Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/21/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider, except as noted below, analysis of 2 types of somatic mutation within the epidermal growth factor receptor (EGFR) gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (eg, erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®])†, in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be eligible for coverage.

Based on review of available data, the Company may consider analysis for the T790M mutation in the gene for the EGFR as a technique to predict treatment response to osimertinib (Tagrisso®‡) in patients who have progressed on or after EGFR-TKI therapy to be eligible for coverage.

Note: These tests are intended for use in patients with advanced NSCLC. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene are considered good candidates for treatment with erlotinib or afatinib. Patients found to be wild type are unlikely to respond to erlotinib or afatinib; other treatment options should be considered.

When 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 2 types of somatic mutation within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—for patients with advanced non-small-cell lung cancer (NSCLC) of squamous cell type to be investigational.*
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Based on review of available data, the Company considers analysis for other EGFR mutations within exons 18 to 24, or other applications related to non-small-cell lung cancer (NSCLC), when patient selection criteria are not met to be investigational.*

Based on review of available data, the Company considers analysis of somatic rearrangement mutations of the ALK gene when patient selection criteria are not met to be investigational.*

Based on review of available data, the Company considers analysis of somatic mutations of the KRAS gene as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in non-small-cell lung cancer (NSCLC) to be investigational.*

Based on review of available data, the Company considers analysis for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2 for targeted therapy in patients with non-small-cell lung cancer (NSCLC) to be investigational.*

Background/Overview

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiotherapy, chemotherapy, and best supportive care. Unfortunately, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30% to 45%. More recently, the identification of specific, targetable oncogenic “driver” mutations in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes, which are predominantly of adenocarcinoma histology. Testing for EGFR mutations in clinical decision making for the treatment of NSCLC is routine. The use of testing for other mutations to direct targeted therapy is not well-established and continues to evolve.

EGFR Gene

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 (monoclonal antibodies) or inhibit intracellular TK activity (small molecule TKIs). 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 cell surface receptors such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Mutations in 2 regions of the EGFR gene (exons 18-24)—small deletions in exon 19 and a point mutation in exon 21 (L858R)—appear to predict tumor response to TKIs such as erlotinib. Likewise, tumors with an acquired exon 20 (T790M) substitution mutation appear to respond to osimertinib following failure of TKI therapy.
The prevalence of *EGFR* mutations in NSCLC varies by population, with the highest prevalence in non-smoking Asian women, with adenocarcinoma, in whom *EGFR* mutations have been reported to be up to 30% to 50%. The reported prevalence in the white population is approximately 10%.

**ALK Gene**

ALK is a TK that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement which leads to a fusion gene and expression of a protein with constitutive TK activity that has been demonstrated to play a role in controlling cell proliferation. The *EML4-ALK* fusion gene results from an inversion within the short arm of chromosome 2.

The *EML4-ALK* rearrangement (“ALK-positive”) is detected in 3% to 6% of NSCLC patients, with the highest prevalence in never-smokers or light ex-smokers who have adenocarcinoma.

**KRAS Gene**

The *KRAS* gene (which encodes RAS proteins) can harbor oncogenic mutations that result in a constitutively activated protein, independent of signaling from the EGFR, possibly rendering a tumor resistant to therapies that target the EGFR. Mutations in the *KRAS* gene, mainly codons 12 and 13, have been reported in 20% to 30% of NSCLC, and occur most often in adenocarcinomas in heavy smokers.

**ROS Gene**

*ROS1* codes for a receptor TK of the insulin receptor family, and chromosomal rearrangements result in fusion genes. The prevalence of *ROS1* fusions in NSCLC varies from 0.9% to 3.7%. Patients with *ROS1* fusions are typically never smokers with adenocarcinoma.

**RET Gene**

Rearranged during transfection (RET) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported. *RET* fusions occur in 0.6% to 2% of NSCLCs and in 1.2% to 2% of adenocarcinomas.

**MET Gene**

*MET* amplification is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR-TKIs.

**BRAF Gene**

RAF proteins are serine/threonine kinases that are downstream of RAS in the RAS-RAF-ERK-MAPK pathway. In this pathway, the *BRAF* gene is the most frequently mutated in NSCLC, in approximately 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the mutations in NSCLC are non-V600E mutations. Most *BRAF* mutations occur more frequently in smokers.

**HER2 Gene**

Human epidermal growth factor receptor 2 (*HER2*) is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. *HER2* is
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
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expressed in approximately 25% of NSCLC. HER2 mutations are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.

**Targeted Therapies**

Three orally administered EGFR-selective small molecule TKIs have been identified for use in treating NSCLC: gefitinib (Iressa, AstraZeneca), erlotinib (Tarceva, OSI Pharmaceuticals), and afatinib (Gilotrif, Boehringer Ingelheim). Gefitinib, erlotinib, and afatinib currently are approved by the U.S. Food and Drug Administration (FDA) for NSCLC. Although gefitinib was originally approved by FDA, a 2004 phase 3 trial suggested that the drug 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. However, in July 2015, FDA approved gefitinib as first-line treatment for metastatic NSCLC in patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Crizotinib is an oral small-molecule TKI that is FDA-approved for patients with locally advanced or metastatic NSCLC who are positive for the ALK gene rearrangement. Ceritinib is a potent ALK inhibitor that is approved for ALK-positive patients who whose cancer has progressed while taking crizotinib or who could not tolerate crizotinib.

For the treatment of KRAS-mutated NSCLC, EGFR-TKIs and anti-EGFR monoclonal antibodies have been investigated as possible treatment options. Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Cetuximab may be 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.

Proposed targeted therapies for the remaining genetic alterations in NSCLC that are addressed in this policy are trastuzumab and afatinib for HER2 mutations, crizotinib for MET amplification, and ROS1 rearrangement, vemurafenib and dabrafenib for BRAF mutations and cabozantinib for RET rearrangements.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

In 2004, erlotinib received initial U.S. FDA approval for second-line treatment of patients with advanced NSCLC. In 2013, erlotinib indications were expanded to include first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. A companion diagnostic test, the cobas® EGFR Mutation Test, was coapproved for this indication. In 2016, FDA approved cobas EGFR Mutation Test v2, a blood-based genetic test to detect EGFR mutations in patients with NSCLC. This version 2 test added detection of the specific mutation (T790M) to the previous version approved in 2013. In July 2013, afatinib was approved by FDA for first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletions or L858R mutations. A companion diagnostic test, the therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, was coapproved for this indication.
Both cobas and therascreen are PCR assays. FDA-approved product labels for both erlotinib and afatinib indicate that EGFR mutations must be “detected by an FDA-approved test” but do not specify which test must be used.

