KRAS Mutation Analysis in Non-small Cell Lung Cancer (NSCLC)

Policy # 00122
Original Effective Date: 03/18/2009
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Note: Epidermal Growth Factor Receptor (EGFR) Mutation Analysis for Patients with Non-Small Cell Lung Cancer (NSCLC) is addressed separately in medical policy 00289.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers analysis of somatic mutations of the KRAS gene as a technique to predict treatment non-response to anti-epidermal growth factor receptor (EGFR) therapy with the tyrosine-kinase inhibitor (TKI) erlotinib and the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab in non-small-cell lung carcinoma (NSCLC) to be investigational.*

Background/Overview
The EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in 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 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 2 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
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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 other than the U.S. All of the patients had advanced or metastatic disease and had been previously treated with at least 1 platinum-containing regimen and were randomly assigned to receive either gefitinib or docetaxel. Of the 1,466 patients, 1,433 were evaluable. Objective tumor response rates and progression-free survival (PFS) and overall survival (OS) were similar for the 2 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 policy 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. 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. Although several of the studies outlined in this policy 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 policy.

Rationale/Source
KRAS and EGFR TKIs
Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from 2 Phase III trials that conducted non-concurrent subgroup analyses of the efficacy of TKIs in patients with wild-type (non-mutated) versus mutated KRAS lung tumors, Phase II trials, retrospective single-arm studies, and 2 meta-analyses.

Pao and colleagues were the first to suggest that patients with KRAS-mutated lung tumors were nonresponsive to treatment with EGFR TKIs. Thirty-six patients with bronchioloalveolar carcinoma underwent KRAS mutation analysis; 9 were found to harbor KRAS mutations. Response was measured by a single radiologist, who graded responses according to Response Evaluation Criteria in Solid Tumors (RECIST), blinded to patient outcome. Zero of the 9 patients with KRAS-mutated tumors responded to erlotinib (p=0.5531).
Zhu and colleagues performed a non-concurrent subgroup analysis of KRAS mutations in a group of patients with advanced NSCLC who had failed standard chemotherapy treatment and had been previously randomized to receive erlotinib or placebo. The original Phase III trial (National Cancer Institute of Canada Clinical Trials Group Study BR.21) was the first to demonstrate a significant survival advantage with the use of an EGFR TKI in previously treated NSCLC patients. In the subsequent analysis, 206 of the original 731 tumors were tested for KRAS mutations, which were identified in 30 (15%) patients. Among the 206 patients tested for KRAS mutations, 118 were assessable for response to erlotinib. Of the 98 patients with wild-type KRAS, 10 (10.2%) responded to erlotinib, whereas of the 20 with mutated KRAS, only 1 patient (5.0%) responded (hazard ratio [HR]: [erlotinib vs. placebo] 1.67 [95% confidence interval [CI]: 0.62–4.50; p=0.31] in patients with KRAS mutations and 0.69 [95% CI: 0.49–0.97; p=0.03] in wild-type patients). In the Cox regression model, the interaction between KRAS mutation status and treatment was p=0.09.

Eberhard and colleagues performed a non-concurrent subgroup analysis of KRAS mutations in a group of previously untreated patients with advanced NSCLC who had been randomly assigned to receive chemotherapy with or without erlotinib. The original Phase III trial (TRIBUTE study) randomly assigned patients to carboplatin and paclitaxel either with erlotinib or with placebo. Of the original 1,079 patients, tumor DNA from 274 patients was sequenced for KRAS mutations. The baseline demographics between patients with available tumor DNA and those without were balanced. KRAS mutations were detected in 55 of the 274 (21%). The response rate for patients with wild-type KRAS tumors was 26%, regardless of which therapy they received. In patients with KRAS-mutated tumors, response rate was 8% for those receiving erlotinib with chemotherapy versus 23% in the group receiving chemotherapy alone (p=0.16; 95% CI for difference: -5% to 35%). Patients with mutated KRAS who received erlotinib had shortened OS of 4.4 months (95% CI: 3.4–12.9 months) versus 13.5 months (95% CI: 11.1–15.9 months) in those who received chemotherapy alone (p=0.019).

In a Phase II, multicenter, open-label study, Jackman and colleagues evaluated the treatment response to erlotinib in chemotherapy-naive patients, 70 years of age or older, who had advanced NSCLC. Of the 80 patients eligible for treatment, 41 had tumor analysis for KRAS mutations. Six of the 41 (15%) had KRAS mutations detected. None of the 6 patients with a KRAS mutation responded to erlotinib, whereas 5 of 35 (14%) patients with wild-type KRAS had a partial response.

