



# Louisiana

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

**Policy #** 00452

**Original Effective Date:** 05/20/2015

**Current Effective Date:** 12/20/2017

*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.*

### EGFR TESTING

Based on review of available data, the Company may consider, except as noted below, analysis of 2 types of somatic variants within the epidermal growth factor receptor (*EGFR*) gene—small deletions in exon 19 and a single-nucleotide variant in exon 21 (L858R)—to predict treatment response to an *EGFR* tyrosine kinase inhibitor (TKI) therapy (eg, erlotinib [Tarceva<sup>®</sup>], gefitinib [Iressa<sup>®</sup>], or afatinib [Gilotrif<sup>®</sup>])<sup>‡</sup>, 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 variants in the *EGFR* gene as a technique to predict treatment response to osimertinib (Tagrisso<sup>®‡</sup>) in patients who have progressed on or after *EGFR* tyrosine kinase inhibitor therapy to be **eligible for coverage**

### 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 variants within the *EGFR* gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—for patients with advanced squamous cell non-small-cell lung cancer (NSCLC) to be **investigational**.\*

Based on review of available data, the Company considers analysis for other *EGFR* variants 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**.\*

### ALK TESTING

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- 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 analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori<sup>®</sup>], ceritinib [Zykadia<sup>™</sup>], alectinib [Alecensa<sup>®</sup>], or brigatinib [Alunbrig<sup>™</sup>])<sup>‡</sup> in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be **eligible for coverage**.

### 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 somatic rearrangement variants of the ALK gene in all other situations to be **investigational**.\*

## BRAF V600E TESTING

### 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 analysis of the BRAF V600E variant to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar<sup>®</sup>] and trametinib [Mekinist<sup>®</sup>])<sup>‡</sup>, in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be **eligible for coverage**.

### 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 the BRAF V600E variant in all other situations to be **investigational**.\*

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### ROS1 TESTING

#### 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 analysis of somatic rearrangement variants of the ROS1 gene to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be **eligible for coverage**.

#### 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 somatic rearrangement variants of the ROS1 gene in all other situations to be **investigational**.\*

### KRAS TESTING

#### 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 somatic variants 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 NSCLC to be **investigational**.\*

### OTHER GENES

#### 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 genetic alterations in the genes HER2, RET, and MET for targeted therapy in patients with NSCLC to be **investigational**.\*

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### Policy Guidelines

These tests are intended for use in patients with advanced non-small-cell lung cancer. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the *EGFR* gene are considered good candidates for treatment with erlotinib, gefitinib or afatinib. Patients with wild-type variants are unlikely to respond to erlotinib or afatinib; for these patients, other treatment options should be considered.

The 2017 guidelines from the National Comprehensive Cancer Network recommend that *EGFR* variants and *ALK* rearrangement testing (category 1) as well as *ROS1* and *BRAF* testing (category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.

The 2013 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology have recommended the following:

- *EGFR* variants and *ALK* rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, smoking history);
- In the setting of fully excised lung cancer specimens, *EGFR* and *ALK* testing is not recommended in lung cancers when an adenocarcinoma component is lacking (eg, pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and
- In the setting of more limited lung cancer specimens (eg, biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, *EGFR* and *ALK* testing may be performed in cases showing squamous cell histology. Clinical criteria (eg, young age, lack of smoking history) may be useful to select a subset of these samples for testing.

### Background/Overview

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, 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* variants and *ALK* rearrangements is routine in clinical decision making for the treatment of NSCLC. The use of testing for other variants to direct targeted therapy 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

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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.

Variants 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 variant 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* variants 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.

### **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 1% to 3% of adenocarcinomas. Unlike melanoma, about 50% of the variants in NSCLC are non-V600E variants. Most *BRAF* variants occur more frequently in smokers.

### **ROS1 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.

### **KRAS Gene**

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

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*EGFR*, *ALK*, *ROS1*, and *KRAS* driver mutations are considered to be mutually exclusive.

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

### **RET Gene**

*RET* (rearranged during transfection) 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 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.

## **TARGETED THERAPIES**

Three orally administered EGFR-selective, small-molecule TKIs have been identified for treating NSCLC: gefitinib (Iressa; AstraZeneca, Cambridge, England), erlotinib (Tarceva; OSI Pharmaceuticals, Melville NY) and afatinib (Gilotrif; Boehringer Ingelheim, Ingelheim, Germany). Gefitinib, erlotinib, and afatinib currently are approved by the U.S. Food and Drug Administration (FDA) for NSCLC.

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* or *ROS1* gene rearrangements. 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. Alectinib is a selective ALK inhibitor with high central nervous system penetration that is active against several secondary resistance variants to crizotinib. Brigatinib is also an ALK inhibitor that may be able to overcome a broad range of the resistance mechanisms in patients who have progressed on or are intolerant to crizotinib.

BRAF or MEK inhibition with TKIs (eg, vemurafenib/dabrafenib or trametinib) was originally approved by FDA for treatment of unresectable or metastatic melanoma with *BRAF* V600 variants. The combination of dabrafenib and trametinib was approved for treatment of metastatic NSCLC in 2017.

For the treatment of *KRAS*-mutated NSCLC, EGFR TKIs and anti-EGFR monoclonal antibodies have been investigated as 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 used in NSCLC.

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Proposed targeted therapies for the remaining genetic alterations in NSCLC addressed are trastuzumab and afatinib for *HER2* variants, crizotinib for *MET* amplification and cabozantinib for *RET* rearrangements.

### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved diagnostic tests.

**Table 1. FDA-Approved Targeted Treatment for NSCLC and Companion Diagnostic Tests**

Treatment	Indication	FDA Approval of Companion Diagnostic Test
Afatinib (Gilotrif)	<ul style="list-style-type: none"> <li>2013: First line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitutions as detected by FDA-approved test</li> <li>2016: Second line for patients with metastatic squamous NSCLC</li> </ul>	2013: theascreen <sup>®</sup> EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen, Netherlands)
Alectinib (Alecensa)	<ul style="list-style-type: none"> <li>2015: Second line for patients with <i>ALK</i>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</li> </ul>	
Ceritinib (Zykadia)	<ul style="list-style-type: none"> <li>2014: Second line for patients with <i>ALK</i>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</li> </ul>	
Crizotinib (Xalkori)	<ul style="list-style-type: none"> <li>2011: Patients with <i>ALK</i>-positive metastatic NSCLC as detected by FDA-approved test</li> </ul>	<ul style="list-style-type: none"> <li>2011: Vysis <i>ALK</i> Break Apart FISH Probe Kit (Abbott Laboratories, Lake Bluff, IL)</li> <li>2015: Ventana <i>ALK</i> (D5F3) CDx Assay (Ventana Medical Systems, Tucson, AZ)</li> </ul>
Crizotinib (Xalkori)	<ul style="list-style-type: none"> <li>2016: Patients with <i>ROS1</i>-positive metastatic NSCLC</li> </ul>	<ul style="list-style-type: none"> <li>2017: Oncomine<sup>™</sup> Dx Target Test (Thermo Fisher Scientific, Waltham, MA)</li> </ul>
Erlotinib (Tarceva)	<ul style="list-style-type: none"> <li>2013: First line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitutions as detected by FDA-approved test</li> <li>2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy</li> <li>2004: Second line for patients with locally advanced or metastatic NSCLC</li> </ul>	<ul style="list-style-type: none"> <li>2013: cobas<sup>®</sup> EGFR Mutation Test (tissue test) (Roche Diagnostics, Indianapolis, IN)</li> <li>2016: cobas EGFR Mutation Test v2 (tissue or blood test) (Roche, Diagnostics, Indianapolis, IN)</li> </ul>
Gefitinib (Iressa)	<ul style="list-style-type: none"> <li>2015: First line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions</li> </ul>	2015: theascreen EGFR Rotor-Gene Q polymerase chain

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Treatment	Indication	FDA Approval of Companion Diagnostic Test
	or exon 21 (L858R) substitutions as detected by FDA-approved test	reaction (RGQ PCR) kit 2017: Oncomine Dx Target Test
	<ul style="list-style-type: none"> <li>2003: Second line for patients with locally advanced or metastatic NSCLC</li> </ul>	
Necitumumab (Portrazza; Eli Lilly, Indianapolis, IN)	<ul style="list-style-type: none"> <li>2015: In combination with gemcitabine and cisplatin, as first line for patients with squamous NSCLC</li> </ul>	
Osimertinib (Tagrisso)	<ul style="list-style-type: none"> <li>2015: Second line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> T790M variants as detected by FDA-approved test, who have not responded to <i>EGFR</i>-blocking therapy</li> </ul>	2015: cobas <i>EGFR</i> Mutation Test v2 (blood test)
Dabrafenib (Tafinlar) and trametinib (Mekinist) combination	<ul style="list-style-type: none"> <li>2017: Used in combination; for treatment of patients with metastatic NSCLC with <i>BRAF</i> V600E variant</li> </ul>	2017: Oncomine Dx Target 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.

### Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD) for mutation testing in NSCLC. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

### Rationale/Source

The evaluation of a prognostic test focuses on 3 main principles: (1) technical reliability (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (prognostic or predictive performance of the test in predicting future risk of clinical disease or response to therapy); and (3) clinical usefulness (ie, a demonstration that the predictive information can be used to improve patient health outcomes).

For any test, it is important to establish its technical reliability, ie, the ability of the test to accurately and reliably measure the characteristic of interest for which the test was designed to identify or measure. Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review. This review focuses on the clinical validity and clinical usefulness.

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### **TARGETED THERAPY FOR ADVANCED-STAGE NON-SMALL-CELL LUNG CANCER**

#### **Clinical Context and Test Purpose**

The purpose of identifying targetable oncogenic “driver mutations” in patients who have NSCLC is to inform a decision whether patients should receive a targeted therapy vs another systemic therapy. Patients who present with advanced disease or recurrence following initial definitive treatment typically receive systemic therapy. Traditionally, the systemic therapy was cytotoxic chemotherapy. However, certain patients may be good candidates for treatment with targeted therapies or immunotherapy. The goal of targeted therapies is to preferentially kill malignant cells without significant damage to normal cells so that there is improved therapeutic efficacy along with decreased toxicity.

The question addressed in this evidence review is this: Does testing for epidermal growth factor receptor (*EGFR*), *BRAF*, *KRAS*, or *HER2* variants; *ALK*, *ROS*, or *RET* rearrangements; or *MET* amplifications improve outcomes in individuals with advanced-stage NSCLC who are being considered for targeted therapy?

The following PICOTS were used to select literature to inform this review.

#### **Patients**

The relevant population of interest is individuals with advanced NSCLC who are being considered for targeted therapy.

#### **Intervention**

The intervention of interest is testing for somatic genome alterations known as “driver mutations,” specifically *EGFR*, *BRAF*, *KRAS*, *BRAF HER2* variants; *ALK*, *ROS*, or *RET* rearrangements; or *MET* amplifications.

#### **Comparator**

The comparator of interest is standard management without testing for driver mutations. Standard management consists primarily of chemotherapy, although some patients are candidates for immunotherapy.

#### **Outcomes**

Beneficial outcomes resulting from a true positive test result are prolonged survival, reduction in toxicity, and improved quality of life associated with receiving a more effective and less toxic targeted therapy instead of chemotherapy in those with driver mutations. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those without driver mutations. Harmful outcomes resulting from a false negative test result include shorter survival from receiving less effective and more toxic chemotherapy in those with driver mutations; possible harmful outcomes resulting from a false positive test result are shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

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### **Time**

Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest are 6 months and 1 year.

### **Setting**

Treatment recommendations for patients with advanced NSCLC are usually made in the tertiary care setting, ideally in consultation with a multidisciplinary team of pathologists, thoracic surgeons, and oncologists.

### **EPIDERMAL GROWTH FACTOR RECEPTOR GENE VARIANTS**

Somatic variants in the tyrosine kinase 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) are the most commonly found *EGFR* variants associated with sensitivity to EGFR tyrosine kinase inhibitors (TKIs; afatinib, erlotinib, gefitinib). These variants are referred to as sensitizing variants. Almost all patients who initially respond to an EGFR TKI eventually develop disease progression. The most common of these secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20.

### **EGFR Variant Frequency**

In 2009, Rosell et al reported *EGFR* variants 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%).

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al (2006) reported *EGFR* variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies. Eberhard et al (2005) observed *EGFR* variants in 6.4% of patients with squamous cell carcinomas (SCCs) and Rosell et al (2009) observed *EGFR* variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes. The acquired *EGFR* T790M variant has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients from 2 studies.

Fang et al (2013) reported *EGFR* variants (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* variant prevalence (all exon 19 deletion or L858R) was 23.8%.

### **Clinical Validity**

*EGFR*-sensitizing and -resistance variants can be detected by direct sequencing, polymerase chain reaction (PCR) technologies, or next-generation sequencing (NGS). Gene sequencing is considered an analytic criterion standard. In 2010, the Canadian Agency for Drugs and Technologies in Health published a rapid response report on *EGFR* variant analysis. Based on 11 observational studies, the report authors

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concluded that PCR-based approaches identify *EGFR* variants with a sensitivity equivalent to that of direct sequencing.

Four tests have been approved as companion diagnostics to detect *EGFR*-resistance variants (exon 19 deletions or exon 21 L858R substitutions) for at least one of the *EGFR* TKIs (afatinib, erlotinib, or gefitinib): the theascreen *EGFR* Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, cobas *EGFR* Mutation Test v1 and v2, and Oncomine Dx Target Test. The cobas v2 test also is approved as a companion diagnostic to detect the T790M resistance variant to select patients for treatment with osimertinib.

The clinical validity of the theascreen RGQ PCR kit was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label randomized controlled trial (RCT) comparing afatinib with chemotherapy in treatment-naive patients with stage IIIB or IV NSCLC, in which the *EGFR* variants for enrollment were determined using a Clinical Trial Assay (CTA) conducted at central laboratories. The positive percent agreement (PPA) of theascreen vs CTA for detection of *EGFR*-sensitizing variants was 98% (95% confidence interval [CI], 95% to 99%) and negative percent agreement (NPA) was 97% (95% CI, 94% to 99%). Overall, a statistically significant efficacy benefit for afatinib vs chemotherapy was reported in the *EGFR*-positive patients as measured by the theascreen *EGFR* RGQ PCR Kit (hazard ratio [HR], 0.49; 95% CI, 0.35 to 0.69) that was similar to the efficacy in the overall population which was *EGFR*-positive by the CTA (HR=0.58; 95% CI, 0.43 to 0.78).

The clinical validity of the cobas *EGFR* Mutation Test v1 was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT comparing erlotinib with chemotherapy in treatment-naive patients with advanced NSCLC. In this RCT, the *EGFR* variants for enrollment were determined with a CTA at a central laboratory using Sanger sequencing first for determination of *EGFR* variants status, followed by confirmatory testing for exon 19 deletions and exon 21 L858R variants. The PPA of cobas vs CTA for detection of *EGFR*-sensitizing variants was 94% (95% CI, 89% to 97%) and NPA was 98% (95% CI, 95% to 99%). Overall, a statistically significant efficacy benefit for erlotinib vs chemotherapy was reported in the *EGFR*-positive patients as measured by the cobas *EGFR* Mutation Test v1 (HR=0.34; 95% CI, 0.21 to 0.54) that was similar to the efficacy in the overall population, which was *EGFR*-positive by the CTA (HR=0.34; 95% CI, 0.23 to 0.49). The cobas *EGFR* Mutation Test v2 expanded the indication for the use of the cobas *EGFR* Mutation Test to add the detection of the exon 20 (T790M) substitution variant in NSCLC patients for whom osimertinib (Tagrisso) treatment is indicated. The clinical validity of the cobas *EGFR* Mutation Test v2 was demonstrated in retrospective analyses of patients enrolled in a phase 2, single-arm study of osimertinib for *EGFR*-sensitizing variant-positive metastatic NSCLC who had progressed following prior therapy with an approved *EGFR* TKI. The osimertinib response rate in the patients identified as *EGFR* T790M-positive by the cobas v2 test was 62% (95% CI, 55% to 69%).

The clinical validity of the Oncomine Dx Target Test was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT, which included newly diagnosed patients with stage IIIB or IV or recurrent NSCLC, in which the *EGFR* variant for enrollment was determined using theascreen. The PPA of Oncomine vs theascreen for detection of *EGFR*-sensitizing variants was 99% (95% CI, 93% to

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100%) and NPA was 99% (95% CI, 96% to 100%). No data on the effectiveness of gefitinib in patients identified as *EGFR*-positive by Oncomine were reported.

*EGFR* variants 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* variant-positive patients compared with wild-type patients regardless of treatment (standard chemotherapy or standard chemotherapy plus erlotinib). The objective radiologic response was 38% vs 23% ( $p=0.01$ ), the median time to progression was 8 months vs 5 months ( $p<0.001$ ), and the median OS was not reached vs 10 months ( $p<0.001$ ).

### Clinical Utility

A TEC Assessment on this topic was published in 2007. It concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of *EGFR* variant 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* variant testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.

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* variant-positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy. Comparators were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively. Among *EGFR* variant-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 variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcome. Similar meta-analyses confirming the PFS and OS results and conclusions for *EGFR*-positive patients have been published.

### Erlotinib

In 2012, Petrelli et al reported on a meta-analysis (13 randomized trials) of 1260 patients with *EGFR*-mutated NSCLC who received TKIs for first-line, second-line, or maintenance therapy. The comparator was standard therapy. Overall, reviewers noted that use of EGFR TKIs increased the chance of obtaining an objective response almost two-fold compared with chemotherapy. Response rates were 70% versus 33% in first-line trials and 47% vs 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.

