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

Policy # 00452
Original Effective Date: 05/20/2015
Current Effective Date: 12/19/2018

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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, analysis of somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with advanced lung adenocarcinoma, large cell carcinoma, advanced squamous cell non-small-cell lung cancer, and non-small-cell lung cancer not otherwise specified 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 other EGFR variants within exons 22 to 24, or other applications related to NSCLC to be investigational.*

ALK 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 anaplastic lymphoma kinase (ALK) gene to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori®], ceritinib [ZykadiaTM], alectinib [Alecensa®], or brigatinib [Alunbrig™])‡ in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded to be eligible for coverage.**
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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®] and trametinib [Mekinist®])‡, 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.*

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.**
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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.*

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 2018 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.
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The 2018 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:

“One set of genes must be offered by all laboratories that test lung cancers, as an absolute minimum: EGFR, ALK, and ROS1. A second group of genes should be included in any expanded panel that is offered for lung cancer patients: BRAF, MET, RET, ERBB2 (HER2), and KRAS, if adequate material is available. KRAS testing may also be offered as a single-gene test to exclude patients from expanded panel testing. All other genes are considered investigational at the time of publication.”

Background/Overview

NON-SMALL-CELL LUNG CANCER

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 tyrosine kinase inhibitors [TKIs]). These targeted therapies dampen signal transduction through pathways downstream to the EGFR, 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 variant 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 the failure of TKI therapy.

The prevalence of *EGFR* variants in NSCLC varies by population, with the highest prevalence in nonsmoking 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%.
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**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.

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

TARGETED THERAPIES
Four orally administered EGFR-selective, small-molecule TKIs have been identified for treating NSCLC: gefitinib (Iressa; AstraZeneca), erlotinib (Tarceva; OSI Pharmaceuticals), afatinib (Gilotrif; Boehringer Ingelheim), and osimertinib (Tagrisso; AstraZeneca). Gefitinib, erlotinib, afatinib, and osimertinib currently are approved by the U.S. Food and Drug Administration (FDA) for NSCLC when EGFR status is confirmed through a companion diagnostic test.

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 confirmed through a companion diagnostic test. 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 confirmed through a companion diagnostic test. The combination of dabrafenib and trametinib was approved for treatment of metastatic NSCLC in 2017 for patients with confirmed BRAF V600 variants.

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.

Targeted therapies currently under investigation and not FDA-approved for the remaining genetic alterations in NSCLC 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>2013: First line for patients with metastatic NSCLC whose tumors have <em>EGFR</em> exon 19 deletions or exon 21 (L858R) substitutions</td>
<td>2013: <em>therascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen)</em></td>
</tr>
<tr>
<td></td>
<td>2016: Second line for patients with metastatic squamous NSCLC</td>
<td>2017: <em>FoundationOne CDx™ (Foundation Medicine)</em></td>
</tr>
<tr>
<td></td>
<td>2018: First line for patients with nonresistant <em>EGFR</em> variants other than exon 19 or exon 21 NSCLC</td>
<td></td>
</tr>
<tr>
<td>Alectinib (Alecensa)</td>
<td>2015: Second line for patients with <em>ALK</em>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
<td>2017: <em>FoundationOne CDx™ (Foundation Medicine)</em></td>
</tr>
<tr>
<td></td>
<td>2017: First line for patients with <em>ALK</em>-positive NSCLC who have not received prior systemic therapy for metastatic disease</td>
<td></td>
</tr>
<tr>
<td>Brigatinib (Alunbrig)</td>
<td>2017: Second line for patients with metastatic <em>ALK</em>-positive NSCLC who have progressed on or are intolerant of crizotinib</td>
<td>Test not specified in FDA approval</td>
</tr>
<tr>
<td>Ceritinib (Zykadia)</td>
<td>2014: Second line for patients with <em>ALK</em>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib</td>
<td>2015: <em>Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems)</em></td>
</tr>
<tr>
<td></td>
<td>2017: First line for patients with <em>ALK</em>-positive metastatic NSCLC</td>
<td>2017: <em>FoundationOne CDx™ (Foundation Medicine)</em></td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>2011: First line for patients with <em>ALK</em>-positive metastatic NSCLC</td>
<td>2011: <em>Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2015: <em>Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2017: <em>FoundationOne CDx™ (Foundation Medicine)</em></td>
</tr>
<tr>
<td></td>
<td>2016: Patients with <em>ROS1</em>-positive metastatic NSCLC</td>
<td>2017: <em>Oncomine™ Dx Target Test (Thermo Fisher Scientific)</em></td>
</tr>
<tr>
<td>Crizotinib (Xalkori)</td>
<td>2016: Patients with <em>ROS1</em>-positive metastatic NSCLC</td>
<td>Test not specified in FDA approval</td>
</tr>
<tr>
<td>Dacomitinib (Vizimpro)</td>
<td>2018: First line for patients with metastatic NSCLC with <em>EGFR</em> exon 19 deletion or exon 21 (L858R) substitutions</td>
<td>2017: <em>Oncomine™ Dx Target Test (Thermo Fisher Scientific)</em></td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar) plus trametinib (Mekinist)</td>
<td>2017: Used in combination for treatment of patients with metastatic NSCLC with <em>BRAF</em> V600E variant</td>
<td>2017: <em>Oncomine™ Dx Target Test (Thermo Fisher Scientific)</em></td>
</tr>
<tr>
<td></td>
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<td>2017: <em>FoundationOne CDx™ (Foundation Medicine)</em></td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>2013: First line for patients with metastatic NSCLC whose tumors have <em>EGFR</em> exon 19 deletions or exon 21 (L858R) substitutions</td>
<td>2013: <em>cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics)</em></td>
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<tr>
<td></td>
<td>2010:Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy</td>
<td>2016: <em>cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics)</em></td>
</tr>
<tr>
<td></td>
<td>2004: Second line for patients with locally advanced or metastatic NSCLC</td>
<td>2017: <em>FoundationOne CDx™ (Foundation Medicine)</em></td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>2015: First line for patients with metastatic NSCLC</td>
<td>2013: <em>therascreen® EGFR</em></td>
</tr>
</tbody>
</table>