In a Phase II trial, Miller and colleagues compared response to erlotinib in 101 patients with lung bronchioloalveolar carcinoma (n=12) or adenocarcinoma, bronchioloalveolar subtype (n=89), according to KRAS mutational status. Of the patients with evaluable tumor, 18 patients (18%) had KRAS-mutated tumors, and none of them responded to erlotinib (0 of 18; 95% CI: 0% to 19%; p<0.01). Response rate was 32% in patients without a KRAS mutation. Median OS in patients with a KRAS-mutated tumor was 13 months versus 21 months in patients with KRAS wild-type tumors (p=0.30).

In a Phase II trial, Giaccone and colleagues studied response to erlotinib in 53 chemotherapy-naive patients with advanced NSCLC. Histologic material was available to assess KRAS mutational status from 29 patients, 10 of whom had mutations. All 10 were nonresponders to erlotinib (p=0.125).
Boldrini and colleagues reported on the association between the status of KRAS and EGFR mutations and several clinical variables in 411 patients with lung adenocarcinoma, as well as a subset analysis of tumor response in patients treated with one of the TKIs (erlotinib or gefitinib). Overall, KRAS mutations were observed in 17.9% of patients. The subset analysis consisted of 21 female patients with stage IV disease who received a TKI as second- or third-line therapy and were assessed for radiographic tumor response using the RECIST. Age of this subpopulation at the time of diagnosis ranged from 40–86 years (mean age 60.8 years). Nineteen of the 21 patients were KRAS wild-type, and of those, 8 showed partial response, 4 had stable disease, and 7 had progressive disease. The 2 patients with KRAS mutations had progressive disease.

Schneider and colleagues reported on the relationship between clinical benefits and putative tumor markers in a subset of patients participating in a global open-label single-arm study (the TRUST study) of erlotinib in advanced NSCLC, involving 7,043 patients in 52 countries. The subset of patients in this publication were all from German centers and consisted of 311 patients with stage IIIB/IV disease treated with erlotinib because they had failed or were not medically suitable for standard first-line chemotherapy. Tumor response was assessed using RECIST. Seventeen patients (15%) had KRAS mutations, and none of them had a response to erlotinib, but 2 had stable disease. The impact of KRAS mutation status on PFS and OS was of borderline statistical significance. The authors concluded that current data do not support selection of patients for treatment with erlotinib on the basis of tumor molecular characteristics and that further studies are needed to determine definitively whether patients with KRAS mutations can derive survival benefit from erlotinib.

Two meta-analyses have been performed on the relationship between KRAS mutations and response to EGFR TKI therapy, and are outlined below. Data were insufficient to make a determination about an association between KRAS mutation status and PFS or OS in these meta-analyses.

Linardou and colleagues performed a meta-analysis which included 17 studies with 1,008 patients, 165 of whom (16.4%) had a KRAS mutation. Eligible studies had to report response (complete or partial) stratified by KRAS mutational status. The studies were also stratified by ethnicity, which of the TKIs patients received (studies included gefitinib and/or erlotinib), response criteria, possible selection bias, and previous treatment, if any. No significant difference was noted between subgroups in terms of response in the presence of a KRAS mutation. The presence of a KRAS mutation was associated with an absence of response to TKIs (sensitivity: 0.21 [95% CI: 0.16-0.28], specificity: 0.94 [95%, 0.89-0.97]; positive likelihood ratio: 3.52; negative likelihood ratio: 0.84). (For the analysis, likelihood ratios were calculated by using pooled estimates for sensitivity and specificity.) The authors conclude that their comprehensive review showed that KRAS mutations confer a high level of resistance to anti-EGFR therapies but that limitations exist, including a lack of individual patient data, which renders conclusions tentative, and that prospective validation should be done. Furthermore, the inadequate reporting of survival data precluded meaningful assessment of the effect of KRAS mutations on survival. Additional limitations to the analysis include the heterogeneity of response endpoints, differences in treatment regimens, patient selection criteria, and the retrospective nature of the analyzed series.
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Mao and colleagues performed a meta-analysis that included 22 studies, with a total of 1,470 patients with NSCLC (1,335 patients were evaluable for response), 231 (16%) of whom had KRAS mutations. Patient populations were heterogeneous with respect to smoking history, tumor histology, stage, ethnicity, treatment received, and response criteria. The primary endpoint was objective response rate, defined as the sum of complete and partial response. The objective response rates for patients with a KRAS mutation and wild-type KRAS were 3% and 26%, respectively. Inadequate reporting of survival data precluded meaningful assessment of the effect of KRAS status on survival in NSCLC patients treated with EGFR TKIs. Data for PFS and OS stratified by KRAS status were available in 8 studies. The median PFS in KRAS mutant and wild-type patients was 3.0 months and 3.9 months, respectively. The median OS in KRAS mutant and wild-type patients was 4.7 months and 10.7 months, respectively. However, only 2 studies presented data on HR with 95% CI for PFS and OS, and therefore, a pooled analysis for HR was not performed.

