ASCO Provisional Clinical Opinion: *KRAS*, Cetuximab, and Panitumumab—Clinical Implications in Colorectal Cancer

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The impetus for ASCO's provisional clinical opinion (PCO) is to alert oncologists of emerging information from recent clinical trials that will assist them in treatment selection of monoclonal antibody therapy for their patients with metastatic colorectal cancer. Accumulating evidence strongly suggests that cetuximab and panitumumab are ineffective in patients with *KRAS* mutations at codon 12 or 13. Thus, colorectal cancer patients with these mutations should be spared the toxicity and economic cost of an ineffective therapy. Presently, it is unknown whether there are other *KRAS* mutations that render anti-EGFR agents ineffective.

The ASCO Health Services Committee (HSC) is charged with accepting, reviewing, and approving proposed PCO topics on behalf of the ASCO Board of Directors. The ASCO HSC algorithm identified the emerging data on *KRAS* mutations at codon 12 and 13 that render EGFR inhibitors ineffective in colorectal cancer. As the ASCO HSC began its work on the *KRAS* PCO, it discovered that the BlueCross BlueShield Association (BSBC) Technology Evaluation Center (TEC) was conducting a comprehensive systematic review of the available evidence on *KRAS* genotype and efficacy of anti-EGFR monoclonal antibody therapy in metastatic colorectal cancer. BCBS TEC made available to the ad hoc committee of the ASCO HSC its reviewed data on *KRAS* mutation and the efficacy of monoclonal anti-EGFR antibodies in colorectal cancer.² This collaborative sharing of data between BCBS TEC and the ASCO HSC ad hoc committee facilitated the promptness with which the PCO could be issued.

Targeted therapies have rapidly gained traction in the treatment of advanced colorectal cancer and are under active investigation in the adjuvant setting. The journey from bench to bedside has been rapid and has generated questions as to how to best optimize therapy. Evidence from recent clinical trials has given us new insight.

The two putative targets are transmembrane receptors that activate intracellular signaling pathways via tyrosine kinase phosphorylation. First is the epidermal growth factor receptor (EGFR; Erb 1 or HER1) that is regulatory in the process of cellular proliferation, adhesion, migration, and cell survival, and is the target of this discussion. Second is the vascular epithelial growth factor receptor (VEGF) that activates a signaling pathway for angiogenesis.³

Two monoclonal antibodies are available that bind selectively to EGFR and block physiologic ligands from binding and

activating EGFR, thus preventing tyrosine kinase phosphorylation and the downstream signaling that follows:

cetuximab and panitumumab. The former is a chimeric monoclonal antibody (immunoglobulin [Ig] G1), and the latter a fully humanized monoclonal antibody (Ig G2). Both bind with EGFR and block EGFR extracellular ligand-binding domains and, therefore, downstream signaling.

Post hoc analyses of five recent randomized and five single-arm studies in which either cetuximab or panitumumab was used demonstrated that the efficacy of these monoclonal antibodies is dependent on the colorectal cancer having wild-type *KRAS*.^{4–11} *KRAS* is a small guanosine phosphate-binding protein that is a key component of the MAPK signaling pathway that regulates cellular proliferation and is activated by phosphorylation of the EGFR tyrosine kinase receptor. Specific *KRAS* mutations render *KRAS* constitutively activated and able to independently initiate MAPK-mediated signaling without activation of the EGFR pathway.

Pathologists have been testing colon cancers for EGFR receptor expression by immunohistochemistry for a long time. The testing is done using well-characterized commercial reagents which perform adequately. However, the testing has not been useful because there is poor correlation between EGFR protein expression in colorectal carcinoma and responsiveness to EGFR antagonists. Patients are treated if any protein expression is demonstrated.

This situation contrasts markedly with the recently reported results on colorectal carcinomas of assays detecting mutations in codons 12 and 13 of the *KRAS* gene, located on chromosome 12.

Pathologists play a key role in the *KRAS* testing process. The pathologist needs to select the block of tumor tissue for the assay so that it contains predominantly viable tumor cells without necrosis or inflammation. The pathologist must also select the laboratory to do the testing, if it is not available in that location. There are two types of tests that may be used, each with distinct advantages and disadvantages. The gold-standard method is direct sequencing analysis, which is labor intensive and requires significant time to perform. The newer method, of which there are several variations, is to do real-time amplification (PCR) of specific areas (codons) of the gene. This latter method is rapid and less expensive, but the specific areas to be probed must be selected in advance. Newer methods of amplification allow smaller sample sizes

and have lower detection limits, but they have not been sufficiently studied to make additional conclusions. Both of the current methods have significant detection limits. However, the significance of a minority of tumor cells possessing the mutation is currently unknown. The pathologist is responsible to define the best laboratory assay based on which assay is readily available in a laboratory with adequate laboratory quality assurance procedures and timely, accurate results. Finally, the pathologist will receive the laboratory results on the assay and must create a pathology report which clearly defines the results in terms that the oncologists treating the patient can understand. He or she must be able to explain the precise result and defend the choice of assay and laboratory to these treating physicians based on his/her thorough knowledge of the options.

The report must clearly describe what tissue was used for the assay (laboratory case number and tissue block number), interpret the result as being either normal or abnormal, and cite the PCO recommendations based on this interpretation. The report should also describe what assay was done, detection limits of the assay, what mutation was found, and what quality measures are in place by the laboratory chosen to do the testing.

KRAS analysis for mutation at codon 12 and 13 averages about \$450.00, which is small in comparison to the cost of a course of either cetuximab or panitumumab. But some health insurance companies do not yet cover this testing, and the ordering clinician should assist the patient with determining whether coverage for testing will be provided. If *KRAS* testing

is a noncovered service, it would be appropriate for the clinician and/or the state oncology society to have a discussion with the health insurance company's medical director regarding the rationale of testing and the desire to avoid giving an ineffective agent that has significant cost and toxicity.

As use of monoclonal antibodies such as cetuximab or panitumumab are not indicated in the adjuvant setting outside a clinical trial, the typical scenario will be a patient who either presents with stage IV disease or has relapsed after a prior, potentially curative resection. In this situation, the managing oncologist should coordinate with the pathologist to have the paraffin block retrieved so that the assay for *KRAS* gene mutation analysis can be performed. A priori testing of all newly diagnosed colorectal cancers for the *KRAS* mutation is not necessary or cost effective at this time, as the majority of patients will not develop metastatic disease.

The opinions expressed herein are the authors' and do not necessarily reflect those of the American Society of Clinical Oncology.

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