A summary of 3 key RCTs establishing the superiority of erlotinib over chemotherapy in the first-line setting is given in Tables 2 and 3. The 3 RCTs included 555 patients with stage IIIB or IV NSCLC. All reported clinically and statistically significant improvement in PFS (HR range, 0.16-0.37) but no improvement in OS with erlotinib compared with chemotherapy. Grade 3 or greater adverse events and serious adverse events occurred in fewer patients in the erlotinib groups.

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**Table 2. Characteristics of RCTs of First-Line Erlotinib vs Chemotherapy in EGFR-Variant NSCLC**

Author (Year); Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Erlotinib	Chemotherapy
Zhou (2011, 2015); OPTIMAL (NCT00874419)	China	22	NR	165 patients with stage IIIB/IV NSCLC	83 assigned to erlotinib (150 mg qd)	82 assigned to carboplatin (AUC5) and gemcitabine (1000 mg/m <sup>2</sup> )
Rosell (2012); EURTAC (NCT00446225)	France, Italy, Spain	42	2007-2011	173 patients with stage IIIB/IV NSCLC	86 assigned to erlotinib (150 mg qd)	87 assigned to cisplatin (75mg/m <sup>2</sup> ), docetaxel (75 mg/m <sup>2</sup> ), or gemcitabine (1250 mg/m <sup>2</sup> )
Wu (2015); ENSURE (NCT01342965)	China, Malaysia, Philippines	30	2011-2012	217 patients with stage IIIB/IV NSCLC	110 assigned to erlotinib (150 mg qd)	117 assigned to gemcitabine (1250 mg/m <sup>2</sup> ) and cisplatin (75 mg/m <sup>2</sup> )

AUC5: area under the concentration time curve of 5.0 mg/mL/min; EGFR: epidermal growth factor receptor; NR: not reported; NSCLC: non-small-cell lung cancer; qd: every day; RCT: randomized controlled trial.

**Table 3. Results of RCTs of First-Line Erlotinib vs Chemotherapy in EGFR-Variant NSCLC**

Study (Year)	Median Progression-Free Survival, mo	Median Overall Survival, mo	Adverse Events, %		
			Serious	Grade 3 or 4	%
OPTIMAL (2011, 2015)	N=154	N=154	N=155	N=155	
Erlotinib	13.1 (10.6 to 16.5)	22.8	2	<ul style="list-style-type: none"> <li>• Neutropenia</li> <li>• Thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>• 0</li> <li>• 0</li> </ul>
Chemotherapy	4.6 (4.2 to 5.4)	27.2	14	<ul style="list-style-type: none"> <li>• Neutropenia</li> <li>• Thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>• 42</li> <li>• 40</li> </ul>
TE (95% CI)	HR=0.16 (0.10 to 0.26)	HR=1.19 (0.83 to 1.71)			
EURTAC (2012)					
Erlotinib	9.7 (8.4 to 12.3)	19.3	6	<ul style="list-style-type: none"> <li>• Rash</li> <li>• Neutropenia</li> <li>• Increased aminotransferase concentrations</li> </ul>	<ul style="list-style-type: none"> <li>• 13</li> <li>• 0</li> <li>• 2</li> </ul>
Chemotherapy	5.2 (4.4 to 5.8)	19.5	20	<ul style="list-style-type: none"> <li>• Rash</li> <li>• Neutropenia</li> <li>• Increased aminotransferase concentrations</li> </ul>	<ul style="list-style-type: none"> <li>• 0</li> <li>• 22</li> <li>• 0</li> </ul>
TE (95% CI)	HR=0.37 (0.25 to 0.54)	HR=1.04 (0.65 to 1.68)			
ENSURE (2015)	N=217	N=217	N=214	N=214	
Erlotinib	11.0	26.3	2.7	<ul style="list-style-type: none"> <li>• Overall</li> <li>• Neutropenia</li> <li>• Leukopenia</li> <li>• Anemia</li> <li>• Rash</li> </ul>	<ul style="list-style-type: none"> <li>• 35.5</li> <li>• 0.9</li> <li>• 0.9</li> <li>• 0.9</li> <li>• 6.4</li> </ul>
Chemotherapy	5.5	25.5	10.6	<ul style="list-style-type: none"> <li>• Overall</li> <li>• Neutropenia</li> <li>• Leukopenia</li> <li>• Anemia</li> <li>• Rash</li> </ul>	<ul style="list-style-type: none"> <li>• 57.7</li> <li>• 25.0</li> <li>• 14.4</li> <li>• 12.5</li> <li>• 1</li> </ul>

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TE (95% CI)	HR=0.34 (0.22 to 0.51)	HR=0.91 (0.63 to 1.31)	Adverse Events, %
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CI: confidence interval; *EGFR*: epidermal growth factor receptor; HR: hazard ratio; NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial; TE: treatment effect.

Many additional publications have provided data on *EGFR* variants in tumor samples obtained from NSCLC patients treated with in erlotinib. 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 variants; four were prospective, single-arm enrichment studies of variant-positive or wild-type patients treated with erlotinib. In 3 studies of *EGFR* variant-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.

### Gefitinib

Three RCTs described in Tables 4 and 5 have compared gefitinib with chemotherapy in the first-line setting. Three RCTs included 668 patients with stage IIIB or IV NSCLC and *EGFR*-sensitizing variants. All reported clinically and statistically significant improvement in PFS (HR range, 0.30-0.49) but no improvement in OS with gefitinib compared with chemotherapy. Grade 3 or greater adverse events occurred in fewer patients in the gefitinib groups. The IPASS trial enrolled patients with and without *EGFR*-sensitizing variants. The investigators reported a significant interaction between treatment and *EGFR* variant status concerning PFS (interaction  $p < 0.001$ ); PFS was longer for gefitinib in patients with *EGFR*-sensitizing variants and shorter for gefitinib in patients without *EGFR*-sensitizing variants.

**Table 4. Characteristics of RCTs of First-Line Gefitinib vs Chemotherapy in *EGFR*-Variant NSCLC**

Author (Year); Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Gefitinib	Chemotherapy
Mok (2009); IPASS (NCT00322452)	9 East Asian countries	87	2006-2007	1217 patients with stage IIIB/IV NSCLC (261 <i>EGFR</i> -positive)	609 assigned to gefitinib (250 mg/d)	608 assigned to paclitaxel (200 mg/m <sup>2</sup> ) and carboplatin (AUC5 or AUC6)
Mitsudomi (2010); West Japan Oncology Group 172 trial; WJTOG3405	Japan	36	2006-2009	177 patients with stage IIIB/IV or recurrent NSCLC	88 assigned to gefitinib (250 mg/d)	89 assigned to cisplatin (80 mg/m <sup>2</sup> ) and docetaxel (60 mg/m <sup>2</sup> )
Maemondo (2010), Inoue (2013); NEJ002	Japan	43	2006-2009	230 patients with stage IIIB/IV NSCLC or postoperative relapse	115 assigned to gefitinib (250 mg/d)	115 assigned to paclitaxel (200 mg/m <sup>2</sup> ) and carboplatin (AUC6)

AUC5: area under the concentration time curve of 5.0 mg/mL/min; AUC6: area under the concentration time curve of 6.0 mg/mL/min; *EGFR*: epidermal growth factor receptor; NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial.

**Table 5. Results of RCTs of First-Line Gefitinib vs Chemotherapy in *EGFR*-Variant NSCLC**

Study (Year)	Median Progression-Free Survival, mo	Median Overall Survival, mo	Adverse Events, %		
			Serious	Grade 3 or 4	%
IPASS (2009)	N=259 <sup>a</sup>	N=259 <sup>a</sup>	N=1196 <sup>b</sup>		

