**KRAS Mutation Analysis in Non-Small Cell Lung Cancer**

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<th>Medical Benefit</th>
<th>Effective Date: 07/01/11</th>
<th>Next Review Date: 03/13</th>
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<tr>
<td>Preauthorization*</td>
<td>No</td>
<td>Review Dates: 05/09, 03/10, 03/11, 03/12</td>
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The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Use Management.** *Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.*

**Description**

The epidermal growth factor receptor (EGFR), a receptor tyrosine kinase (TK), is frequently overexpressed and activated in non-small-cell lung cancer (NSCLC). Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain with a monoclonal antibody, or inhibit intracellular tyrosine kinase activity with a small molecule (tyrosine kinase inhibitor or TKI). These targeted therapies dampen signal transduction through pathways downstream to the EGF receptor, such as the RAS/RAF/MAPK cascade. RAS proteins are G-proteins that cycle between active and inactive forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

The KRAS gene (which encodes for the RAS proteins) can harbor oncogenic mutations that result in a constitutively activated protein, independent of signaling from the EGF receptor, possibly rendering a tumor resistant to therapies that target the EGF receptor.

**TKIs**

Two TKIs are used to treat NSCLC: erlotinib and gefitinib.

Erlotinib (Tarceva®) received approval from the U.S. Food and Drug Administration (FDA) in November 2004 as salvage therapy for advanced NSCLC, based on results of a Phase III clinical trial that demonstrated a modest survival benefit: 6.7 months median survival compared to 4.7 months in the placebo group. Gefitinib (Iressa®) was approved by the FDA in 2003 through the agency’s accelerated approval process, based on the initially promising results of Phase II trials. The labeled indication was limited to patients with NSCLC who had failed two or more prior chemotherapy regimens. However, in December 2004, results of Phase III trials became available, suggesting that gefitinib was not associated with a survival benefit. In May 2005, the FDA revised the labeling of gefitinib to further limit its use to patients who were currently benefiting from the drug, or who had benefited in the past, and that no new patients were to be given the drug.

Although gefitinib fell out of use in the U.S. in 2005, it continued to be used elsewhere in the world, and a study was published (Iressa in NSCLC Trial Evaluating Response and Survival vs. Taxotere, or INTEREST trial) that involved 1,466 patients from 24 countries outside of the U.S. (1) All of the patients had advanced or metastatic disease and had been previously treated with at least one platinum-containing regimen and were randomly assigned to receive either gefitinib or docetaxel. Of the 1,466 patients, 1,433 were able to be evaluated. Objective tumor response rates and progression-free survival (PFS) and overall survival (OS) were similar for the two groups; however, gefitinib was associated with lower rates of treatment-related adverse events than...
docetaxel. The authors stated that based on their findings, they are hopeful that gefitinib can return as a treatment for lung cancer in the U.S.

Because gefitinib is currently in very limited use in the U.S., and only as part of a special access program, this Protocol will only address studies that assess the response to erlotinib in relation to the presence or absence of KRAS mutations in NSCLC.

**Anti-EGFR monoclonal antibodies**

Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Recent conclusive evidence has shown that patients with metastatic colorectal cancer whose tumors harbor KRAS mutations do not respond to EGFR monoclonal antibodies, as summarized in a TEC Assessment. (2) Cetuximab is used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy.

KRAS mutation analysis is commercially available to test NSCLC, and laboratories performing the test include Genzyme Genetics and Medical Solutions™.

Several studies have shown that EGFR and KRAS mutations are mutually exclusive. (3) Although several of the studies outlined in this Protocol that analyzed KRAS mutations also tested for other markers in NSCLC (e.g., EGFR mutations), only the data from each study as they relate to KRAS are presented in the Protocol.

**Related Protocol:**

Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC)

**Corporate Medical Guideline**

Analysis of somatic mutations of the KRAS gene is considered investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitor erlotinib and the anti-EGFR monoclonal antibody cetuximab in non-small cell lung carcinoma.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


