K-Ras Mutations Are Changing Practice in Advanced Colorectal Cancer

By Caroline McNeil

Last month, an expert panel said that patients with advanced colorectal cancer should not be treated with cetuximab or panitumumab if their tumors have mutations in the K-Ras oncogene. The major new recommendation from the National Comprehensive Cancer Network (NCCN), based on a consensus of experts at 21 comprehensive cancer centers across the United States, reflects a change in practice that is already affecting thousands of patients, altering reimbursement policies, and changing the design of clinical trials.

“This really is a sea change in practice,” said Leonard Saltz, M.D., a professor of medicine at Memorial Sloan-Kettering Cancer Center in New York and a member of the NCCN colorectal cancer panel.

Cetuximab and panitumumab are monoclonal antibodies targeted at epidermal growth factor receptors (EGFRs) on tumor cells. They work by blocking the growth signals that the receptor sends to the cell nucleus. In trials, both have improved progression-free survival in metastatic colorectal cancer and have won approval from the U.S. Food and Drug Administration and the European Medicines Agency.

But data from single-arm trials published last year suggested that cetuximab and panitumumab worked only in some patients—those with nonmutated, or wild-type, K-Ras genes. This year, several analyses of results from large, prospective, randomized trials added weight to those earlier findings. In one trial, led by Rafael Amado, M.D., at Amgen in Thousand Oaks, Calif., the improvement in progression-free survival was limited to patients with wild-type K-Ras; those with mutant K-Ras had progression-free
survival similar to patients in the control arm who were on the best supportive care. On the basis of this analysis, which was first reported at the European Cancer Conference in October 2007 and published in the Journal of Clinical Oncology in April, the European Medicines Agency amended its labeling for panitumumab, restricting its use to patients with wild-type K-Ras tumors.

Even more supporting data came out at the annual meeting of the American Society of Clinical Oncology (ASCO) in June. At the plenary session, Eric Van Cutsem, M.D., Ph.D., from the Gastroenterology Hospital in Leuven, Belgium, reported similar results from a retrospective analysis of patients on the CRYSTAL trial. This large phase III trial had shown that cetuximab improved progression-free survival when added to standard first-line treatment for metastatic colorectal cancer. However, that benefit now appears to be limited to patients with wild-type K-Ras Van Cutsem reported.

Another study presented at the ASCO meeting—a retrospective analysis of the results of the European OPUS trial of cetuximab in colorectal cancer—also showed that patients with K-Ras mutant tumors had a lower progression-free survival on the cetuximab arm than patients with wild-type K-Ras on that arm. Most recently, an analysis of the National Cancer Institute of Canada’s CO.17 trial showed that patients with mutant K-Ras tumors, who were taking cetuximab, had a 50% shorter progression-free and overall survival compared with those with wild-type K-Ras. The results were published in the New England Journal of Medicine in October.

Laboratory studies have shown that K-Ras, which is part of the signaling pathway between the EGFR and the cell nucleus, is continually activated when it has specific mutations on codons 12 and 13. The constantly turned on protein continues to send growth signals to the nucleus, even when the EGFR is blocked.

“It is apparent that patients with mutant K-Ras do not derive benefit from the addition of either cetuximab or panitumumab. I believe it is now warranted to test all patients being considered for [EGFR-directed therapy] for RAS mutations,” she said.

Clinical Effect
This conclusion, now shared by NCCN and others, will affect an estimated 35%–45% of patients with advanced colorectal cancer. The European regulatory agency has already changed the cetuximab label, restricting its use, like that of panitumumab, to patients with wild-type K-Ras.

In the U.S., the FDA has not announced whether it is considering label changes, but insurers are taking note of the findings. Next year, United Health Care, one of the nation’s largest private insurers, will start covering panitumumab and cetuximab only for patients with wild-type K-Ras, said Lee Newcomer, M.D., the company’s senior vice president for oncology. United has been using the NCCN guidelines since March to guide coverage decisions. However, it will not require the K-Ras test for coverage until the spring quarter of 2009 to give community hospitals time to set up testing arrangements, Newcomer said. United will require the test only for the initial use of cetuximab or panitumumab.

The Centers for Medicare and Medicaid Services also use the NCCN guidelines (along with other drug compendia) to make coverage decisions, so the NCCN recommendations are expected to affect almost anyone older than 65 years with advanced colorectal cancer.

Anecdotal evidence suggests that many oncology practices are already testing for K-Ras mutations before using one of the EGFR-targeted agents. Informal reports from large national laboratories, for example, indicate that they have had thousands of requests for the tests since the ASCO meeting, Newcomer said.