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				Adverse Events, %	
Gefitinib	≈9.6 <sup>c</sup>	NR	16.3%	<ul style="list-style-type: none"> <li>Rash</li> <li>Diarrhea</li> <li>Neurotoxic effects</li> <li>Neutropenia</li> <li>Anemia</li> <li>Leukopenia</li> </ul>	<ul style="list-style-type: none"> <li>3.1</li> <li>3.8</li> <li>0.3</li> <li>3.7</li> <li>2.2</li> <li>1.5</li> </ul>
Chemotherapy	≈5.8 <sup>c</sup>	NR	15.6%	<ul style="list-style-type: none"> <li>Rash</li> <li>Diarrhea</li> <li>Neurotoxic effects</li> <li>Neutropenia</li> <li>Anemia</li> <li>Leukopenia</li> </ul>	<ul style="list-style-type: none"> <li>0.8</li> <li>1.4</li> <li>4.9</li> <li>67.1</li> <li>10.6</li> <li>35.0</li> </ul>
TE (95% CI)	HR=0.48 (0.36 to 0.64)	HR=0.78 (0.50 to 1.20)			
WJTOG3405 (2010)					
	N=172	N=172	NR	N=172	
Gefitinib	9.2 (8.0 to 13.9)	34.8 (26.0 to 39.5)		<ul style="list-style-type: none"> <li>ALT/AST elevation</li> <li>Rash</li> <li>Fatigue</li> <li>Neutropenia</li> <li>Leucocytopenia</li> <li>Anemia</li> </ul>	<ul style="list-style-type: none"> <li>27.5</li> <li>2.3</li> <li>2.3</li> <li>0</li> <li>0</li> <li>0</li> </ul>
Chemotherapy	6.3 (5.8 to 7.8)	37.3 (31.2 to 45.5)		<ul style="list-style-type: none"> <li>ALT/AST elevation</li> <li>Rash</li> <li>Fatigue</li> <li>Neutropenia</li> <li>Leucocytopenia</li> <li>Anemia</li> </ul>	<ul style="list-style-type: none"> <li>2.3</li> <li>0</li> <li>2.3</li> <li>84</li> <li>50</li> <li>17</li> </ul>
TE (95% CI)	HR=0.49 (0.34 to 0.71)	HR=1.25 (0.88 to 1.78)			
NEJ002 (2010, 2013)					
	N=224		NR	N=227	
Gefitinib	10.8	27.7		<ul style="list-style-type: none"> <li>Rash</li> <li>Neuropathy</li> <li>Arthralgia</li> <li>Pneumonitis</li> <li>Aminotransferase elevation</li> <li>Neutropenia</li> <li>Anemia</li> <li>Thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>5.3</li> <li>0</li> <li>0.9</li> <li>2.6</li> <li>26.3</li> <li>0.9</li> <li>0</li> <li>0</li> </ul>
Chemotherapy	5.4	26.6		<ul style="list-style-type: none"> <li>Rash</li> <li>Neuropathy</li> <li>Arthralgia</li> <li>Pneumonitis</li> <li>Aminotransferase elevation</li> <li>Neutropenia</li> <li>Anemia</li> <li>Thrombocytopenia</li> </ul>	<ul style="list-style-type: none"> <li>2.7</li> <li>6.2</li> <li>7.1</li> <li>0</li> <li>0.9</li> <li>65.5</li> <li>5.3</li> <li>3.5</li> </ul>
TE (95% CI)	HR = 0.30 (0.22 to 0.41)	HR=0.89 (0.63 to 1.24)			

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ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; *EGFR*: epidermal growth factor receptor; HR: hazard ratio; NR: not reported; NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial; TE: treatment effect.

<sup>a</sup> Analysis includes all patients with safety data.

<sup>b</sup> Analysis includes all patients with safety data.

<sup>c</sup> Estimated from figure.

### Afatinib

Unlike erlotinib and gefitinib, which selectively inhibit EGFR, afatinib inhibits not only EGFR but also HER2 and HER4, and may have activity in patients with acquired resistance to TKIs; such patients often harbor a T790M variant (substitution of threonine by methionine at codon 790) in *EGFR* exon 20. The efficacy and safety of afatinib were evaluated in the LUX-Lung series of studies.

LUX-Lung 3 was an RCT in 345 patients with stage IIIB or IV, *EGFR* variant-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* variants (exon 19 deletion or *L858R* substitution variant in exon 21). Patients received afatinib or chemotherapy (cisplatin plus pemetrexed). In stratified analysis of patients with common *EGFR* variants, the 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). The median PFS for the 10% of patients who had other *EGFR* variants was not reported, but the 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). The 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, the 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 1% of the chemotherapy group. Similar results were reported in 2014 phase 3 trial conducted in 364 Asian patients (Lux-Lung 6) comparing afatinib with gemcitabine plus cisplatin. PFS was 11.0 in the afatinib group and 5.6 months in the chemotherapy group (HR=0.28; 95% CI, 0.20 to 0.39) and the response rate was 67% and 23%.

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

- LUX-Lung 2 was a single-arm study (2012) of afatinib in 129 patients (87% Asian, 12% white) with *EGFR* variant-positive disease. Patients had been treated with 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* variants (exon 19 deletion or *L858R*) and in 39% of 23 patients with other *EGFR* variants. The median PFS was 13.7 months in patients with common *EGFR*

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variants and 3.7 months in patients with other *EGFR* variants (p not reported). Results for variant-negative patients were not reported.

- LUX-Lung 1 and LUX-Lung 4 enrolled patients who had progressed on previous treatment with erlotinib, gefitinib, or both for advanced disease. Neither study prospectively genotyped patients. In the LUX-Lung 1 double-blind RCT, 96 (66% Asian, 33% white) of 585 enrolled patients were *EGFR* variant-positive (76 common *EGFR* variant-positive). In this group, the 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 variant-negative patients, the 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 (2013) of afatinib in 62 Japanese patients. Objective responses occurred in 2 (5%) of 36 patients with common *EGFR* variants and in none of 8 patients with other *EGFR* variants (p>0.05).

### **Comparative Effectiveness of *EGFR* TKIs**

As the previous sections have shown, erlotinib, gefitinib, and afatinib all have improved efficacy compared with chemotherapy in patients who have NSCLC and *EGFR*-sensitizing variants and are well tolerated. RCTs directly comparing the *EGFR* TKIs have been conducted.

Yang et al (2017) published a meta-analysis of studies comparing erlotinib, gefitinib, and afatinib. Eight randomized trials (n=2225 patients) and 82 cohort studies (n=15,396 patients) were included. However, results were not presented for trials vs cohort studies separately. Of the 8 RCTs identified, three were published in journals not available through PubMed, one was available as an abstract only, one was conducted in squamous cell NSCLC, and one did not require testing to confirm *EGFR* variant status for enrollment; these RCTs will not be discussed further. The two remaining studies are briefly discussed below.

Both RCTs have compared gefitinib with erlotinib in patients who had *EGFR*-sensitizing variants. Urata et al (2016) reported on a phase 3 RCT of 401 patients with *EGFR* variants randomized to gefitinib or erlotinib. The median PFS was 8.3 months (95% CI, 7.2 to 9.7 months) for patients receiving gefitinib and 10.0 months for those receiving erlotinib (95% CI, 8.5 to 11.2 months). Rash was more common with erlotinib (18.1% vs 2.2%) while both alanine aminotransferase elevation and aspartate aminotransferase elevation were more common with gefitinib (6.1% vs 2.2% and 13.0% vs 3.3%, respectively). Similarly, Yang et al (2017) reported a median PFS of 13.0 for erlotinib and 10.4 months for gefitinib (HR=0.81; 95% CI, 0.62 to 1.05) in 256 patients with no differences in rates of grade 3 or 4 adverse events.

LUX-7 was a phase 2b, head-to-head trial of afatinib vs gefitinib for the treatment of first-line *EGFR* variant-positive (del19 and L858R) adenocarcinoma of the lung. LUX-7 included 319 patients in a 1:1 ratio to afatinib 40 mg/d or gefitinib 250 mg/d, stratified by variant type (del19 and L858R) and brain metastases (present vs 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). The objective response rate (ORR) was significantly

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higher in the afatinib group (70% vs 56%; p=0.01). Several grade 3 or 4 adverse events were more common with afatinib compared with gefitinib including diarrhea (13% vs 1%) and rash (9% vs 3%); liver enzyme elevations were more common with gefitinib (0% vs 9%). Serious events occurred in 11% of patients in the afatinib group and 4% in the gefitinib group.

### **Osimertinib**

In 2015, the U.S. FDA granted accelerated approval to osimertinib for treatment of metastatic *EGFR* T790M variant-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* variants including the T790M variant. Approval was based on 2 multicenter, single-arm studies.

The osimertinib label describes the 2 studies. Eligible patients had metastatic *EGFR* T790M variant-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 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 the following: 4 patients with interstitial lung disease/pneumonitis; 4 patients with pneumonia, and 2 patients with cerebral vascular accident/cerebral hemorrhage.

One RCT has been conducted and is described in Tables 6 and 7. Osimertinib was associated with clinically and statistically significantly prolonged PFS and higher response rates compared with chemotherapy with lower rates of grade 3 and 4 adverse events. However, interstitial lung disease-like adverse events and QT prolongation were more common with osimertinib.

**Table 6. Osimertinib Randomized Controlled Trial Characteristics in *EGFR*-Variant NSCLC**

Author (Year); Study	Countries	Sites	Dates	Participants	Description of Interventions	
					Osimertinib	Chemotherapy
Mok (2017); AURA3 (NCT02151981)	18 countries in North America, Europe, Australia, Asia	126	2014-2015	419 T790M-positive advanced NSCLC who had disease progression after first- line EGFR-TKI therapy	n=279 to osimertinib (80 mg/d)	n=140 to platinum- pemetrexed (500 mg/m <sup>2</sup> of body-surface area) plus carboplatin (target AUC5 or cisplatin [75 mg/m <sup>2</sup> ])

AUC5: area under the concentration time curve of 5.0 mg/mL/min; *EGFR*: epidermal growth factor receptor; NSCLC: non-small-cell lung cancer; TKI: tyrosine kinase inhibitor.