In August 2011, based on 2 multicenter, single-arm trials, crizotinib (Xalkori Capsules; Pfizer) was granted accelerated approval by FDA for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test. FDA approved the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular) concurrently with the crizotinib approval. This companion diagnostic test is designed to detect rearrangements of the ALK gene in NSCLC and captures all ALK gene rearrangements. In November 2013, crizotinib received full approval. In July 2015, an additional test, the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems), was approved by FDA for the qualitative detection of ALK in patients with NSCLC. If the test indicates the presence of ALK, the patient may be considered for treatment with crizotinib.

In July 2015, FDA approved gefitinib as a first-line treatment for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations detected by an FDA-approved test. The FDA news release on gefitinib approval mentioned the companion diagnostic test therascreen EGFR RGQ PCR.

In November 2015, osimertinib (Tagrisso; AstraZeneca Pharmaceuticals) was granted accelerated approval by FDA for the treatment of patients with NSCLC with a specific EGFR mutation (T790M) who have not responded to previous EGFR-blocking therapy.

Table 1 summarizes the FDA-approved treatments for patients with NSCLC whose tumors are EGFR-positive or ALK-positive, along with the concurrently approved diagnostic tests.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>• 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions as detected by FDA-approved test</td>
<td>2013: therascreen EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit</td>
</tr>
<tr>
<td></td>
<td>• 2016: Second line for patients with metastatic squamous NSCLC</td>
<td></td>
</tr>
<tr>
<td>Alectinib (Alecensa)</td>
<td>• 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
<td></td>
</tr>
<tr>
<td>Ceritinib (Zykadia)</td>
<td>• 2014: Second line for patients with ALK-positive metastatic NSCLC who have progressed on</td>
<td></td>
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</table>
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

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<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
</table>
| Crizotinib (Xalkori) | • 2011: Patients with **ALK**-positive metastatic NSCLC as detected by FDA-approved test  
             • 2016: Patients with **ROS1**-positive metastatic NSCLC | • 2011: Vysis ALK Break Apart FISH Probe Kit  
             • 2015: Ventana ALK (D5F3) CDx Assay |
| Erlotinib (Tarceva)   | • 2013: First line for patients with metastatic NSCLC whose tumors have **EGFR** exon 19 deletions or exon 21 (**L858R**) substitutions as detected by FDA-approved test  
             • 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles with platinum-based chemotherapy  
             • 2004: Second line for patients with locally advanced or metastatic NSCLC | • 2013: cobas EGFR Mutation Test (tissue test)  
             • 2016: cobas EGFR Mutation Test v2 (blood test) |
| Gefitinib (Iressa)      | • 2015: First line for patients with metastatic NSCLC whose tumors have **EGFR** exon 19 deletions or exon 21 (**L858R**) substitutions as detected by FDA-approved test  
             • 2003: Second line for patients with locally advanced or metastatic NSCLC | 2015: therascreen EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit |
| Necitumumab (Portrazza) | • 2015: In combination with gemcitabine and cisplatin, as first line for patients with squamous NSCLC | |}
| Osimertinib (Tagrisso)  | • 2015: Second line for patients with metastatic NSCLC whose tumors have **EGFR** T790M mutations as detected by FDA-approved test, who have not responded to **EGFR**-blocking therapy | 2015: cobas EGFR Mutation Test v2 (blood test) |

ALK: anaplastic lymphoma kinase; **EGFR**: epidermal growth factor receptor; FDA: Food and Drug Administration; FISH: fluorescence in situ hybridization; NSCLC: non-small-cell lung cancer; PCR: polymerase chain reaction.

**Rationale/Source**

**Epidermal Growth Factor Receptor**

Two publications demonstrated that the underlying molecular mechanism underpinning dramatic responses in these favorably prognostic groups appeared to be the presence of activating somatic mutations in the TK domain of the **EGFR** gene, notably small deletions in exon 19 and a point mutation in exon 21 (**L858R**, indicating substitution of leucine by arginine at codon position 858). These can be detected by direct sequencing or polymerase chain reaction (PCR) technologies.

A TEC Assessment on this topic was first published in November 2007. The Assessment concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of **EGFR** mutation testing to predict erlotinib sensitivity or to guide treatment in patients with NSCLC. This Assessment was updated in 2010, with revised conclusions indicating that **EGFR** mutation testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
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A 2013 meta-analysis of 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC reported improved progression-free survival (PFS) in EGFR mutation–positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy. (Comparisons were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively.) Among EGFR mutation–negative patients, PFS was improved with EGFR-TKIs compared with placebo maintenance but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either mutation-positive or mutation-negative patients. Statistical heterogeneity was not reported for any outcome. The authors concluded that EGFR mutation testing is indicated to guide treatment selection in NSCLC patients.

Similar meta-analyses confirming the PFS and OS results and conclusions for EGFR-positive patients have been published.

Erlotinib
Thirteen publications provide data on EGFR mutations in tumor samples obtained from NSCLC patients in erlotinib treatment studies. Nine of these were nonconcurrent prospective studies of treatment-naive and previously treated patients who received erlotinib and were then tested for the presence or absence of mutations; 4 (see Table 2) were prospective 1-arm enrichment studies of mutation-positive or wild-type patients treated with erlotinib. In 3 studies of EGFR mutation–positive patients, objective radiologic response was 40% to 70%, median PFS was 8 to 14 months, and median OS was 16 to 29 months. In patients with wild-type tumors, objective radiologic response was 3.3%, PFS was 2.1 months, and OS was 9.2 months.

Table 2. Clinical Response in Prospective Studies of Erlotinib Therapy in Patients with EGFR Gene Mutation–Positive Advanced NSCLC

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>No. Mutated/No. Tested (%)</th>
<th>Objective Radiologic Response, %</th>
<th>Median PFS (95% CI), mo</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutation-positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackman et al (2009)</td>
<td>84 enrolled</td>
<td>70</td>
<td>13</td>
<td>28.7</td>
</tr>
<tr>
<td>Rosell et al (2009)</td>
<td>350 / 2105 (16.6%)</td>
<td>70</td>
<td>14 (11.3 to 16.7)</td>
<td>27 (24.9 to 33.1)</td>
</tr>
<tr>
<td>Sun et al (2011)</td>
<td>144 / 164 (32%)</td>
<td>40</td>
<td>8</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>EGFR mutation-negative (wild-type)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshioka et al (2010)</td>
<td>30 enrolled</td>
<td>3.3</td>
<td>2.1</td>
<td>9.2</td>
</tr>
</tbody>
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Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
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CI: confidence interval; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival.

