will also allow a reduction in the financial burden associated with these agents. There are obviously other unidentified markers that may explain the lack of response to anti-EGFR therapy in patients who have WT *K-Ras* tumors. Furthermore, the question arises as to how to treat a patient who has progressive disease following

treatment with bevacizumab (Avastin, Genentech) but has mutant *K-Ras*. There are other potential pathways downstream of *K-Ras* that could be of interest in this setting. For example, the MEK inhibitors, which are in phase I/II development now, may have potential.

### H&O Is *K-Ras* mutation status relevant in other solid-tumor malignancies?

**CE** *K-Ras* mutations have been found in other solid-tumor malignancies, including cancers of the lung and pancreas. In pancreatic cancer, cetuximab has recently been demonstrated not to be of added benefit in a randomized, phase III trial of gemcitabine (Gemzar, Eli Lilly) with or without cetuximab conducted by the Southwest Oncology Group. Greater than 70% of patients with pancreatic cancer have mutant *K-Ras*, but to date, it does not serve as a predictive marker. There are data from lung cancer trials to show that mutated *K-Ras* is also associated with a lack of response to the small-molecule tyrosine kinase inhibitors of EGFR, erlotinib (Tarveca, Genentech) and gefitinib (Iressa, AstraZeneca) and is a predictive marker in lung cancer.

### H&O Do you believe screening for *K-Ras* will become routine in the setting of colorectal cancer?

**CE** Many physicians both in the academic and community settings found the data on the predictive value of *K-Ras* to be significant. In the past, clinicians would prescribe anti-EGFR therapy without any knowledge of whether it would be effective. Now, we have a predictive marker to help guide us in treatment decision making. It is expected the European Agency for the Evaluation of Medicinal Products will be routinely screening patients prior to administration of panitumumab for *K-Ras* mutation status. Currently, at our institution, The University of Texas M. D. Anderson Cancer Center, screening patients for *K-Ras* has become a standard procedure to help guide therapy. The tests used to screen for *K-Ras* mutation status are relatively easy to use, but because multiple assays exist, physicians have many options. It remains to be seen whether a standard assay will be adopted in the United States.

### Suggested Readings

- Freeman D, Juan T, Meropol NJ, et al. Association of somatic KRAS gene mutations and clinical outcome in patients (pts) with metastatic colorectal cancer (mCRC) receiving panitumumab monotherapy. *Eur J Cancer*. 2007;5(4):Abstract 3014.
- Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and *K-Ras* mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol*. 2007;25:3230-3237.
- Van Cutsem E, Peeters M, Siena S. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*. 2007;25:1658-1664.