Saltz said that testing for K-Ras mutations has been guiding colorectal cancer therapy since last January at Memorial Sloan-Kettering.

“Some people see this as bad news because it means that 35%–45% of metastatic [colorectal cancer] patients won’t be treated with these agents,” he said. “My argument is that it’s a good thing since we can avoid the risks, discomfort, and cost of these agents in a patient with no realistic chance of benefit.”

Saltz also pointed out that in some trials, not only have patients with K-Ras mutant tumors not responded to cetuximab, but some have had worse progression-free survival than their counterparts in control arms. “We should test for K-Ras mutations, and we should act on the results of that test. Patients whose tumors have K-Ras mutations should not be treated, at any time in the course of their therapy, with an anti-EGFR monoclonal antibody,” he said.

Future Research
One of the most immediate consequences of the ASCO reports was the amendment of three large, ongoing cetuximab trials for patients with colorectal cancer. The eligibility criteria for the phase III, cooperative group trials in colorectal cancer, supported by the National Cancer Institute, have been modified, and from now on, only patients with wild-type K-Ras tumors will be accrued. “We felt the risk–benefit ratio for colorectal cancer patients with mutant K-Ras tumors had changed,” said Margaret Mooney, M.D., in NCI’s Cancer Therapy Evaluation Program. “The preponderance of the evidence—from the ASCO trials, from the single-arm studies, from the Amado trial—indicated that patients with mutant K-Ras tumors would not benefit from cetuximab.”
Two of the trials have already been amended. These include CALGB 80405, which is testing cetuximab and/or bevacizumab with the standard treatments known as FOLFOX and FOLFIRI in previously untreated patients with metastatic colorectal cancer, and NCCTG 0147, which is testing FOLFOX with and without cetuximab in stage III colorectal cancer. The third, SWOG 0600, is testing FOLFIRI or irinotecan with cetuximab, plus or minus bevacizumab, in patients with metastatic colorectal cancer that has progressed after first-line therapy that included bevacizumab therapy. “The investigators are in the process of amending this trial,” Mooney said.

The importance of K-Ras mutations does not appear to be limited to colorectal cancer. Studies of non–small-cell lung cancer have suggested that erlotinib and gefitinib, both tyrosine kinase inhibitors targeted at EGFR, are also more effective in patients with wild-type K-Ras. William Pao, M.D., at Memorial Sloan-Kettering and colleagues reported in 2005 that K-Ras mutations on codons 12 and 13 predicted a lack of response to erlotinib and gefitinib as single agents. Several other studies have had similar results since then, including a trial of chemotherapy combined with erlotinib. An estimated 15%–30% of non–small-cell lung cancer patients have mutant K-Ras tumors.

So far, testing for K-Ras mutations to guide non–small-cell lung cancer treatment decisions has not made it into national guidelines, such as NCCN’s. Eckhardt said that “it needs more study. But the data do support continuing efforts to evaluate K-Ras in randomized studies in the other diseases when EGFR-directed therapy is being used or investigated.” At Memorial Sloan-Kettering, Pao said that they have been genotyping non–small-cell lung cancer tumors since 2005 and using the results to guide treatment. “It is becoming more accepted,” he said.

The K-Ras findings—all from retrospective, subgroup analyses of completed trials—have also highlighted the need for prospective biomarker studies. The first such trial, which opened in October, is intended primarily to test whether non–small-cell lung cancer patients with extra copies of EGFR are more likely to respond to erlotinib. But the trial will also evaluate K-Ras mutation status as a secondary endpoint, according to NCI spokesperson Michael Miller. The phase III trial, chaired by the North Central Cancer Treatment Group’s Alex A. Adjei, M.D., Ph.D., at Roswell Park Cancer Center in Buffalo, N.Y., will randomize patients to receive either erlotinib or pemetrexed, which is not targeted at EGFR, after chemotherapy. Known as MARVEL (Marker Validation for Erlotinib in Lung Cancer), or N0723, the trial will accrue patients over 4 years with 1 or 2 years of follow-up.

Although this trial is designed primarily to determine the predictive power of a biomarker, there is increasing pressure for all treatment trials to include biomarker analysis. The results of the retrospective analyses are robust in [colorectal cancer],” Eckhardt said, but “in the future, we should expend greater efforts to develop biomarkers in concert with early clinical trials so that biomarker validation becomes the norm in large randomized phase III studies.”