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</table>
| Osimertinib (Tagrisso) | whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions 2003: Second line for patients with locally advanced or metastatic NSCLC | Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit  
- 2017: Oncomine™ Dx Target Test  
- 2017: FoundationOne CDx™ (Foundation Medicine)  
- 2017: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) |
|                     |                                                                          |  
- 2015: Second line for patients with metastatic NSCLC whose tumors have EGFR T790M variants as detected by FDA-approved test, who have not responded to EGFR-blocking therapy  
  • 2018: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R variants |  
- 2015: cobas® EGFR Mutation Test v2 (blood test)  
- 2017: FoundationOne CDx™ (Foundation Medicine) |

**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**
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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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 non-small-cell lung cancer (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 following practice is currently being used to target therapy for advanced-stage NSCLC: 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, reduced toxicity, and improved quality of life associated with receiving a more effective and less cytotoxic targeted therapy than 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 cytotoxic chemotherapy in those with driver mutations; possible harmful outcomes
resulting from a false positive test result are a shorter survival from receiving potentially ineffective targeted treatment and delay in initiation of chemotherapy in those without driver mutations.

**Timing**
Due to the poor prognosis of advanced NSCLC, the duration of follow-up for the outcomes of interest is 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.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The evidence is presented below, by variant (EGFR, ALK, BRAF, ROS1, KRAS, HER2, RET, MET) and by recommended therapy.

**EGFR 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 TKIs experience 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**
Fang et al (2013) reported EGFR variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (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%.
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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 SCC and Rosell et al (2009) observed EGFR variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes.

In 2 other studies, the acquired EGFR T790M variant has been estimated to be present in 50% to 60% of TKI-resistant cases in approximately 200 patients.

FDA-Approved Companion Diagnostic Tests for EGFR Variants

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. A report by the Canadian Agency for Drugs and Technologies in Health, conducted by Mujoomdar et al (2010) analyzed EGFR variants. Based on 11 observational studies, the report authors concluded that PCR-based approaches identify EGFR variants with a sensitivity equivalent to that of direct sequencing.

Several 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, gefitinib, or osimertinib): the therascreen EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, cobas EGFR Mutation Test v1 and v2, Oncomine Dx Target Test, and FoundationOne CDx (see Table 1). 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 therascreen RGQ PCR kit was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label 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 therascreen 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 therascreen 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 include 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 therascreen. The PPA of Oncomine vs therascreen for detection of EGFR-sensitizing variants was 99% (95% CI, 93% to 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.

The clinical validity of FoundationOne CDx was demonstrated by assessing concordance of the test with results from mass spectrometry, gel sizing, fluorescence in situ hybridization (FISH), and immunohistochemistry of clinical tumor tissue specimens. Test sensitivity ranged from 95% to 99% across alteration types, with a positive predictive value exceeding 99%. No data on the effectiveness of targeted therapy in patients identified as EGFR-positive by FoundationOne CDx were reported.

**Tyrosine Kinase Inhibitors**

**Combined Analyses**

A meta-analysis by Lee et al (2013), which evaluated 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 using 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.

A TEC Assessment (2007) evaluated EGFR variants and TKI therapy in advanced NSCLC. 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. An updated Assessment
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(2010), with revised conclusions, indicated that EGFR variant testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.

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

Erlotinib
Systematic Reviews
Petrelli et al (2012) reported 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% vs 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.

Randomized Controlled Trials
A summary of the characteristics and results 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 improvements in PFS (HR range, 0.16-0.37) but no improvements in OS with erlotinib vs chemotherapy. Grade 3 or greater adverse events and serious adverse events occurred in fewer patients in the erlotinib groups.