In 2011, Zhou et al reported the results of a phase 3 prospective clinical trial of first-line treatment of Chinese patients with EGFR mutation (exon 19 deletion or L858R)-positive NSCLC (87% adenocarcinoma) randomized to treatment with erlotinib (n=83) or standard chemotherapy (gemcitabine plus carboplatin, n=82). Progression free survival was significantly longer in patients who received erlotinib (13.1 vs 4.5 months; hazard ratio [HR], 0.16; p<0.001). Patients treated with erlotinib experienced fewer grade 3 and 4 toxic effects and more clinically relevant improvements in quality of life than those who received chemotherapy. Final OS results from OPTIMAL were published in 2015. Median OS was 23 months in the erlotinib group and 27 months in the chemotherapy group with no significant differences OS in the overall population (HR=1.19; 95% CI, 0.83 to 1.71; p=0.26), the exon 19 deletion subpopulation (HR=1.52; 95% CI, 0.91 to 2.52; p=0.10) or the exon 21 L858 mutation subpopulation (HR=0.92; 95% CI, 0.55 to 1.54; p=0.74). However, patients who received sequential combination of EGFR TKI and chemotherapy had significantly improved OS compared with those who received EGFR TKI or chemotherapy only (30 months versus 21 or 11 months, respectively; p<0.001). Results were similar in a European population in the 2012 EURTAC trial (NCT00446225), a multicenter, open-label, randomized phase 3 trial. Adult patients with EGFR mutations (exon 19 deletion or L858R mutation in exon 21) with NSCLC were randomized. Eighty-six received erlotinib and 87 received standard chemotherapy. A planned interim analysis showed that the primary end point had been met. At the time the study was halted (January 2011), median PFS was 9.7 months (95% confidence interval [CI], 8.4 to 12.3 months) versus 5.2 months (95% CI, 4.5 to 5.8 months) in the erlotinib and standard chemotherapy groups, respectively (HR=0.37; 95% CI, 0.25 to 0.54; p<0.001). Six percent of patients receiving erlotinib had treatment-related severe adverse events compared with 20% of those receiving a standard chemotherapy regimen.

In 2012, Petrelli et al reported a meta-analysis of 13 randomized trials of 1260 patients with EGFR mutated NSCLC who received TKIs for first-line, second-line, or maintenance therapy and compared outcomes with standard therapy. Overall, they noted that in patients, use of EGFR-TKIs increased the chance of obtaining an objective response almost 2-fold when compared with chemotherapy. Response rates were 70% versus 33% in first-line trials and 47% versus 28.5% in second-line trials. TKIs reduced the hazard of progression by 70% in all trials and by 65% in first-line trials; however, they did not improve OS.

In a 2010 pooled analysis of patients with EGFR mutations (most commonly exon 19 deletions and L858R substitution mutations in exon 21), median PFS was 13.2 months in patients treated with erlotinib and 5.9 months in patients treated with standard chemotherapy (p<0.001).

Nine other studies (total N=630 patients) have compared outcomes in EGFR mutation–positive and EGFR wild-type patients who were treated with erlotinib (see Table 3). Objective radiologic response rates ranged from 0% to 83% (median, 45%) in patients with EGFR mutation–positive tumors and from 0% to 18% (median, 5.5%) in patients with wild-type tumors. The 5 studies that statistically evaluated results demonstrated statistically significant increases in objective radiologic response among patients with EGFR mutation–positive tumors. PFS ranged from 6.8 to 13.1 months (median, 12.5 months) in patients with
EGFR mutation–positive tumors and from 1.4 to 5 months (median, 2.5 months) in patients with wild-type tumors. In all studies reporting these data, patients with EGFR mutation–positive tumors showed a trend or a statistically significant increase in PFS. OS ranged from 10 to 35 months (median, 21 months) in patients with EGFR mutation–positive tumors and from 3 to 12 months (median, 8.1) in patients with wild-type tumors. In all cases reporting these data, EGFR mutation–positive tumors showed a trend or a statistically significant increase in OS.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Overall Radiologic Response (Range), %</th>
<th>Median PFS (Range), mo</th>
<th>Median OS (Range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutation–positive patients</td>
<td>45 (0-83)</td>
<td>12.5 (6.8-13.1)</td>
<td>21 (10-35)</td>
</tr>
<tr>
<td>Wild-type patients</td>
<td>5.5 (0-18)</td>
<td>2.5 (1.4-5)</td>
<td>8.1 (3-12)</td>
</tr>
<tr>
<td>Untested patients (intention-to-treat); FDA label NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR: not reported; OS: overall survival; PFS: progression-free survival.</td>
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</table>

In a 2013 randomized controlled trial (RCT), Garassino et al in Italy compared the efficacy of erlotinib and docetaxel as second-line therapy in 219 EGFR wild-type patients with metastatic NSCLC who had received previous platinum-based therapy. Most patients (69%) had adenocarcinoma; 25% had squamous cell carcinoma (SCC). With a median follow-up of 33 months, median PFS was 2.9 months with docetaxel and 2.4 months with erlotinib (adjusted HR=0.71; 95% CI, 0.53 to 0.95; p=0.02). Median OS was 8.2 months with docetaxel and 5.4 months with erlotinib (adjusted HR=0.73; 95% CI, 0.53 to 1.00; p=0.05). Grade 3 or higher skin adverse events occurred in 14% of the erlotinib group and did not occur in the docetaxel group. Grade 3 or higher neutropenia occurred only in the docetaxel group (20%). As stated in an accompanying editorial, “[T]he efficacy of EGFR tyrosine kinase inhibitors is very limited for second-line treatment of wild-type EGFR NSCLC.” A 2013 meta-analysis of 3 trials in patients with wild-type EGFR reported improved OS with erlotinib treatment in second- and third-line and maintenance settings. However, 75% of patients in the control arms in this analysis received placebo.

EGFR mutations may provide prognostic information (about disease recurrence and survival), as well as predictive information (about treatment response). In a 2005 study by Eberhard et al, improved outcomes were observed for EGFR mutation–positive patients compared with wild-type patients regardless of treatment (standard chemotherapy or standard chemotherapy plus erlotinib). Objective radiologic response was 38% versus 23% (p=0.01), median time to progression was 8 months versus 5 months (p<0.001), and median OS was not reached versus 10 months (p<0.001).

Afatinib
Unlike erlotinib (and gefitinib) that selectively inhibit EGFR, afatinib inhibits not only EGFR but also HER2 and HER4 and may have activity in patients with acquired resistance to TKIs (who often harbor a T790M mutation [substitution of threonine by methionine at codon 790] in EGFR exon 20). The efficacy and safety of afatinib was evaluated in the LUX-Lung series of studies.
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
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LUX-Lung 3 was an RCT in 345 patients with stage IIIB or IV, EGFR mutation–positive, lung adenocarcinoma who were previously untreated for advanced disease. Seventy-two percent of patients were Asian, 26% were white, and 90% (308 patients) had common EGFR mutations (exon 19 deletion or L858R substitution mutation in exon 21). Patients received either afatinib or chemotherapy (cisplatin plus pemetrexed). In stratified analysis of patients with common EGFR mutations, median PFS was 13.6 months for the afatinib group and 6.9 months for the chemotherapy group (HR=0.47; 95% CI, 0.34 to 0.65; p=0.001). Median PFS for the 10% of patients who had other EGFR mutations was not reported, but median PFS for the entire patient sample was 11.1 months in the afatinib group and 6.9 months in the chemotherapy group (HR=0.58; 95% CI, 0.43 to 0.78; p=0.001). Incidence of objective response in the entire patient sample was 56% in the afatinib group and 23% in the chemotherapy group (p=0.001). With a median follow-up of 16.4 months, median OS was not reached in any group; preliminary analysis indicated no difference in OS between the 2 treatment groups in the entire patient sample (HR=1.12; 95% CI, 0.73 to 1.73; p=0.60). Patients in the afatinib group reported greater improvements in dyspnea, cough, and global health status/quality of life than those in the chemotherapy group. Grade 3 or higher diarrhea, rash, and paronychia (nail infection) occurred in 14%, 16%, and 11% of afatinib-treated patients, respectively, and in no patients in the chemotherapy group. Grade 3 or higher mucositis (primarily stomatitis) occurred in 9% of the afatinib group and 0.9% of the chemotherapy group.