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**Table 7. Osimertinib Randomized Controlled Trial Results in EGFR-Variant NSCLC**

Study (Year)	PFS, mo	OS, mo	ORR (95% CI%)	Grade ≥3 AEs, %	ILD-Like AEs, %	Prolongation of QT Interval, %
AURA3(2017)	N=419		N=419	N=415	N=415	N=415
Osimertinib	10.1	NR	71% (65 to 76)	23	4	4
Platinum–pemetrexed	4.4	NR	31% (24 to 40)	47	1	1
TE (95% CI)	HR=0.30 (0.23 to 0.41; p<0.001)		OR=5.4 (3.5 to 8.5)			

AE: adverse event; CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; ILD: interstitial lung disease; NR: not reported; NSCLC: non-small-cell lung cancer; OR: odds ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TE: treatment effect.

### Section Summary: Epidermal Growth Factor Receptor Gene Variants

Several RCTs, nonconcurrent prospective studies, and single-arm enrichment studies have demonstrated that patients with EGFR-sensitivity variants benefit from erlotinib, gefitinib, or afatinib therapy and patients with EGFR-resistance variant (T790M) benefit from osimertinib. These observations have been made in populations primarily with adenocarcinomas. Currently, there is little evidence to indicate that EGFR variant testing can guide treatment selection in patients with squamous cell histology. FDA has approved several companion diagnostics for detecting EGFR variants to aid in selecting NSCLC patients for treatment with erlotinib, gefitinib, afatinib and osimertinib.

Patients who are found to have wild-type tumors are unlikely to respond to erlotinib, gefitinib, or afatinib. They patients should be considered candidates for alternative therapies.

### ALK GENE REARRANGEMENTS

ALK gene rearrangements most often consist of an inversion in chromosome 2 which leads to fusion with the echinoderm microtubule-associated protein like 4 (EML4) gene and a novel fusion oncogene EML4-ALK. This inversion causes abnormal expression and activation of ALK tyrosine kinase. This rearrangement occurs in 3% to 6% of NSCLC.

### Clinical Validity

Several methods are available to detect ALK gene rearrangements or the resulting fusion proteins in tumor specimens including fluorescence in situ hybridization (FISH), immunohistochemistry, reverse transcription polymerase chain reaction (RT-PCR) of cDNA, and NGS. Two tests have been approved by FDA as companion diagnostics to detect ALK rearrangements for treatment with crizotinib: the Vysis ALK Break Apart FISH Probe Kit and Ventana ALK (D5F3) CDx Assay.

The Vysis kit is a FISH-based assay. The clinical validity of the Vysis ALK Break Apart FISH Probe Kit was demonstrated in a retrospective analysis of patients screened for a phase 2, open-label single-arm study of crizotinib in patients with stage IIIB or IV NSCLC. The response rate for crizotinib in 136 ALK-positive patients was 50% (95% CI, 42% to 59%) with a median duration of response of 42 weeks (range, 6-42). The response rate for 19 ALK-negative patients was 26% (95% CI, 9% to 51%).

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The Ventana assay is an immunohistochemical-based assay. The clinical validity of the Ventana ALK (D5F3) CDx Assay was demonstrated in a retrospective analysis of patients screened for an open-label RCT of crizotinib vs platinum-doublet chemotherapy in patients with stage IIIB or IV NSCLC. The concordance between the Ventana and Vysis tests were calculated using patient samples analyzed at an independent, central laboratory. The PPA was 86.0% (95% CI, 80.2% to 90.4%) and the NPA was 96.3% (94.7% to 97.4%). Overall, in 343 patients who were *ALK*-positive by the Vysis assay, crizotinib was associated with longer PFS compared with chemotherapy (HR=0.45; 95% CI, 0.36 to 0.60). In the subset of 141 patients who were also *ALK*-positive by the Ventana assay, the results were similar (HR=0.40; 95% CI, 0.25 to 0.64). In the 25 patients that were *ALK*-positive by the Vysis assay and *ALK*-negative by the Ventana assay, the relative effect of crizotinib was not clear (HR=1.71; 95% CI, 0.43 to 6.79).

### Clinical Utility

#### **Crizotinib**

The accelerated approval of crizotinib by FDA was based on phase 1 and 2 trials in which crizotinib showed marked antitumor activity in patients with *ALK*-positive advanced NSCLC, with an ORR of 60% and PFS range from 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 before the trial. The extent of metastatic disease was 95% and 91% in 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 crizotinib as part of a separate study. The median PFS was 7.7 months in the crizotinib group vs 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 rates with crizotinib were 65% (95% CI, 58% to 72%) vs 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). The median follow-up for OS was 12.2 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 than 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 plus 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 vs chemotherapy, respectively (HR for progression or death with crizotinib, 0.45; 95% CI, 0.35 to 0.60; p<0.001); ORRs (complete and partial responses) were 74% and 45%, respectively (p<0.001). The median OS was not reached in either group; the probability of 1-year survival with crizotinib was 84% and 79% with

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chemotherapy. Crizotinib was associated with patient-reported greater reduction in lung cancer symptoms and greater improvements in quality of life.

### **Other ALK Inhibitors**

Three other ALK TKIs are FDA-approved but without separate companion diagnostics. Ceritinib has demonstrated superior efficacy concerning PFS when compared with chemotherapy in both the first-line and second-line (following crizotinib) settings in the ASCEND-4 and ASCEND-5 RCTs. Alectinib was associated with response rates of approximately 50% in patients who had progressed on crizotinib in 2 phase 2 studies. Alectinib has also shown superior efficacy and lower toxicity when compared with crizotinib in the first-line setting in the ALEX and J-ALEX phase 3 RCTs. Brigatinib has shown promise in early phase 1 and phase 2 studies with PFS of almost 13 months in patients with crizotinib-refractory disease.

### **Section Summary: ALK Gene Rearrangements**

Crizotinib was granted accelerated approval by FDA in 2011 for patients with locally advanced or metastatic NSCLC, based on ORRs observed in 2 single-arm trials. Two subsequent phase 3 trials have shown superior PFS and tumor response rates and improved quality of life in patients with crizotinib vs chemotherapy, in both previously untreated and untreated *ALK*-positive advanced NSCLC. FDA has approved 2 companion diagnostics for detecting *ALK* gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib.

### **BRAF GENE VARIANTS**

#### **Clinical Validity**

*BRAF* variants are detected by PCR sequencing or NGS methods. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect *BRAF* V600E variants to aid in selecting NSCLC patients for treatment with combination dabrafenib (Tafinlar) and trametinib (Mekinist) therapy. The Oncomine test is an NGS oncology panel that detects, among other variants, *BRAF* V600E variants from DNA isolated from FFPE tumor tissue samples. The clinical validity of the detection of *BRAF* V600E variants by the test was evaluated by retrospective analyses of a phase 2, multicenter, nonrandomized study including patients with a *BRAF* V600E variant who had progressed on prior treatment or were treatment naive who were treated with dabrafenib in combination with trametinib in the study. Patients were screened for a *BRAF* V600E variant based on local lab tests used at each of the enrollment sites. No FDA-approved test was available for detection of *BRAF* V600E variants in FFPE NSCLC specimens so a validated PCR assay, *BRAF* V600 PCR Mutation Test, also was used to estimate concordance. The concordance between the Oncomine test and the *BRAF* V600 PCR Mutation Test was 100% for PPA (95% CI, 95% to 100%) and 100% for NPA (95% CI, 97% to 100%). The response rate in the 57 previously treated patients in the study that were *BRAF*-positive by local lab test was 67% (95% CI, 53% to 79%) compared with 73% (95% CI, 50% to 89%) for the 22 patients that were also *BRAF*-positive by Oncomine. The response rate in the 36 treatment-naive patients who were *BRAF*-positive by local lab test was 61% (95% CI, 44% to 77%) compared with 61% (95% CI, 39% to 80%) in the 23 patients who were also *BRAF*-positive by Oncomine.

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### Clinical Utility

In June 2017, FDA approved an additional indication for use of dabrafenib and trametinib combination therapy in patients with NSCLC with *BRAF* V600E variant as detected by an FDA-approved test. The Oncomine Dx Target Test was approved as a companion diagnostic. The dabrafenib and trametinib product labels describe the results of an open-label, multicenter study of patients enrolled 3 cohorts: cohorts A and B had received at least one previous platinum-based chemotherapy regimen with demonstrated disease progression but no more than 3 prior systemic regimens; cohort C could not have received prior systemic therapy for metastatic disease. Trial results for cohorts A and B have also been published in Planchard (2016)<sup>79</sup> and Planchard (2016) and are shown in the table below. Cohort A (n=78) received dabrafenib; cohorts B (n=57) and C (n=36) received dabrafenib and trametinib combination therapy. The response rate in cohort C (treatment-naive, received combination therapy) was 61% (95% CI, 44% to 77%).

The characteristics and results of key nonrandomized trials of BRAF or MEK inhibitors in NSCLC are described in Tables 8 and 9. In summary, the response rate for dabrafenib monotherapy in 78 patients who had progressed on chemotherapy was 33% at 11 months median follow-up while the response rate for 19 patients (17 of whom had progressed on chemotherapy) treated with vemurafenib monotherapy was 42% at 8 weeks. Response rates for dabrafenib and trametinib combination therapy were higher than 60% in patients who had progressed on prior treatment and those that were treatment-naive. Toxicities were similar to those seen in melanoma patients taking BRAF or MEK inhibitors. SCCs and other dermatological side effects were reported.