KRAS and anti-EGFR monoclonal antibodies
Two Phase III trials, BMS-099 and FLEX, investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC. Subsequently, an investigation of KRAS mutational status and cetuximab treatment has been performed from both trials.

In the multicenter Phase III trial BMS099, 676 chemotherapy-naïve patients with stage IIIB or IV NSCLC were assigned to taxane and carboplatin with or without cetuximab. The primary endpoint was PFS, overall response rate, OS, quality of life, and safety. The addition of cetuximab did not significantly improve PFS; however, there was a statistically significant improvement in overall response rate in the cetuximab group. There was a trend in OS favoring cetuximab; however, it did not reach statistical significance. Subsequently, a retrospective, correlative analysis of this trial was conducted to identify molecular markers for the selection of patients most likely to benefit from cetuximab. Of the original 676 patients enrolled, 202 (29.9%) had tumor samples available for KRAS testing. KRAS mutations were present in 35 patients (17%). Among patients with wild-type KRAS, OS was similar between the cetuximab-containing arm (n=85) and the chemotherapy alone arm (n=82) (HR 0.93; 95% CI: 0.67-1.30; p=0.68; median survival time of 9.7 and 9.9 months, respectively). Among patients with KRAS mutations, OS was similar between the cetuximab-containing arm (n=13) and the chemotherapy alone arm (n=22) (HR 0.907; 95% CI: 0.45-2.07; p=0.93; median survival time of 16.8 and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions between the presence of KRAS mutations and the outcomes evaluated, and differences that favored the addition of cetuximab in the KRAS mutant subgroup were consistent with those observed in patients with wild-type KRAS and in the overall study population. The authors concluded that the data should be interpreted with caution, given the small subgroup sample size and retrospective nature of the analysis, but that the results do not appear to show a similar correlation with the lack of cetuximab benefit established in patients with KRAS-mutated metastatic colorectal cancer.

In the open-label randomized Phase III FLEX trial, 1,125 patients with stage III or IV chemotherapy-naïve NSCLC were randomly assigned to receive either chemotherapy (cisplatin and vinorelbine) plus cetuximab (n=557) or chemotherapy alone (n=568). The primary endpoint was OS. The patients who received chemotherapy plus cetuximab survived longer than those in the chemotherapy-only group (median 11.3 months versus 10.1 months; HR for death 0.871 [95% CI: 0.762-0.996]; p=0.04). Subsequently, of the
patients for whom KRAS status could be determined (395 of 1,125 or 35%), KRAS mutation status was performed on archival tumor tissue. The results, which are only available in abstract form, reported a KRAS mutation in 75 of the 395 tumor samples (19%). Among the patients with a KRAS mutation, OS in the cetuximab-containing arm (n=38) versus the chemotherapy-alone arm (n=37) was similar (HR 1.00; 95% CI: 0.60-1.66; p=1.0; median survival time of 8.9 months vs. 11 months respectively). Among patients with wild-type KRAS, OS in the cetuximab-containing arm (n=161) versus the chemotherapy-alone arm (n=159) was similar (HR 0.96; 95% CI: 0.75-1.66; p=1.23; median survival time of 11.4 months versus 10.3 months respectively).

PFS observed in the cetuximab-containing and chemotherapy alone arms was similar between patients with mutant and wild-type KRAS. Response rates in the cetuximab-containing arm in patients with KRAS mutant and wild-type tumors were 36.8% and 37.3%, respectively (p=0.96). Overall, the outcome with cetuximab was observed regardless of KRAS mutational status.

**National Cancer Institute Clinical Trials Database (PDQ®)‡ and Clinicaltrials.gov**

**KRAS and EGFR TKIs**

A Phase III trial is currently actively assessing overall survival with the combination regimen of ARQ 197 (tivantinib, a novel MET inhibitor) plus erlotinib versus placebo plus erlotinib for the treatment of locally advanced or metastatic non-squamous, non-small-cell lung cancer in patients who have received 1 or 2 prior systemic anti-cancer therapies. (NCT01244191) EGFR and KRAS mutation status will be collected prior to randomization. Estimated enrollment is 988, with an estimated study completion date of July 2013.

A Phase III trial is currently recruiting patients to assess progression-free survival and secondarily overall survival with dacomitinib, another selective tyrosine kinase inhibitor, compared to erlotinib for the treatment of advanced NSCLC in patients who have received one or more prior anti-cancer therapies. (NCT01360554) KRAS mutation status will be collected at baseline. Estimated enrollment is 800, with an estimated study completion date of February 2013.