Three other published LUX-Lung studies evaluated patients with stage IIIB or IV lung adenocarcinoma who were previously treated for advanced disease, but each had design flaws that limit the interpretation of results.

- LUX-Lung 2 was a single-arm study of afatinib in 129 patients (87% Asian, 12% white) with EGFR mutation–positive disease. Patients had been treated with previous chemotherapy but not with EGFR-targeted therapy; approximately half of patients (enrolled after a protocol amendment) were chemotherapy-naive. Objective responses (primarily partial responses) were observed in 66% of 106 patients with common EGFR mutations (exon 19 deletion or L858R) and in 39% of 23 patients with other EGFR mutations. Median PFS was 13.7 months in patients with common EGFR mutations and 3.7 months in patients with other EGFR mutations (p not reported). Results for mutation-negative patients were not reported.

- LUX-Lung 1 and LUX-Lung 4 enrolled patients who had progressed on previous erlotinib, gefitinib, or both for advanced disease. Neither study prospectively genotyped patients. In the LUX-Lung 1 double-blind RCT, 96 of 585 enrolled patients (66% Asian, 33% white) were EGFR mutation–positive (76 common EGFR mutation–positive). In this group, median PFS was 3.3 months in the afatinib group and 1.0 month in the placebo group (HR=0.51; 95% CI, 0.31 to 0.85; p=0.009). In 45 mutation-negative patients, median PFS was 2.8 months in the afatinib group and 1.8 months in the placebo group, a statistically nonsignificant difference (p=0.22), possibly due to small group sizes. LUX-Lung 4 was a single-arm study of afatinib in 62 Japanese patients. Objective responses occurred in 2 of 36 patients with common EGFR mutations (5%) and in none of 8 patients with other EGFR mutations (p>0.05).

Preliminary results from the LUX-7 trial were presented in 2016. LUX-7 was a phase 2b, head-to-head trial of afatinib versus gefitinib for the treatment of first-line EGFR mutation-positive (del19 and L858R) adenocarcinoma of the lung. LUX-7 included 319 patients in a 1:1 ratio to receive afatinib 40 mg/d or
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

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gefitinib 250 mg/d, stratified by mutation type (del19 and L858R) and brain metastases (present/absent). In the overall population, PFS was significantly improved with afatinib than with gefitinib (HR=0.73; 95% CI, 0.57 to 0.95; p=0.02). Time-to-treatment failure also showed improvement in favor of afatinib (HR=0.73; 95% CI, 0.58 to 0.92; p=0.01). ORR was significantly higher in the afatinib group (70% vs 56%; p=0.01).

Osimertinib
In November 2015, FDA granted accelerated approval to osimertinib for treatment of metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy. The therapy was approved along with an FDA-approved companion test, the cobas EGFR Mutation Test v2, which is a blood-based genetic test to detect EGFR mutations including the T790M mutation. Approval was based on 2 multicenter, single-arm studies. Results were presented at the European Lung Cancer Conference in 2016, but have not yet been published in the peer reviewed literature.

The osimertinib label describes the 2 studies. Eligible patients had metastatic EGFR T790M mutation-positive NSCLC and had progressed on prior systemic therapy, including an EGFR TKI. Patients received osimertinib 80 mg once daily. The first study enrolled 201 patients; the second study enrolled 210 patients. The major efficacy outcome measure of both trials was objective response rate (ORR) assessed by a blinded, independent review committee. The median duration of follow-up of 4.2 months in the first study and 4.0 months in the second. The ORR was similar in the 2 studies. The pooled ORR was 59% (95% CI, 54% to 64%); 0.5% achieved complete response and 59% achieved partial response. The most common adverse reactions were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Serious adverse reactions reported in 2% or more patients were pneumonia and pulmonary embolus. Fatal adverse reactions included: 4 patients with interstitial lung disease/pneumonitis; 4 patients with pneumonia, and 2 patients with cerebral vascular accident/cerebral hemorrhage.

EGFR Mutation Frequency
In 2009, Rosell et al reported EGFR mutations in 16.6% of the overall patient sample but noted an increased prevalence in women (69.7%), patients who never smoked (66.6%), and patients with adenocarcinomas (80.9%). Based on these findings, Rosell et al recommended EGFR mutation screening in women with lung cancer with nonsquamous cell tumors and have never smoked. Other reports on the mutation frequencies have found higher prevalences among East Asians when compared with other ethnicities (38% vs 15%, respectively). Although there is a greater proportion of EGFR mutations in these special populations (women, never smokers, patients with adenocarcinoma, and/or Asians), many patients without these selected demographics still exhibit EGFR mutations and would benefit from erlotinib treatment.

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al reported EGFR mutations in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies. Although histology appeared to be the strongest discriminator, results varied across studies. For example, Eberhard et al observed EGFR mutations in 6.4% of patients with SCCs and Rosell et al observed EGFR mutations in 11.5% of patients with large cell carcinomas. (Both studies had small sample sizes.) The acquired EGFR T790M mutation has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients from 2 studies.
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Case series based on the Sanger Institute’s Catalogue of Somatic Mutations in Cancer (COSMIC) have reported low incidence of observed EGFR mutation in patients with squamous cell cancer: 2.7% with an upper confidence limit for the true incidence of 3.6%. This recommendation was based on a case series of 13 patients with squamous or pseudosquamous histology. However, 7 (54%) patients were subsequently determined to have adenocarcinoma histology. All 6 remaining patients were never smokers, and all 6 had an exon 19 deletion or L858R substitution mutation in EGFR.

Two studies support the potential value of EGFR mutation testing in patients with SCC, particularly in Asian populations. However, similar studies have not been reported in non-Asian populations or in populations treated with erlotinib. A 2009 study by Park et al of preselected Korean patients treated with gefitinib reported EGFR mutations in 3 (15%) of 20 male smokers with SCC, a patient subgroup expected to have a low prevalence of EGFR mutations based on demographics. Clinical response was observed in 2 of 3 mutation-positive patients and 1 of 17 wild-type patients; median PFS was 5.8 months in the group with mutated EGFR and 2.4 months in the wild-type group (p=0.07). In vivo analyses by Dobashi et al showed that in Japanese patients with both adenocarcinomas and SCCs, EGFR mutations were associated with downstream phosphorylation of EGFR and constitutive activation of the EGFR pathway.

