ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Guest Section Editor: Axel Grothey, MD

Colorectal Cancer in Focus

Testing for *RAS* Mutations in Patients With Metastatic Colorectal Cancer

Heinz-Josef Lenz, MD
Professor of Medicine and Preventive Medicine
Division of Medical Oncology
Keck School of Medicine at the University of Southern California
Los Angeles, California

H&O When should oncologists order *RAS* testing for their patients with metastatic colorectal cancer (CRC)?

HJL The best time for *RAS* testing in metastatic CRC is at diagnosis. We have evidence that *RAS* testing is important in decision-making for first-, second-, and third-line therapy. Although *RAS* testing has no role in decision-making regarding adjuvant therapy, ongoing research is addressing its prognostic value in this setting.

Some oncologists have raised the possibility of testing all colon cancer samples at the time of initial resection in case the tumors recur and tissue is difficult to obtain from the original surgery. I personally have not been doing this, but all patients with metastatic CRC need to be tested at the time of diagnosis because this will affect treatment decisions.

H&O How should oncologists use the results of RAS testing to guide treatment with EGFR-targeting agents?

HJL If any mutation is present in *KRAS* or *NRAS*, EGFR inhibitors should not be used. If no mutation is present, EGFR inhibitors should be considered as possible treatment options for newly diagnosed metastatic disease.

H&O Should patients with metastatic CRC also be tested for *NRAS*?

HJL At the moment, *NRAS* testing is not available in most laboratories in the United States. I do think, however, that based on the data recently presented at the American Society of Clinical Oncology (ASCO) annual meeting, the European Society for Medical Oncology (ESMO) annual meeting, and the World Congress on Gastrointestinal Cancer, testing should include exons 2, 3, and 4 of *KRAS* and exons 2 and 3 (and possibly 4) of *NRAS*. The presence of mutations in any of these exons has been shown to predict no benefit from epidermal growth factor receptor (EGFR) inhibitors, such as panitumumab (Vectibix, Amgen) and cetuximab (Erbitux, Bristol-Myers Squibb and Lilly); in fact, harm may occur when EGFR inhibitors are given with combination chemotherapy, such as fluorouracil, leucovorin, and oxaliplatin (FOLFOX).

The European Medicines Agency (EMEA) has already mandated that physicians do *KRAS* and *NRAS* testing on these exons. Only after testing can panitumumab be given in combination with FOLFOX.

The EMEA acted very quickly in demanding *KRAS* and *NRAS* testing, and the US Food and Drug Administration (FDA) is sure to follow suit in approving these

tests. US physicians should begin testing for *NRAS* as soon as the test is available.

H&O Which codons should be tested?

HJL All mutations in exons 2, 3, and 4 of *KRAS* and exons 2 and 3 of *NRAS* that were described in the PRIME (Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy); PEAK (A Phase 2 Study of Panitumumab Plus mFOLFOX6 vs Bevacizumab Plus mFOLFOX6 for First Line Treatment of Metastatic Colorectal Cancer Subjects With Wild-Type *KRAS*); and FIRE-3 (5-FU, Folinic Acid and Irinotecan [FOLFIRI] Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First Line Treatment Colorectal Cancer [CRC]) trials should be tested. Early results from PEAK were presented at the 2013 ASCO Gastrointestinal Cancers Symposium, and updated expanded *RAS* analyses from FIRE-3 were presented at the 2013 ESMO annual meeting.

Access to expanded *RAS* testing is currently limited, but I am sure that all of the US laboratories will add tests for these exons in the near future. If we test for the additional mutations in exons 3 and 4 of *KRAS*, as well as exons 2 and 3 of *NRAS*, we will identify between 15% and 20% of *KRAS/NRAS* mutations that would be considered wild-type based on testing of exon 2 alone. This has important clinical significance in selecting patients for EGFR inhibitors.

The codons that we are looking at specifically in both *NRAS* and *KRAS* are codons 12 and 13 in exon 2, codons 59 and 61 in exon 3, and codons 117 and 146 in exon 4.

H&O How have the PRIME, PEAK, and FIRE-3 studies affected our understanding of *RAS* mutations?

HJL PEAK was a randomized, phase 2 trial that compared FOLFOX plus bevacizumab (Avastin, Genentech) with FOLFOX plus panitumumab. The study found that with expanded *RAS* analyses, the progression-free survival was significantly longer with FOLFOX/panitumumab than with FOLFOX/bevacizumab. The study also showed that the additional mutations in *KRAS* and *NRAS* that were identified provided the same negative prediction of response to EGFR inhibitors as did the *KRAS* mutations in exon 2. With better patient selection, the endpoint of progression-free survival became statistically significant.

Even more convincing were the results of the PRIME trial. PRIME was a randomized, phase 3 trial of more than 1100 patients randomized to either FOLFOX or FOLFOX/panitumumab. The increase in overall survival —from 19.7 to 23.9 months in patients with a *KRAS* exon 2 mutation—was not statistically significant. When all of the additional *KRAS* and *NRAS* mutations were included, however, overall survival was significantly increased to 26 months (P=.043)

These data from PEAK and PRIME support the importance of *RAS* testing; better patient selection based on *KRAS* and *NRAS* testing leads to better clinical outcomes with EGFR inhibitors.

Data from the FIRE-3 trial that were recently presented at the 2013 European Cancer Congress in Amsterdam found that with additional *KRAS* and *NRAS* testing, overall survival went up to 33 months. All the data have suggested that patients with wild-type *KRAS* and *NRAS* on expanded analyses benefit from EGFR inhibitors.

H&O What other trials are looking at the role of *RAS* mutations in the treatment response?

HJL An important trial that we hope to see presented at the ASCO meeting in 2014 is CALGB (The Cancer and Leukemia Group B)/SWOG C80405, which is the largest head-to-head comparison between cetuximab and bevacizumab. The majority of patients in this trial received FOLFOX as the backbone of chemotherapy, whereas in FIRE-3, all patients received FOLFIRI. The results of this trial could be important in evaluating whether cetuximab in combination with FOLFOX or FOLFIRI will cause harm in patients with mutant-type *RAS*.

H&O What do oncologists need to know about the various *RAS* tests that are in use?

HJL We are seeing the development of increasingly sensitive technologies for detecting *RAS* mutations.

With gene sequencing or allele-specific polymerase chain reaction, we were able to pick up mutations that affected 1% to 5% of cells. With newer technologies such as beaming technology, we are able to pick up mutations that affect just 0.1% of cells—1 out of a thousand. What we do not know is whether such low levels of mutation fraction will have clinical significance, and at what point EGFR inhibitors should be withheld. There is some chance that in the future, we may begin to consider the fraction of the mutation.

H&O What are other biomarkers can be used to further refine the patient population eligible for EGFR antibody therapy?

HJL The most promising marker beside *KRAS* and *NRAS* is PI3-kinase. The other gene is *PTEN*, which has been associated with resistance but has not been validated in prospective trials. Another promising marker is the

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expression level of EGFR ligands amphiregulin and epiregulin. All of these are being tested in the large FIRE-3 and CALGB/SWOG C80405 clinical trials.

Suggested Readings

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369(11):1023-1034.

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Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK (study 20070509): a randomized phase II study of mFOLFOX6 with either panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) in patients (pts) with unresectable wild-type (WT) *KRAS* metastatic colorectal cancer (mCRC) [ASCO Gastrointestinal Cancers Symposium abstract 446]. *J Clin Oncol*. 2012;30(suppl 34).

Stintzing S, Jung A, Rossius L, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: a randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. Presented at: European Cancer Congress 2013; September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract LBA17.