Protocol

KRAS Mutation Analysis in Non-Small-Cell Lung Cancer

(20455)

Medical Benefit		**Effective Date**: 07/01/11	**Next Review Date**: 03/15
Preauthorization	No	**Review Dates**: 05/09, 03/10, 03/11, 03/12, 03/13, 03/14	

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.*** *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 TK 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.

Background

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

Three TKIs are used to treat NSCLC:

- Erlotinib (Tarceva®) was approved by the U.S. Food and Drug Administration (FDA) in November 2004 as salvage therapy for advanced NSCLC, based on one Phase 3 clinical trial that demonstrated a modest survival benefit: 6.7 months median survival compared with 4.7 months in the placebo group. In 2010, erlotinib was additionally approved as maintenance therapy for platinum-sensitive advanced NSCLC, based on one Phase 3 trial that showed a one-month improvement in median overall survival (OS): 12.0 months compared with 11.0 months in the placebo group.
- Gefitinib (Iressa®) was FDA-approved in 2003 through the agency's accelerated approval process, based on initially promising results from Phase 2 trials. The labeled indication was limited to patients with NSCLC who had failed two or more previous chemotherapy regimens. However, in December 2004, Phase 3 trial results became available, suggesting that gefitinib was not associated with a survival benefit. In May 2005, FDA revised gefitinib labeling, further limiting its use to patients who had previously benefitted or were currently benefiting from the drug; no new patients were to be given gefitinib.

- Although gefitinib fell out of use in the U.S. in 2005, it continued to be used elsewhere in the world, and a study of 1466 non-U.S. patients from 24 countries was published in 2005 (Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere, or INTEREST trial). (1) Patients with advanced or metastatic disease who had been previously treated with at least one platinum-containing regimen were randomized to gefitinib or docetaxel. Of 1466 patients, 1433 (98%) were evaluable. Objective tumor response rates, progression-free survival (PFS), and OS were similar between the two groups; however, gefitinib was associated with lower rates of treatment-related adverse events than docetaxel. Based on their findings, the authors expressed their hope that gefitinib may return as a treatment for lung cancer in the U.S.

- Afatinib (Gilotrif™) was FDA-approved in July 2013 for use in patients with *EGFR*-mutated, advanced NSCLC. Afatinib is not reviewed in this Protocol. (See Related Protocols, below.)

Because gefitinib is only available in the U.S. through a special access program, this Protocol will address only studies of erlotinib in 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 2008 TEC Assessment. (2) Cetuximab is used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy. Panitumumab is not generally used in NSCLC.

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

Several studies have shown that *EGFR* and *KRAS* mutations are mutually exclusive. (3) Several studies outlined in this Protocol analyzed *KRAS* mutations as well as other markers in NSCLC (e.g., *EGFR* mutations); only data related to *KRAS* are presented in this Protocol.

Related Protocols

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

KRAS and BRAF Mutation Analysis in Metastatic Colorectal Cancer

Policy (Formerly 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.

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