In contrast, Fang et al (2013) reported EGFR mutations (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage SCC. In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never smokers, 21% women), EGFR mutation prevalence (all exon 19 deletion or L858R) was 23.8%. Objective response occurred in 26.7% of 15 EGFR mutation–positive and 2.1% of 48 mutation-negative patients (p=0.002). Median PFS was 3.9 months and 1.9 months, respectively (p=0.19). Based on these findings, the authors concluded that routine EGFR mutation testing of all SCC specimens was not justified.

EGFR Mutation Testing
Gene sequencing is generally considered an analytic criterion standard. In 2010, the Canadian Agency for Drugs and Technologies in Health published a rapid response report on EGFR mutation analysis. Based on 11 observational studies, the report authors concluded that PCR-based approaches identify EGFR mutations with a sensitivity equivalent to that of direct sequencing.

Section Summary
Several RCTs, nonconcurrent prospective studies, and single-arm enrichment studies demonstrate that detection of EGFR gene mutations identifies patients with NSCLC who are likely to benefit from erlotinib or afatinib therapy and who are therefore ideal candidates for treatment with these drugs. These observations have been made in populations of patients with primarily adenocarcinomas. Currently, there is little evidence to indicate that EGFR mutation testing can guide treatment selection in patients with squamous cell histology.

Patients who are found to have wild-type tumors are unlikely to respond to erlotinib or afatinib. These patients should be considered candidates for alternative therapies.
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/21/2016

**ALK Gene**

The accelerated approval of crizotinib by the FDA was based on phase 1 and 2 trials in which crizotinib showed marked antitumor activity in patients with ALK-positive advanced NSCLC, with objective response rates of 60% and PFS of 7 to 10 months. These results were confirmed in 2 subsequent phase 3 trials.

A phase 3, open-label trial randomized 347 patients with previously treated, locally advanced or metastatic ALK-positive lung cancer to oral crizotinib twice daily (n=173) or chemotherapy (n=174) every 3 weeks. All patients had received 1 platinum-based chemotherapy regimen prior to the trial. The extent of disease was metastatic in 95% and 91% of patients in the crizotinib and chemotherapy groups, respectively, and tumor histology was adenocarcinoma in 95% and 94%, respectively. The primary end point was PFS. Patients in the chemotherapy group who experienced progressive disease were allowed to cross over to receive crizotinib as part of a separate study. Median PFS was 7.7 months in the crizotinib group versus 3.0 months in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; p<0.001). Partial response (PR) rates with crizotinib were 65% (95% CI, 58 to 72), versus 20% (95% CI, 14 to 26) with chemotherapy (p<0.001). Interim analysis of OS showed no significant improvement with crizotinib compared with chemotherapy (HR for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; p=0.54). Median follow-up for OS was 12.2 months and 12.1 months in the crizotinib and chemotherapy groups, respectively. Patients reported greater reductions in lung cancer symptoms and greater improvement in global quality of life with crizotinib compared with chemotherapy.

A phase 3, open-label trial compared crizotinib and chemotherapy in 343 previously untreated patients with ALK-positive advanced nonsquamous NSCLC. Patients were randomized to oral crizotinib twice daily or pemetrexed with either cisplatin or carboplatin every 3 weeks for up to 6 cycles. If there was disease progression for patients receiving chemotherapy, crossover to crizotinib was allowed. PFS was the primary end point. PFS was 10.9 months compared with 7.0 months for the group that received crizotinib versus chemotherapy, respectively (HR for progression or death with crizotinib, 0.45; 95% CI, 0.35 to 0.60; p<0.001); objective response rates (complete and partial responses) were 74% and 45%, respectively (p=0.001). Median OS was not reached in either group; the probability of 1-year survival with crizotinib was 84% and with chemotherapy 79%. Crizotinib was associated with patient reported greater reduction in lung cancer symptoms and greater improvements in quality of life.

**Section Summary**

Crizotinib was granted accelerated approval by FDA in August 2011, for patients with locally advanced or metastatic NSCLC, based on objective response rates observed in 2, single-arm trials. Two subsequent phase 3 trials showed superior PFS and tumor response rates and improved quality of life in patients with crizotinib versus chemotherapy, in both previously untreated, ALK-positive advanced NSCLC and in patients who had received previous chemotherapy.

**KRAS Gene Mutations**

**KRAS and EGFR-TKIs**

Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from post hoc analyses of 2 phase 3 trials of TKIs in patients with wild-type (nonmutated) versus KRAS-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and 2 meta-analyses.
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Pao et al (2005) 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 (25%) were found to harbor KRAS mutations. Response was by a single radiologist, who was blinded to patient outcome, using RECIST (Response Evaluation Criteria in Solid Tumors). None of 9 patients with KRAS-mutated tumors responded to erlotinib (p=0.553).

Zhu et al (2008) performed a post hoc subgroup analysis of KRAS mutations in patients with advanced NSCLC who had failed standard chemotherapy and had been previously randomized to receive erlotinib or placebo. The original phase 3 trial (National Cancer Institute of Canada Clinical Trials Group Study BR.21; 2005) was the first to demonstrate a significant survival advantage with the use of an EGFR-TKI in previously treated NSCLC patients. In post hoc analysis, 206 (28%) of the original 731 tumors were tested for KRAS mutations, which were identified in 30 patients (15%). Among the 206 tested patients, 118 (57%) were assessable for response to erlotinib. Of 98 patients with wild-type KRAS, 10 (10.2%) responded to erlotinib; of 20 patients with mutated KRAS, 1 patient (5.0%) responded (HR [erlotinib vs placebo] in patients with mutated KRAS, 1.67; 95% CI, 0.62 to 4.50; p=0.31); HR in wild-type patients, 0.69; 95% CI, 0.49 to 0.97; p=0.03). In Cox regression, the interaction between KRAS mutation status and treatment was not statistically significant (p=0.09).

Eberhard et al (2005) performed a post hoc subgroup analysis of KRAS mutations in previously untreated patients with advanced NSCLC who had been randomly assigned to receive chemotherapy with or without erlotinib. The original phase 3 trial (TRIBUTE; 2005) randomly assigned patients to carboplatin plus paclitaxel either with or without erlotinib. Of the original 1079 patients, tumor DNA from 274 patients (25%) was sequenced for KRAS mutations. Baseline demographics between patients with available tumor DNA and those without were balanced. KRAS mutations were detected in 55 of 274 patients (21%). Response rate for patients with wild-type KRAS was 26%, regardless of treatment received. In patients with KRAS-mutated tumors, response rate was 8% for those receiving chemotherapy with erlotinib and 23% for those receiving chemotherapy alone (p=0.16; 95% CI for difference: -5% to 35%); median OS was 4.4 months (95% CI, 3.4 to 12.9) in patients who received erlotinib and 13.5 months (95% CI, 11.1 to 15.9) in those who received chemotherapy alone (p=0.019).