**Table 8. Study Characteristics of Key Nonrandomized Trials of BRAF or MEK Inhibitors in BRAF-Variant NSCLC**

Author (Year)	Study Type	Country	Dates	Participants	Treatment	Median FU, mo
Planchard et al (2016) NCT01336634	Single-arm, open-label phase 2 trial	9 countries in North America, Europe, Asia	2011-2014	Adults, stage IV, <i>BRAF</i> V600E variant, progression after chemotherapy	Dabrafenib (150 mg bid)	10.7
Planchard et al (2016); NCT01336634	Single-arm, open-label phase 2 trial	9 countries in North America, Europe, Asia	2013-2015	Adults, stage IV, <i>BRAF</i> V600E variant, progression after chemotherapy	Dabrafenib (150 mg bid) plus trametinib (2 mg/d)	11.6
Hyman et al (2015); NCT01524978	Single-arm, open-label phase 2 trial	Germany, Spain, U.K., U.S., France	2012-2014	<i>BRAF</i> V600 variant-positive nonmelanoma cancers including NSCLC	Vemurafenib (960 mg bid)	6 <sup>a</sup>

bid: twice a day; FU: follow-up; NSCLC: non-small-cell lung cancer.

<sup>a</sup> Estimated from a figure.

**Table 9. Results of Key Nonrandomized Trials of BRAF or MEK Inhibitors in BRAF-Variant NSCLC**

Study (Year)	Response (95% CI), %	PFS (95% CI), mo	Overall Survival	Adverse Events, %			
				Grade 3 or 4	%	Serious	%
Planchard et	N=78	N=78	N=78	N=78		N=78	

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al (2016)	33 (23 to 45) <sup>a</sup>	5.5 (3.4 to 7.3)	Median, 12.7 mo	<ul style="list-style-type: none"> <li>• Overall</li> <li>• Cutaneous SCC</li> <li>• Asthenia</li> <li>• BCC</li> </ul>	<ul style="list-style-type: none"> <li>• 39</li> <li>• 12</li> <li>• 5</li> <li>• 5</li> </ul>	<ul style="list-style-type: none"> <li>• Overall</li> </ul>	<ul style="list-style-type: none"> <li>• 42</li> </ul>
Planchard et al (2016)	N=57	N=57	N=57	N=57		N=57	
	63 (49 to 76)	9.7 (6.9 to 19.6)	At 6 mo, 82%	<ul style="list-style-type: none"> <li>• Overall</li> <li>• Neutropenia</li> <li>• Hyponatremia</li> </ul>	<ul style="list-style-type: none"> <li>• 49</li> <li>• 9</li> <li>• 7</li> </ul>	<ul style="list-style-type: none"> <li>• Overall</li> <li>• Pyrexia</li> <li>• Anemia</li> <li>• Cutaneous SCC</li> </ul>	<ul style="list-style-type: none"> <li>• 56</li> <li>• 16</li> <li>• 5</li> <li>• 4</li> </ul>
Hyman et al (2015)	N=19	N=20	N=20	• N=95 <sup>b</sup>			
	At 8 wk, 42 (20 to 67)	Median, 7.3 (3.5 to 10.8)	At 12 mo, 66% (36% to 85%)	<ul style="list-style-type: none"> <li>• Overall</li> <li>• Rash</li> <li>• Fatigue</li> <li>• Arthralgia</li> </ul>	<ul style="list-style-type: none"> <li>• 73</li> <li>• 16</li> <li>• 12</li> <li>• 4</li> </ul>		

AE: adverse events; BCC: basal cell carcinoma; CI: confidence interval; NSCLC: non-small-cell lung cancer; PFS: progression-free survival; SCC: squamous cell carcinoma.

<sup>a</sup> The response rate in the Food and Drug Administration product label for this cohort was 27% (18% to 38%).

<sup>b</sup> Only reported for entire cohort including all cancer types

Case reports have documented a response to vemurafenib in patients with NSCLC and a *BRAF* variant.

### Section Summary: *BRAF* Gene Variants

FDA has approved a companion diagnostic for detecting *BRAF* variants to aid in selecting NSCLC patients for treatment with combination *BRAF* and MEK inhibitors, dabrafenib and trametinib. The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. FDA expanded the indication for dabrafenib and trametinib to include the treatment of NSCLC patients whose tumors have a *BRAF* V600E variant based on a multicenter, single-arm study that included a cohort of 57 patients who had progressed on prior therapy and a cohort of 36 treatment-naïve patients. Dabrafenib and trametinib combination therapy was very effective in patients with a *BRAF* V600E variant with a response rate of about 60% in both cohorts. Lower response rates were reported in other nonrandomized studies of *BRAF* inhibitor monotherapy in patients who had previously progressed on prior treatments.

### *ROS1* GENE REARRANGEMENTS

#### Clinical Validity

Several methods are available to detect *ROS1* translocations including FISH, immunohistochemistry, quantitative real-time reverse transcription-PCR (qRT-PCR), and some NGS panels. FISH is considered the standard method. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori). The Oncomine test is an NGS oncology panel that detects, among other variants, fusions in *ROS1* from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples. The clinical validity of the detection of *ROS1* rearrangements by the test was evaluated by retrospective analysis of FFPE NSCLC specimens obtained from patients enrolled in a *ROS1* cohort from an ongoing single-arm, phase 1 safety

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study of crizotinib in patients with advanced cancer. *ROS1* fusion status was determined by a validated FISH comparator test for the study. Concordance between the Oncomine Dx Target Test and the FISH test as well as clinical outcomes were reported in the Summary of Safety and Effectiveness Data. A total of 157 specimens were included. The PPA for Oncomine vs FISH was 80% (95% CI, 59 to 93) and NPA was 100% (95% CI, 97% to 100%). For all *ROS1*-positive patients, as originally detected for enrollment into the *ROS1* cohort, the response rate was 72% (95% CI, 58% to 84%). For *ROS1*-positive patients as detected by Oncomine, the response rate was 83% (95% CI, 36% to 99.6%).

### Clinical Utility

In 2016, after an expedited review, the FDA expanded the indication for crizotinib 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 *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. Characteristics and results of this and other nonrandomized studies are shown in Tables 10 and 11. A companion *ROS1* biomarker diagnostic test was not approved at the time of the crizotinib indication expansion. However, the Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori).

In summary, a nonrandomized trial and an observational study of crizotinib have shown response rates of greater than 70% in patients with *ROS1* rearrangements, the majority of which had progressed on prior therapy. One nonrandomized trial of ceritinib reported response rates of about 60%. Adverse events were similar to those seen in patients with *ALK* rearrangements using *ALK* TKIs. Common low-grade side effects include gastrointestinal side effects, visual impairment, and pain. Grade 3 or higher adverse events include liver function abnormalities and pneumonia.

**Table 10. Study Characteristics of Key Nonrandomized Trials and Observational Studies of Crizotinib or Ceritinib for *ROS1* Rearrangements in NSCLC**

Author (Year)	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Shaw et al (2014)	Open-label, single-arm, expansion cohort of phase 1 study	Australia, Korea, U.S.	2010-2013	Adults with <i>ROS1</i> rearrangement, 86% had received prior therapy	Crizotinib (250 mg bid)	16.4
Mazieres et al (2015)	Retrospective study	Six European countries	NR	<i>ROS1</i> rearrangement, 97% had received previous chemotherapy	Crizotinib (250 mg bid)	NR
Lim et al (2017)	Open-label, single-arm, phase 2 study	Korea	2013-2016	Adults with <i>ROS1</i> rearrangement who had progressed on prior therapy, 94% crizotinib-naive	Ceritinib (750 mg/d)	14.0

bid: twice a day; NR: not reported; NSCLC: non-small-cell lung cancer.

