Moving Forward With Expanding to an “All-RAS Mutational Analysis” in Metastatic Colorectal Cancer: Beyond KRAS Mutations

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The advent of biologic agents such as those that target the epidermal growth factor receptor (EGFR) has favorably impacted outcomes for patients with metastatic colorectal cancer (mCRC). An important downstream component of EGFR is the RAS signaling pathway. RAS proteins mainly include KRAS and NRAS. Activating KRAS mutations occur in 30% to 50% of colorectal tumors, most commonly in exon 2 as point mutations in codon 12 followed by mutations in codon 13. NRAS mutations occur in 3% to 5% of colorectal tumors.

Since initial approval of the EGFR-directed monoclonal antibodies cetuximab (2004) and panitumumab (2006) for clinical use in mCRC, strategies to improve selection of the appropriate patients have constantly been refined. In 2005, the first confirmation that immunohistochemical analysis for EGFR expression has no predictive value in selecting or excluding patients allowed the use of these agents to be expanded to all eligible patients. In November 2008, the NCCN Colorectal Panel recommended routine KRAS (exon 2 codons 12/13) mutational testing based on consistent findings from multiple retrospective analyses of large clinical trials confirming that KRAS mutational status had predictive value for the use of anti-EGFR monoclonal antibodies in mCRC. This move effectively restricted the use of these agents to approximately 60% of all patients with nonmutated KRAS mCRC, sparing the remainder of patients the risk of toxicities and the cost in the absence of a clear benefit.

After this restriction, early reports suggested a possible clinical benefit for cetuximab in patients with mCRC with KRAS G13D mutations. However, another report from 3 randomized trials failed to suggest a similar benefit from panitumumab in the presence of a KRAS G13D mutation. These inconsistent results, the absence of a clear biology, and the overall poor outcome associated with the KRAS G13D mutation made this finding inconsequential to actual clinical practice pending further clinical validation. The NCCN Colorectal Cancer Panel continues to recommend against the use of anti-EGFR therapy in patients with codon 13 mutations.

More recent data suggest that testing for additional RAS mutations (KRAS exons 3 or 4 and NRAS exon 1, 2, 3, or 4) present in 16% of tumors previously identified as KRAS (exon 2 codons 12/13) wild-type may allow for further refinement. A predefined retrospective analysis of the large prospective randomized trial PRIME (FOLFOX4 [leucovorin, 5-FU, and oxaliplatin] +/- panitumumab in first-line treatment of mCRC) suggests that the presence of these additional RAS mutations predict for lack of benefit. Data from the large phase II randomized study PEAk (FOLFOX plus panitumumab vs FOLFOX plus bevacizumab in first-line treatment of mCRC) confirmed the results from PRIME. This initiated a label change clarifying that panitumumab in combination with oxaliplatin-based chemotherapy is not indicated in the treatment of patients with RAS (KRAS or NRAS) mutation-positive mCRC.

Despite these preliminary findings, there was very little uptake for incorporating an all-RAS mutational analysis before using EGFR inhibitors in mCRC. Why the initial reluctance? In addition to the lack of available standardized testing to include all RAS mutations, additional confirmatory data from studies, especially those incorporating cetuximab or irinotecan (which remains the preferred chemotherapeutic backbone...
for use with EGFR inhibitors), were needed before wide clinical applicability could be adopted.

At the 2013 European Cancer Congress, presentation of a retrospective analysis of the data from the randomized FIRE-3 study (FOLFIRI [leucovorin, 5-FU, and irinotecan] plus cetuximab vs FOLFIRI plus bevacizumab in first-line treatment of mCRC) suggested that the presence of the additional RAS mutations (KRAS exons 3 or 4 and NRAS exon 1, 2, 3, or 4) predict for lack of benefit. Importantly, and similar to concerning findings from PRIME, FIRE-3 confirmed a potential harmful effect and loss of benefit for administration of EGFR inhibitors in the presence of the additional described RAS mutations.

The consistent findings from the FIRE-3, PRIME, and PEAK trials support expansion of genetic profiling for patients with mCRC to an all-RAS mutational analysis. This will allow patients with any RAS mutation to be excluded from exposure to agents associated with potential harm and unnecessary costs.

The biggest challenge, however, remains wide patient accessibility to standardized expanded RAS mutational testing. Although the additional RAS mutations are rare, both payers and providers should note that the cost of additional testing is relatively small compared with the costs of administering EGFR inhibitors in this subset of patients.

Expanding RAS mutational testing improves selection and, ultimately, outcomes for patients with mCRC who are eligible to receive EGFR inhibitors. Unfortunately, a significant proportion of patients with nonmutated RAS mCRC receiving EGFR inhibitors will not show response, and resistance will eventually develop in all tumors. The expansion of RAS mutational testing increases the overall pool of patients with no further options beyond antiangiogenic strategies by appropriately excluding those with RAS mutations from receiving EGFR-directed therapies. Because a plateau in the results achieved seems to be approaching again, new strategies for groups who receive minimal or no benefit from EGFR inhibitors continue to be desperately needed. Further refinement will depend on identifying additional biomarkers that predict resistance or response to EGFR inhibitors and other potential targeted therapies. This will certainly pose significant challenges for future prospective trials as we continue to identify increasingly smaller genetically defined subsets of patients with mCRC. A centralized biorepository with prospective biomarker analysis and validation and improved study design will make this effort likely to succeed in mCRC, as already exemplified in lung and breast cancers.

For the past few years, strategies to improve the selection of patients for anti-EGFR therapy have constantly been refined. Given the consistent results now seen in multiple trials, upfront determination of an all-RAS mutational analysis beyond KRAS exon 2 to include KRAS exons 2 through 4 and NRAS exons 1 through 4 should be strongly considered. Patients with any RAS mutation should be excluded from receiving cetuximab or panitumumab. An urgent effort, however, is required to improve access to standardized expanded RAS mutational testing to help achieve this goal.