In a 2007 phase 2, multicenter, open-label study, Jackman et al evaluated treatment response to erlotinib in chemotherapy-naïve patients 70 years of age or older who had advanced NSCLC. Of 80 patients eligible for treatment, 41 (51%) had KRAS mutation analysis; 6 patients (15%) were mutation-positive, none of whom responded to erlotinib. Five (14%) of 35 patients with wild-type KRAS had a partial response.

In a 2008 phase 2 trial, Miller et al assessed response to erlotinib in 101 patients with lung bronchioloalveolar carcinoma (n=12) or adenocarcinoma, bronchioloalveolar subtype (n=89), according to KRAS mutational status. Eighteen patients (18%) had KRAS-mutated tumors, and none of them responded to erlotinib (95% CI, 0% to 19%; p<0.01). In patients without a KRAS mutation, response rate was 32%. Median OS in patients with KRAS-mutated tumor was 13 months versus 21 months in patients with KRAS wild-type tumor (p=0.30).
In a 2006 phase 2 trial, Giaccone et al 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 (34%) had mutations. All 10 were nonresponders to erlotinib (p=0.125).

In 2009, Boldrini et al reported on the association between KRAS and EGFR mutation status and several clinical variables in 411 patients with lung adenocarcinoma, and presented a subgroup analysis of tumor response in patients treated with erlotinib or gefitinib. KRAS mutations were observed in 17.9% of all patients. The subset analysis comprised 21 women with stage IV disease who received a TKI as second- or third-line therapy and were assessed for radiographic tumor response using RECIST. Mean age of this subpopulation at the time of diagnosis was 60.8 years (range, 40-86). Nineteen (90%) of 21 women were KRAS wild-type, and of those, 8 (42%) showed partial response, 4 (21%) had stable disease, and 7 (37%) had progressive disease. Two patients with KRAS mutations had progressive disease.

Schneider et al (2008) reported on the relationship between clinical benefit and putative tumor markers in a subgroup of patients participating in a global open-label, single-arm study of erlotinib in advanced NSCLC, involving 7043 patients in 52 countries (the TRUST study). The subgroup in this publication was from German centers and comprised 311 patients with stage IIIB/IV disease who were 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 had a response to erlotinib; 2 patients had stable disease. The impact of KRAS mutation status on OS (p=0.06) and PFS (p not reported) was of borderline statistical significance. The authors concluded that current data did not support selection of patients for treatment with erlotinib on the basis of tumor molecular characteristics and that further studies were needed to determine definitively whether patients with KRAS mutations can derive survival benefit from erlotinib.

Rulli et al reported results from biomarker analyses in the TAILOR trial. TAILOR enrolled patients from 52 Italian hospitals and genotyped patients for KRAS and EGFR mutation status. Wild-type EGFR patients (n=218) received first-line platinum-based chemotherapy and then were randomly allocated at progression to erlotinib or docetaxel. KRAS mutations were present in 23% of randomized patients. The presence of a KRAS mutation was not associated with PFS (HR=1.01; 95% CI, 0.71 to 1.41; p=0.98) or OS (HR=1.24; 95% CI, 0.87 to 1.77; p=0.23). The treatment effect did not differ by KRAS status (test for interaction: OS p=0.97; PFS p=0.42).

Papadimitrakopoulou et al reported results of the BATTLE-2 phase 2 study in 2016. The BATTLE-2 program is an umbrella study evaluating effects of targeted therapies focusing on KRAS-mutated cancers. Two hundred patients with advanced NSCLC tumors who did not have EGFR mutations or ALK gene fusions whose cancer was refractory to more than 1 prior therapy were assigned to 1 of 4 arms using adaptive randomization: erlotinib (n=22), erlotinib plus MK-2206 (n=42), MK-2206 plus AZD6244 (n=75), or sorafenib (n=61), stratified by KRAS status. AZD6244 and MK2206 are targeted small-molecule drugs that inhibit MEK and AKT, respectively. Sorafenib is a multitargeted signal transduction inhibitor that inhibits raf-kinases, vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor-B, and c-kit. Only 186 evaluable patients were included in analyses. The 8-week disease control rate was 20%, 25%, 62%, and 44% for the 4 treatment groups, respectively, in the KRAS mutation positive patients. For KRAS
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/21/2016

wild-type patients, disease control rate was 36%, 57%, 49%, and 47%, respectively. Median PFS did not differ by KRAS status.

Meta-analyses on the relation between KRAS mutations and response to EGFR-TKI therapy are outlined next. Pooled data were insufficient to make a determination about an association between KRAS mutation status and treatment effects on PFS or OS.

Linardou et al (2008) performed a meta-analysis of 17 studies with 1008 patients, 165 (16.4%) of whom had a KRAS mutation. Eligible studies reported response (complete or partial) stratified by KRAS mutational status. Primary end points were sensitivity and specificity of KRAS testing, defined as KRAS mutation carriers showing no response to erlotinib (stable disease or progressive disease) and KRAS wild-type patients showing a response, respectively. Sensitivity and specificity were assessed overall and in subgroups defined by TKI received (gefitinib and/or erlotinib), response criteria (RECIST or World Health Organization), possible selection bias, and previous chemotherapy, if any. There was no significant difference in sensitivity or specificity across subgroups. The presence of a KRAS mutation was associated with a lack of response to TKIs (sensitivity, 0.21; 95% CI, 0.16 to 0.28; specificity, 0.94; 95% CI, 0.89 to 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 reviewers concluded that KRAS mutations conferred a high level of resistance to anti-EGFR therapies; however, this conclusion is tentative due to study limitations (eg, lack of individual patient data, heterogeneity of response end points, treatment regimens, patient selection criteria, retrospective design of included studies). Furthermore, incomplete reporting of survival data precluded meaningful assessment of the effect of KRAS mutation on survival.

Mao et al (2010) performed a meta-analysis of 22 studies in 1470 patients with NSCLC (1335 [91%] evaluable for response), 231 (17%) of whom had KRAS mutations. Studies were heterogeneous in patient populations (smoking history, tumor histology, stage, ethnicity, treatment received) and response criteria. The primary end point was objective response rate, defined as the sum of complete and partial response. Objective response rates for patients with mutated KRAS and wild-type KRAS were 3% and 26%, respectively. Incomplete 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. Median PFS in KRAS-mutated and wild-type patients was 3.0 months and 3.9 months, respectively. Median OS in KRAS-mutated and wild-type patients was 4.7 months and 10.7 months, respectively. However, only 2 studies presented HRs with 95% CIs for PFS and OS, and therefore, pooled analysis to derive an overall HR was not performed.