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**Table 11. Results of Key Nonrandomized Trials and Observational Studies of Crizotinib or Ceritinib for *ROS1* rearrangements in NSCLC**

Study (Year)	Response (95% CI), %	Median PFS (95% CI), mo	OS (95% CI)	Adverse Events, %			
				Grade 3 or 4	%	All Grades	%
Shaw et al (2014)	N=50	N=50	N=50	N=50		N=50	
	72 (58 to 84)	19.2 mo (14.4 to not reached)	At 12 mo: 85% (72% to 93%)	<ul style="list-style-type: none"> <li>• Hypophosphatemia</li> <li>• Neutropenia</li> <li>• Elevated ALT</li> </ul>	<ul style="list-style-type: none"> <li>• 10</li> <li>• 10</li> <li>• 4</li> </ul>	<ul style="list-style-type: none"> <li>• Visual impairment</li> <li>• Diarrhea</li> <li>• Nausea</li> <li>• Peripheral edema</li> <li>• Constipation</li> <li>• Vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• 82</li> <li>• 44</li> <li>• 40</li> <li>• 40</li> <li>• 34</li> <li>• 34</li> </ul>
Mazieres et al (2015)	N=29	N=30		N=30			
	80 (CI NR)	9.1 mo (CI NR)	NR	<ul style="list-style-type: none"> <li>• Grade 3 NR</li> <li>• Grade 4 or 5</li> </ul>	<ul style="list-style-type: none"> <li>• NR</li> <li>• 0</li> </ul>	NR	
Lim et al (2017)	N=28	N=32	N=32	N=32		N=32	
	62 (45 to 77)	9.3 mo (0 to 22)	24 mo (5 to 43)	<ul style="list-style-type: none"> <li>• Overall</li> <li>• Fatigue</li> <li>• Pneumonia</li> <li>• Hyperglycemia</li> <li>• Increased AST</li> <li>• Increased ALT</li> </ul>	<ul style="list-style-type: none"> <li>• 37</li> <li>• 16</li> <li>• 6</li> <li>• 9</li> <li>• 9</li> <li>• 6</li> </ul>	<ul style="list-style-type: none"> <li>• Diarrhea</li> <li>• Nausea</li> <li>• Anorexia</li> <li>• Vomiting</li> <li>• Cough</li> <li>• Abdominal pain</li> <li>• Musculoskeletal pain</li> </ul>	<ul style="list-style-type: none"> <li>• 78</li> <li>• 59</li> <li>• 56</li> <li>• 53</li> <li>• 47</li> <li>• 41</li> <li>• 41</li> </ul>

AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; PFS: progression-free survival; NR: not reported; NSCLC: non-small-cell lung cancer; OS: overall survival.

Kim et al (2013) reported on clinical outcomes in 208 never-smokers with NSCLC adenocarcinoma, according to *ROS1*-rearrangement status. *ALK* rearrangements and *EGFR* variants were concurrently analyzed. The patients had clinical stages ranging from I to 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* variant. Patients with *ROS1* rearrangement had a higher ORR 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 recommended targeted therapy for patients with NSCLC and this genetic alteration.

### Section Summary: *ROS1* Gene Rearrangements

FDA has approved a companion diagnostic for detecting *ROS1* gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori). The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. FDA expanded the indication for crizotinib to include the treatment of patients whose tumors have a *ROS1* rearrangement based on a multicenter, single-arm study including 50 patients, the majority of whom had progressed on prior therapy.

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# Louisiana

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

Policy # 00452

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Crizotinib was very effective in patients with *ROS1* rearrangements with a response rate of about 70%. Similar response rates were reported in other nonrandomized studies of crizotinib and ceritinib.

### **KRAS GENE VARIANTS**

#### **Clinical Validity**

*KRAS* variants can be detected by direct sequencing, PCR technologies or NGS. Although *KRAS* is the most common driver mutation in NSCLC, there are currently no targeted therapies specifically approved for patients with NSCLC with *KRAS* variants and therefore, no FDA-approved companion diagnostics.

#### **Clinical Utility**

##### ***KRAS* Variants and EGFR TKIs**

Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analyses of phase 3 trials of TKIs in patients with wild-type (nonmutated) vs *KRAS*-mutated lung tumors; phase 2 trials; a large prospective study; retrospective single-arm studies; and meta-analyses.

##### *Systematic Reviews*

Meta-analyses on the relation between *KRAS* variants and response to EGFR-TKI therapy are outlined next. The pooled data were insufficient to determine an association between *KRAS* variant 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* variant. Eligible studies reported response (complete or partial) stratified by *KRAS* variant status. Primary end points were sensitivity and specificity of *KRAS* testing, defined as *KRAS* variant 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 (Response Evaluation Criteria in Solid Tumors [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* variant was associated with a lack of response to TKIs (sensitivity, 21%; 95% CI, 16% to 28%; specificity, 94%; 95% CI, 89% to 97%; positive likelihood ratio, 3.52; negative likelihood ratio, 0.84). (For the analysis, likelihood ratios were calculated using pooled estimates for sensitivity and specificity.) Reviewers concluded that *KRAS* variants 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* variant 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* variants. Studies were heterogeneous in patient populations (smoking history, tumor histology, stage, ethnicity, treatment received) and response criteria. The primary end point was ORR, defined as the sum of complete and partial response. ORRs for patients

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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. The median PFS in *KRAS*-mutated and wild-type patients was 3.0 months and 3.9 months, respectively. The 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, a 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* variant in NSCLC. The *KRAS* variant 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. The *KRAS* variant 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* variants were excluded.

### *Retrospective Analyses of Trials*

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* variant analysis; 9 (25%) were found to harbor *KRAS* variants. The response was by a single radiologist, blinded to patient outcome, using RECIST criteria. None of 9 patients with *KRAS*-mutated tumors responded to erlotinib ( $p=0.553$ ).

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

In a 2006 phase 2 trial, Giaccone et al studied the response to erlotinib in 53 chemotherapy-naive patients with advanced NSCLC. Histologic material was available to assess *KRAS* variant status from 29 patients, 10 (34%) of whom had variants. All 10 were nonresponders to erlotinib ( $p=0.125$ ).

In a 2007 phase 2, multicenter, open-label study, Jackman et al evaluated treatment response to erlotinib in chemotherapy-naive patients 70 years of age or older who had advanced NSCLC. Of 80 patients eligible for

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treatment, 41 (51%) had *KRAS* variant analysis; 6 (15%) patients were variant-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* variant status. Eighteen (18%) patients had *KRAS*-mutated tumors, and none responded to erlotinib (95% CI, 0% to 19%; p<0.01). In patients without a *KRAS* variant, the response rate was 32%. The median OS in patients with *KRAS*-mutated tumor was 13 months vs 21 months in patients with *KRAS* wild-type tumor (p=0.30).

Zhu et al (2008) performed a post hoc subgroup analysis of *KRAS* variants in patients with advanced NSCLC who had failed standard chemotherapy and had been previously randomized to 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* variants, which were identified in 30 (15%) patients. 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 (5.0%) patient 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* variant status and treatment was not statistically significant (p=0.09).

Rulli et al (2015) reported on results from biomarker analyses in the TAILOR trial. TAILOR enrolled patients from 52 Italian hospitals and genotyped patients for *KRAS* and *EGFR* variant 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* variants were present in 23% of randomized patients. The presence of a *KRAS* variant 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 on 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* variants 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* variant-positive patients. For *KRAS*

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

### *Observational Studies*

Schneider et al (2008) reported on the relation 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 was from German centers and comprised 311 patients with stage IIIB or 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 (15%) patients had *KRAS* variants, and none responded to erlotinib; 2 patients had stable disease. The impact of *KRAS* variant 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 the 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* variants can derive a survival benefit from erlotinib.

In 2009, Boldrini et al reported on the association between *KRAS* and *EGFR* variant 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* variants 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. The mean age of this subpopulation at the time of diagnosis was 60.8 years (range, 40-86 years). 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* variants had progressive disease.

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 randomly matched on tumor, node, metastasis (TNM) stage, time of first visit within 1 year, and histology, to both *EGFR* variant-positive and *KRAS/EGFR* wild-type patients. Seventy (4%) patients received EGFR-TKI therapy. In this group, median PFS was 11.8 months and 2.0 months in patients with *EGFR* and *KRAS* variants, respectively, and 1.9 months in wild-type patients; compared with wild-type patients, PFS was statistically longer in patients with *EGFR* variants ( $p<0.001$ ) but no different in patients with *KRAS* variants ( $p=0.48$ ). The authors observed that "the presence of an *EGFR* variant, but not a *KRAS* variant, 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) variant 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 vs 2.0 months in *KRAS* wild-type patients ( $n=160$  [92%]); the difference was not statistically significant ( $p=0.120$ ). Median OS in this treated group was 5.7 months in *KRAS*-mutated patients vs 8.2 months in *KRAS* wild-type patients, a statistically significant difference ( $p=0.039$ ). The authors concluded that *KRAS* variant

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status may have a negative prognostic role but a predictive role was not confirmed. "Patients with squamous cell NSCLC harboring these variants could benefit from targeted treatment and should not be excluded from treatment with EGFR TKIs."

### ***KRAS and Anti-EGFR Monoclonal Antibodies***

Two phase 3 trials (BMS099, FLEX) investigated platinum-based chemotherapy with and without cetuximab in the first-line setting for advanced NSCLC. Subsequently, investigations of *KRAS* variant status and cetuximab treatment were performed for both trials.

In the multicenter, phase 3 BMS099 trial (2010), 676 chemotherapy-naive patients with stage IIIB or 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, QOL, 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 was not statistically significant. A post hoc correlative analysis 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* variants were present in 35 (17%) patients. 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 months and 9.9 months, respectively). Among patients with *KRAS* variants, 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 months and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions between the presence of *KRAS* variants and outcomes evaluated; 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 did not support an association between *KRAS* variant and lack of cetuximab benefit similar to that observed in patients with *KRAS*-mutated metastatic colorectal cancer. However, the results should be interpreted with caution due to small subgroup sample sizes and retrospective nature of the analysis.