**KRAS and anti-EGFR monoclonal antibodies**

A Phase III randomized trial is actively assessing carboplatin and paclitaxel with or without bevacizumab and/or cetuximab in treating patients with stage IV or recurrent NSCLC. (NCT00946712) Primary outcomes are PFS and OS, and one secondary outcome is to evaluate the role of KRAS mutations in terms of cetuximab efficacy. Expected enrollment is 1,546, with an estimated trial completion date of June 2012.

**KRAS and MAPK Kinase (MEK) inhibitors**

A Phase II trial is currently recruiting participants to assess the effect of AZD6244 (mitogen-activated protein kinase [MAPK] inhibitor) with and without erlotinib in patients who have not responded to previous therapy for NSCLC. (NCT01229150) KRAS mutation status will be assessed and utilized to stratify patients into treatment groups. Half of the KRAS wild type and mutated KRAS patients will receive AZD6244 + erlotinib. The remaining wild type patients will receive erlotinib alone, and the remaining mutated KRAS patients will receive AZD6244 alone. Outcomes of interest are progression-
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Free survival, clinical response rate, adverse events, and overall survival. The estimated enrollment is 100 participants with an estimated completion date of September 2014. Another Phase II study recruiting several types of cancer patients, including advanced NSCLC patients, will also treat KRAS mutated patients with the MEK inhibitor AZD6244 (NCT01306045). The total estimated enrollment of this study is 600 patients with an estimated completion in January 2017.

KRAS and heat shock protein 90 (HSP90) inhibitors
A Phase II trial is currently recruiting patients with advanced NSCLC who have failed 2 or more previous lines of chemotherapy. (NCT01124864) Patients will be assessed for EGFR, KRAS, and EML4-ALK mutations, and treated with AUY922, a HSP90 inhibitor that degrades mutated EGFR. Outcomes of interest are treatment efficacy and overall survival. The estimated enrollment is 150 participants with an estimated completion in November 2013.

Guidelines and Position Statements
National Comprehensive Cancer Network (NCCN) Guidelines
NCCN guidelines state that KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy, but make no specific recommendations.

No recommendation for KRAS testing is made in the NCCN guidelines as to the use of cetuximab in patients with NSCLC.

Summary
It remains unclear whether assessment of KRAS mutation status will be clinically useful with regard to anti-EGFR therapy in the treatment of NSCLC.

KRAS and EGFR TKIs
Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from 2 Phase III trials that conducted non-concurrent subgroup analyses of the efficacy of TKIs in patients with wild-type (non-mutated) versus mutated KRAS lung tumors, Phase II trials, retrospective single-arm studies, and 2 meta-analyses. Although studies have shown that a KRAS mutation in patients with NSCLC confers a high level of resistance to TKIs, data are insufficient to make a determination about an association between KRAS mutation status and survival in these patients.

KRAS and anti-EGFR monoclonal antibodies
A lack of response to the EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and the use of these drugs is mostly restricted to patients with wild-type KRAS. The expectation that KRAS mutation status would also be an important predictive marker for cetuximab use in NSCLC has not been shown. In 2 randomized trials with non-concurrent subgroup analyses of KRAS mutation status and the use of cetuximab with chemotherapy, KRAS mutations did not appear to identify patients who would not benefit from anti-EGFR antibodies, as the outcomes observed with cetuximab were regardless of KRAS mutational status.
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Future challenges
An editorial highlights the challenges in biomarker testing and validation in patients with NSCLC, as summarized here. First, the purest evaluation of a biomarker would be from a study of treatment compared with observation or placebo, allowing for the assessment of the prognostic importance of the marker in the untreated control arm and the assessment of the predictive effect by comparing the treated and untreated arms. However, it is not feasible to conduct placebo-controlled studies in first-, second- or third-line treatment of NSCLC, as agents of proven benefit are available. Therefore, studies must compare targeted agents with another treatment or must add the targeted therapy to a standard therapy. A further confounding factor is that the effect of the standard therapy may also be different in the biomarker subsets. Finally, many of the studies of targeted therapies suffer from crossover at the time of disease progression, making assessment of overall survival extremely difficult.

The results of ongoing Phase III trials may guide the future management of NSCLC with TKIs and anti-EGFR monoclonal antibodies according to KRAS mutational status.

References
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Policy History

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03/04/2009 Medical Director review
03/18/2009 Medical Policy Committee approval. New policy.
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03/05/2010 Medical Director review
03/19/2010 Medical Policy Committee approval. No change to policy.
03/03/2011 Medical Director review
03/16/2011 Medical Policy Committee approval. No change to policy.
03/01/2012 Medical Director review
03/21/2012 Medical Policy Committee approval. Changes to policy statement to indicate that testing to predict non-response to anti-EGFR monoclonal antibody (cetuximab) is also investigational.
03/07/2013 Medical Policy Committee review
03/20/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2015

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2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. reference to federal regulations.

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