Pan et al (2016) published a meta-analysis of 41 studies (total N=13,103 patients) of prognostic and predictive values of the KRAS mutation in NSCLC. KRAS mutation was significantly associated with poorer OS (HR=1.6; 95% CI, 1.4 to 1.8) and DFS (HR=1.57; 95% CI, 1.2 to 2.1) in early-stage resected NSCLC, and with inferior outcomes of EGFR-TKIs treatment (RR=0.21; 95% CI, 0.1 to 0.4) in advanced NSCLC. KRAS mutation was still significantly associated with poorer OS (HR=1.4; 95 % CI, 1.2 to 1.6) and PFS (HR=1.4; 95 % CI, 1.1 to 1.6) of EGFR TKIs when patients with EGFR mutations were excluded.
Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single institution in China. Patients with mutated KRAS were random matched on tumor, node, metastasis (TNM) stage, time of first visit within 1 year, and histology, to both EGFR mutation–positive and KRAS/EGFR wild-type patients. Seventy patients (4%) received EGFR-TKI therapy. In this group, median PFS was 11.8 and 2.0 months in patients with EGFR and KRAS mutations, respectively, and 1.9 months in wild-type patients; in comparison with wild-type patients, PFS was statistically longer in patients with EGFR mutations (p<0.001) but no different in patients with KRAS mutations (p=0.48). The authors observed that "the presence of an EGFR mutation, but not a KRAS mutation, was predictive of responsiveness to EGFR TKI treatment."

Fiala et al (2013) reported on a retrospective analysis of patients with squamous cell NSCLC who underwent EGFR, KRAS, and PIK3CA (phosphatidylinositide-3-kinase catalytic subunit-alpha) mutation testing. Of 215 patients tested, 16 (7.4%) had mutated KRAS. Of 174 tested patients who were treated with an EGFR-TKI (erlotinib or gefitinib), median PFS in 14 KRAS-mutated patients was 1.3 months versus 2.0 months in KRAS wild-type patients (n=160 [92%]); the difference was not statistically significant (Kaplan-Meier log-rank test, p=0.120). Median OS in this treated group was 5.7 months in KRAS-mutated patients versus 8.2 months in KRAS wild-type patients, a statistically significant difference (Kaplan-Meier log-rank test, p=0.039). The authors concluded that KRAS mutation status may have a negative prognostic role but a predictive role was not confirmed. "Patients with squamous cell NSCLC harboring these mutations could benefit from targeted treatment and should not be excluded from treatment with EGFR TKIs."

Two reviews published in 2013 concluded that, in comparison with KRAS mutation testing, EGFR mutation status is the preferred predictive marker for response to EGFR-TKIs in patients with NSCLC.

**KRAS and Anti-EGFR Monoclonal Antibodies**

Two phase 3 trials, BMS-099 and FLEX, investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC. Subsequently, investigations of KRAS mutation status and cetuximab treatment were performed for both trials.

In the multicenter phase 3 BMS099 trial (2010), 676 chemotherapy-naive patients with stage IIIB/IV NSCLC were assigned to taxane and carboplatin with or without cetuximab. The primary end point was PFS; secondary end points were 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, this was not statistically significant. A post hoc 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 enrolled patients, 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 to 1.30; p=0.68; median survival, 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=0.91; 95% CI, 0.45 to 2.07; p=0.93; median survival, 16.8 and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions between the presence of KRAS mutations and outcomes evaluated;
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/21/2016

treatment differences favoring the addition of cetuximab in the KRAS-mutated subgroup were consistent with those observed in the wild-type KRAS subgroup and in the overall study population. The authors concluded that the results do not support an association between KRAS mutation and lack of cetuximab benefit similar to that observed in patients with KRAS-mutated metastatic colorectal cancer. However, results should be interpreted with caution due to small subgroup sample sizes and retrospective nature of the analysis.

In this open-label, randomized, phase 3 FLEX trial, 1125 chemotherapy-naive patients with stage III/IV, NSCLC were randomly assigned to receive either chemotherapy (cisplatin and vinorelbine) plus cetuximab (n=557) or chemotherapy alone (n=568). The primary end point was OS. Patients who received chemotherapy plus cetuximab survived longer than those who received chemotherapy only (median OS, 11.3 months vs 10.1 months, respectively; HR for death, 0.87; 95% CI, 0.76 to 1.00; p=0.04). Subsequently, KRAS mutation testing was performed on archival tumor tissue of 395 (35%) of 1125 patients. KRAS mutations were detected in 75 tumors (19%). Among patients with mutated KRAS, OS in the cetuximab-containing (n=38) and chemotherapy-alone arms (n=37) was similar (median OS, 8.9 months vs 11.1 months, respectively; HR=1.00; 95% CI, 0.60 to 1.66; p=1.0). Among patients with wild-type KRAS, OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (median OS, 11.4 months vs 10.3 months, respectively; HR=0.96; 95% CI, 0.75 to 1.23; p=0.74). PFS also was similar in cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR=0.97; 95% CI, 0.76 to 1.24) and wild-type (HR=0.84; 95% CI, 0.50 to 1.40) KRAS. Response rates in the cetuximab-containing arm in patients with KRAS-mutated and wild-type tumors were 36.8% and 37.3%, respectively (p=0.96). Overall, there was no indication that KRAS mutation status was predictive of cetuximab effect in NSCLC.

Section Summary
KRAS and EGFR-TKIs
Data on the role of KRAS mutations in NSCLC and response to erlotinib are available from post hoc analysis of 2 phase 3 trials that compared TKI efficacy in patients with wild-type (nonmutated) versus KRAS-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and 2 meta-analyses. Although studies have shown that KRAS mutations in patients with NSCLC confer a high level of resistance to TKIs, data are insufficient to assess any association between KRAS mutation status and survival in these patients.

A lack of response to EGFR monoclonal antibodies has been established in metastatic colorectal cancer, and use of these drugs is largely restricted to patients with wild-type KRAS. The expectation that KRAS mutation status also would be an important predictive marker for cetuximab response in NSCLC has not been shown. In 2 randomized trials with post hoc analyses of KRAS mutation status and use of cetuximab with chemotherapy, KRAS mutations did not identify patients who would not benefit from anti-EGFR antibodies, as outcomes with cetuximab were similar regardless of KRAS mutation status.

ROS Gene
In March 2016, FDA expanded the indication for crizotinib after an expedited review to include the treatment of patients whose metastatic NSCLC tumors have a ROS1 rearrangement. The approval was based on a 2014 multicenter, single-arm study that enrolled 50 patients with advanced NSCLC who tested positive for
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/21/2016

ROS1 rearrangement. The study was an expansion cohort of the phase 1 PROFILE 1001 Trial. Patients were given oral crizotinib (250 mg twice daily) in continuous 28-day cycles; the median duration of treatment was 65 weeks. The ORR was 72% (95% CI, 58% to 84%), with 3 complete responses and 33 partial responses. The median duration of response was 18 months and median PFS was 19 months. Survival at 12 months was 85% (95% CI, 72% to 93%). A companion ROS1 biomarker diagnostic test was not approved at the time of the crizotinib indication expansion.