In the open-label, randomized, phase 3 FLEX trial (2009), 1125 chemotherapy-naive patients with stage III or IV, NSCLC were randomized to 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* variant testing was performed on archival tumor tissue of 395 (35%) of 1125 patients. *KRAS* variants were detected in 75 (19%) tumors. Among patients with mutated *KRAS*, the median OS in the cetuximab-containing (n=38) and chemotherapy-alone arms (n=37) was similar (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*, the median OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (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 the cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR=0.97; 95% CI, 0.76 to 1.24) and

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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* variant status was predictive of cetuximab effect in NSCLC.

### MEK Inhibitors

Two RCTs have compared a MEK inhibitor (with or without chemotherapy) with chemotherapy alone in patients with *KRAS*-variant advanced NSCLC after progression with first-line therapy. The characteristics and results are shown in Tables 12 and 13. MEK inhibitor therapy did not improve PFS compared with docetaxel alone; response rates were similar or marginally improved. Grade 3 or higher adverse events were more frequent with MEK inhibitor therapy compared with docetaxel.

**Table 12. RCT Characteristics of MEK Inhibitors for *KRAS*-Variant NSCLC**

Author (Year); Study	Countries	Sites	Dates	Participants	Description of Interventions	
					MEK Inhibitor	Chemotherapy
Blumenschein (2015); NCT01362296	U.S., Korea, 6 European countries	60	2011-2012	129 patients with stage IV NSCLC and progression following first-line platinum-containing chemotherapy	86 assigned to trametinib (2 mg/d)	43 assigned to docetaxel (75 mg/m <sup>2</sup> )
Janne (2017); SELECT1 (NCT01933932)	25 countries in North and South American, Australia, Europe	202	2013-2016	510 patients with advanced NSCLC and progression following first-line therapy	254 assigned to selumetinib (75 mg bid) plus docetaxel (75 mg/m <sup>2</sup> )	256 assigned to docetaxel (75 mg/m <sup>2</sup> )

bid: twice a day; NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial.

**Table 13. RCT Results for MEK Inhibitors for *KRAS*-Variant NSCLC**

Study (Year)	Progression-Free Survival	Overall Survival	ORR (95% CI), %	Adverse Events, %		
				Grade ≥3	%	Serious
Blumenschein (2015) Trametinib	N=129 12 wk	N=129 8 mo	N=129 12	N=130		N=130
				<ul style="list-style-type: none"> <li>• Overall</li> <li>• Rash</li> <li>• Diarrhea</li> <li>• Asthenia</li> <li>• Hypertension</li> <li>• Neutropenia</li> <li>• Decreased neutrophils</li> </ul>	<ul style="list-style-type: none"> <li>• 41</li> <li>• 6</li> <li>• 5</li> <li>• 5</li> <li>• 9</li> <li>• 0</li> <li>• 0</li> </ul>	37
Docetaxel	11 wk	Not yet reached	12			
				<ul style="list-style-type: none"> <li>• Overall</li> <li>• Rash</li> <li>• Diarrhea</li> <li>• Asthenia</li> <li>• Hypertension</li> <li>• Neutropenia</li> <li>• Decreased neutrophils</li> </ul>	<ul style="list-style-type: none"> <li>• 37</li> <li>• 0</li> <li>• 2</li> <li>• 0</li> <li>• 0</li> <li>• 14</li> <li>• 7</li> </ul>	21

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			Adverse Events, %		
TE (95% CI)	HR=1.14 (0.75 to 1.75)	HR=0.97 (0.52 to 1.83)			
SELECT1(2017)	N=510	N=510	N=510	N=505	N=505
Selumetinib plus docetaxel	3.9 mo	8.7 mo	20.1	<ul style="list-style-type: none"> <li>• Overall • 67</li> <li>• Diarrhea • 7</li> <li>• Asthenia • 9</li> <li>• Dyspnea • 8</li> <li>• Anemia • 5</li> <li>• Neutropenia • 7</li> </ul>	49
Docetaxel	2.8 mo	7.9 mo	13.7	<ul style="list-style-type: none"> <li>• Overall • 45</li> <li>• Diarrhea • 3</li> <li>• Asthenia • 3</li> <li>• Dyspnea • 2</li> <li>• Anemia • 4</li> <li>• Neutropenia • 4</li> </ul>	32
TE (95% CI)	HR=0.93 (0.77 to 1.12)	HR=1.05 (0.85 to 1.30)	OR=1.61 (1.00 to 2.62)		

CI: confidence interval; HR: hazard ratio; NSCLC: non-small-cell lung cancer; OR: odds ratio; ORR: objective response rate; RCT: randomized controlled trial; TE: treatment effect.

### Section Summary: KRAS Gene Variants

Data on the role of *KRAS* variants in NSCLC and response to erlotinib are available from post hoc analysis of trials, observational studies, and meta-analyses. Although studies have shown that *KRAS*-variants in patients with NSCLC confer a high level of resistance to TKIs, data are insufficient to assess any additional benefit to *KRAS* testing beyond *EGFR* testing.

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* variant 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* variant status and use of cetuximab with chemotherapy, *KRAS* variants did not identify patients who would benefit from anti-*EGFR* antibodies, because outcomes with cetuximab were similar regardless of *KRAS* variant status.

Two RCTs have compared a MEK inhibitor with docetaxel in patients with *KRAS*-variant advanced NSCLC who had progression following first-line therapy. The MEK inhibitor did not improve PFS compared with docetaxel; the response rate was marginally improved. Grade 3 or higher adverse events were more frequent with the MEK inhibitors.

### HER2 GENE VARIANTS

Mazières et al (2013) reported on a retrospective review of a consecutive series of patients with NSCLC tested for a *HER2* variant, and they assessed clinicopathologic characteristics and patient outcomes by variant status. A *HER2* variant was identified in 65 (1.7%) of 3800 patients, and was mutually exclusive of other driver variant (*EGFR*, *ALK*, *BRAF*), with the exception of 1 case in which both an *HER2* and *KRAS*

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variant were identified. The patient population in which a *HER2* variant 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* variants ( $p < 0.001$ ) were predictive of outcomes; *HER2* and *HER3* biomarkers were not significant in a treatment-by-biomarker interaction test.

Shen et al (2015) retrospectively reviewed 111 patients from a Uyur 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 ( $p = 0.12$ ). The 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,  $p = 0.09$ ).

### **RET GENE REARRANGEMENTS**

In a phase 2, prospective trial (2013) for patients with *RET* fusion-positive tumors, preliminary data on 3 patients treated with cabozantinib showed a partial response in 2 patients and stable disease in the third, approaching 8 months.

### **MET GENE AMPLIFICATIONS**

A phase 2 trial (2013) of *MET*-positive NSCLC, in which patients were treated with an anti-*MET* antibody plus erlotinib, showed improved PFS and OS.

### **SUMMARY OF EVIDENCE**

For individuals who have advanced-stage NSCLC who are being considered for targeted therapy who receive testing for *EGFR* variants 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, quality of life, and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and progression-free survival, 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 *BRAF* variants and *ROS1* rearrangements, the evidence includes nonrandomized trials

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and observational studies of BRAF and MEK inhibitors and crizotinib or ceritinib, respectively. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Studies have shown that combination therapy with dabrafenib and trametinib for *BRAF* V600E variant NSCLC and crizotinib for NSCLC with *ROS1* rearrangements result in response rates of 60% and 70%, respectively, with acceptable toxicity profiles. 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* or *HER2* variants, *RET* rearrangements, or *MET* amplifications, the evidence includes for *KRAS* post hoc analyses trials, observational studies, and meta-analyses; for the other variants, the evidence includes a phase 2 trial with preliminary data, and retrospective analyses of very small case series and case reports. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, quality of life, and treatment-related morbidity. Studies have shown that *KRAS* variants in patients with NSCLC confer a high level of resistance to TKIs; data are insufficient to assess any additional benefit to testing for *KRAS* variants to select for EGFR TKIs beyond *EGFR* testing. In 2 randomized trials with post hoc analyses of *KRAS* variant status and use of the anti-EGFR monoclonal antibody cetuximab with chemotherapy, *KRAS* variants did not identify patients who would benefit from anti-EGFR antibodies, because outcomes with cetuximab were similar regardless of *KRAS* variant status. In two randomized controlled trials of advanced *KRAS*-variant positive disease, MEK inhibitors did not improve progression-free survival compared with docetaxel. Studies for *HER2*, *RET*, and *MET* variant testing have reported response rates and progression-free survival 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.

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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  
 12/07/2017 Medical Policy Committee review  
 12/20/2017 Medical Policy Implementation Committee approval. Added ROS1 and BRAF testing to medically necessary statement. Rationale reorganized. Criteria reformatted.

Next Scheduled Review Date: 12/2018

### **Coding**

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HCPCS	No codes
ICD-10 Diagnosis	C34.00-C34.02 C34.10-C34.12 C34.2 C34.30-C34.32 C34.80-C34.82 C34.90-C34.92

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\*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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  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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