Bergethon et al conducted a retrospective analysis of the clinical characteristics and treatment outcomes of patients with NSCLC with a ROS1 rearrangement. They screened 1073 patients from multiple institutions for ROS1 rearrangements using a fluorescence in situ hybridization assay and correlated ROS1 status with clinical characteristics, OS, and, when available, ALK-rearrangement status. Clinical data were extracted from medical record review. In vitro studies with human NSCLC cell lines were also conducted to assess the responsiveness of cells with ROS1 rearrangements to crizotinib. Of the tumors screened, 18 (1.7%) had ROS1 rearrangements and 31 (2.9%) had ALK rearrangements. All ROS1-positive tumors were adenocarcinomas. Patients with ROS1 rearrangements were significantly younger (median age, 49.8 years) and more likely to be never-smokers than the ROS1-negative patients (each p<0.001). No survival difference was observed between the ROS1-positive and -negative groups. The in vitro studies showed evidence of sensitivity to crizotinib.

Kim et al reported clinical outcomes in 208 never-smokers with NSCLC adenocarcinoma, according to ROS1-rearrangement status. ALK rearrangements and EGFR mutations were concurrently analyzed. The patients had clinical stages ranging from I-IV, but most were stage IV (41.3%). Of the 208 tumors, 3.4% (n=7) were ROS1 rearranged. ROS1 rearrangement was mutually exclusive from ALK rearrangement, but 1 of 7 ROS1-positive patients had a concurrent EGFR mutation. Patients with ROS1 rearrangement had a higher objective response rate and longer median PFS on pemetrexed than those without a rearrangement. In patients with ROS1 rearrangement, PFS with EGFR-TKIs was shorter than those patients without the rearrangement. None of the ROS1 positive patients received ALK inhibitors (eg, crizotinib), which is the proposed targeted therapy for patients with NSCLC and this genetic alteration.

RET Gene
In a phase 2 prospective trial for patients with RET fusion–positive tumors, preliminary data on 3 patients treated with cabozantinib showed a partial response in 2 patients, and 1 with stable disease approaching 8 months.

MET Gene
A phase 2 trial of MET-positive NSCLC, in which patients were treated with an anti-MET antibody plus erlotinib, showed improved PFS and OS.

BRAF Gene
Rare case reports have documented a response to vemurafenib in patients with NSCLC and a BRAF mutation.
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/21/2016

HER2 Gene
Mazières et al reported on a retrospective review of a consecutive series of patients with NSCLC tested for a HER2 mutation, and they assessed clinicopathologic characteristics and patient outcomes by mutation status. A HER2 mutation was identified in 65 (1.7%) of 3800 patients, and was mutually exclusive of other driver mutations (EGFR, ALK, BRAF), with the exception of 1 case in which both an HER2 and KRAS mutation were identified. The patient population in which a HER2 mutation was found had a median age of 60 years (range, 31-86 years), 69% were women, and 52% were never-smokers. All tumors were adenocarcinomas, and 50% were stage IV (n=33). Patients with stage IV disease received conventional chemotherapy and, of these, 16 patients also received HER2-targeted therapy as additional lines of therapy (for a total of 22 individual anti-HER2 treatments that were evaluable). Four patients had progressive disease, 7 had disease stabilization, and 11 with partial response. PFS for patients with HER2 therapies was 5.1 months.

Mok et al reported on the biomarker subgroup analyses from the FASTACT-2 study in 2016. FASTACT-2 is a multicenter, randomized, placebo-controlled, double-blind, phase 3 study of intercalated first-line erlotinib or placebo with gemcitabine and platinum, followed by maintenance therapy with erlotinib or placebo, for Asian patients with stage IIIB or IV NSCLC. In addition to analyzing for EGFR, HER2 and HER3 biomarkers were analyzed by immunohistochemistry. Only EGFR mutations (p<0.001) were predictive of outcomes; HER2 and HER3 biomarkers were not significant in a treatment-by-biomarker interaction test.

Shen et al retrospectively reviewed 111 patients from a Uygur population who received gefitinib 250 mg once daily and were evaluated for HER2 expression. HER2 overexpression was detected in 24 patients. The ORR in patients with and without HER2 overexpression was 29% and 14%, respectively (p=0.12). Median PFS and OS in patients with and without HER2 overexpression did not differ statistically significantly (PFS, 4.7 months vs 3.9 months, p=0.09; OS, 21 months vs 19 months, p=0.09).

Ongoing and Unpublished Clinical Trials
Currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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<td>Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer</td>
<td>650</td>
<td>Oct 2017</td>
</tr>
<tr>
<td>Unpublished</td>
<td>Archer 1009: A Randomized, Double Blind Phase 3 Efficacy And</td>
<td>877</td>
<td>Sep 2015</td>
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Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/21/2016

Safety Study Of Pf-00299804 (Dacomitinib) Versus Erlotinib For The Treatment Of Advanced Non-small Cell Lung Cancer Following Progression After, Or Intolerance To, At Least One Prior Chemotherapy

NCT: national clinical trial.
Denotes industry-sponsored or cosponsored trial.

Summary of Evidence
For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for EGFR mutations and ALK rearrangements, the evidence includes phase 3 studies comparing TKIs with chemotherapy. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy in terms of tumor response rate and PFS, with a reduction in toxicity and improvement in quality of life. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have advanced stage NSCLC who are being considered for targeted therapy who receive testing for KRAS, HER2, or BRAF mutations, ROS or RET rearrangements, or MET amplifications, the evidence includes for KRAS post hoc analyses of phase 3 trials, phase 2 trials, a large prospective study, retrospective single-arm studies, and 2 meta-analyses; for the other mutations, the evidence includes a phase 2 trial with preliminary data on 3 patients, and retrospective analyses of very small case series and case reports. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and treatment-related morbidity. Studies have shown that KRAS mutations in patients with NSCLC confer a high level of resistance to TKIs; data are insufficient to assess any association between KRAS mutation status and survival in these patients, and the impact of testing for these mutations on clinical management is unknown. In 2 randomized trials with post hoc analyses of KRAS mutation status and use of anti-EGFR monoclonal antibody cetuximab with chemotherapy, KRAS mutations did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of KRAS mutation status. Studies for ROS, RET, MET, HER2, and BRAF mutation testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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Page 25 of 27
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

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05/07/2015 Medical Policy Committee review
05/20/2015 Medical Policy Implementation Committee approval. New policy. Replaced policy 00122 and 00289.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Added coverage statement for analysis for the T790M mutation and added brand names to the coverage statements.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 12/2017

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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<tr>
<td>CPT</td>
<td>81235, 81479, 88342, 88364, 88365</td>
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<tr>
<td>HCPCS</td>
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<td>ICD-10 Diagnosis</td>
<td>C34.00-C34.02, C34.10-C34.12, C34.2, C34.30-C34.32, C34.80-C34.82, C34.90-C34.92</td>
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</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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