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

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Erlotinib</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al (2015)37, ENSURE (NCT01342965)</td>
<td>China, Malaysia, Philippines</td>
<td>30</td>
<td>2011-2012</td>
<td>217 patients with stage IIIB/IV NSCLC</td>
<td>110 assigned to erlotinib (150 mg qd)</td>
<td>117 assigned to gemcitabine (1250 mg/m²) and cisplatin (75 mg/m²)</td>
</tr>
<tr>
<td>Rosell et al (2012)38, EURTAC (NCT00446225)</td>
<td>France, Italy, Spain</td>
<td>42</td>
<td>2007-2011</td>
<td>173 patients with stage IIIB/IV NSCLC</td>
<td>86 assigned to erlotinib (150 mg qd)</td>
<td>87 assigned to cisplatin (75mg/m²), docetaxel (75 mg/m²), or gemcitabine (1250 mg/m²)</td>
</tr>
<tr>
<td>Zhou et al (2011, 2015)39,40, OPTIMAL (NCT00874419)</td>
<td>China</td>
<td>22</td>
<td>NR</td>
<td>165 patients with stage IIIB/IV NSCLC</td>
<td>83 assigned to erlotinib (150 mg qd)</td>
<td>82 assigned to carboplatin (AUC5) and gemcitabine (1000 mg/m²)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>Serious</th>
<th>Grade 3 or 4</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENSURE (2015)37</td>
<td>N</td>
<td>217</td>
<td>217</td>
<td>214</td>
<td>214</td>
</tr>
</tbody>
</table>

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

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<table>
<thead>
<tr>
<th>Trial</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>Adverse Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>11.0</td>
<td>26.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>35.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td>6.4</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5.5</td>
<td>25.5</td>
<td>10.6</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>57.7</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td>25.0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td></td>
<td>14.4</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

HR (95% CI) 0.34 (0.22 to 0.51) 0.91 (0.63 to 1.31)

EURTAC (2012)³⁸

Erlotinib 9.7 (8.4 to 12.3) 19.3 6
- Rash
- Neutropenia
- Increased AT concentrations

Chemotherapy 5.2 (4.4 to 5.8) 19.5 20
- Rash
- Neutropenia
- Increased AT concentrations

HR (95% CI) 0.37 (0.25 to 0.54) 1.04 (0.65 to 1.68)

OPTIMAL (2011, 2015)³⁹,⁴⁰

N 154 154 155 155

Erlotinib 13.1 (10.6 to 16.5) 22.8 2
- Neutropenia
- Thrombocytopenia

Chemotherapy 4.6 (4.2 to 5.4) 27.2 14
- Neutropenia
- Thrombocytopenia

HR (95% CI) 0.16 (0.10 to 0.26) 1.19 (0.83 to 1.71)

AT: aminotransferase; CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial.

Many additional publications have provided data on EGFR variants in tumor samples obtained from NSCLC patients treated with 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 others were prospective, single-arm enrichment studies of variant-positive or wild-type patients treated with erlotinib. In 3 studies of EGFR variant-positive patients, the 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, the objective radiologic response was 3.3%, PFS was 2.1 months, and OS was 9.2 months.

**Gefitinib**

**Systematic Reviews**

A Cochrane review by Sim et al (2018) compared the use of gefitinib with no therapy or chemotherapy as first-line, second-line, or maintenance therapy for NSCLC. The literature search was conducted in February 2017 and identified 35 RCTs (total N=12,089 patients) for inclusion. For the general population of patients with NSCLC, gefitinib did not improve OS when given as first- or second-line therapy but did improve PFS.
when administered as maintenance therapy. In the subset of patients with EGFR variants, gefitinib improved PFS compared with first- and second-line chemotherapy and improved both OS and PFS when administered as maintenance therapy.

**Randomized Controlled Trials**

Three RCTs described in Tables 4 and 5 have compared gefitinib with chemotherapy in the first-line setting. The 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 Iressa Pan-Asia Study (IPASS) trial enrolled patients with and without EGFR-sensitizing variants. The investigators reported a significant interaction between treatment and EGFR variant status for 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. Another 3-arm RCT in Tables 4 and 5 compared a combination of chemotherapy plus gefitinib with chemotherapy alone and gefitinib alone. Patients in the combined treatment arm experienced longer OS compared with chemotherapy and gefitinib alone.

Wu et al (2017) conducted a post hoc subgroup analysis focusing on Asian patients in the IPASS trial who were randomized to gefitinib (n=88) or carboplatin/paclitaxel (n=98). The analysis found that patients with the EGFR variant who received gefitinib experienced longer PFS than patients receiving chemotherapy (HR=0.5; 95% CI, 0.4 to 0.8).

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

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Description of Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gefitinib Alone</td>
</tr>
<tr>
<td>Han et al (2017)(^{56})</td>
<td>China</td>
<td>1</td>
<td>2011-2015</td>
<td>121 patients with advanced lung adenocarcinoma</td>
<td>41 assigned to gefitinib (250 mg/d)</td>
</tr>
<tr>
<td>Mok (2009)(^{53}); IPASS (NCT00322452)</td>
<td>9 East Asian countries</td>
<td>87</td>
<td>2006-2007</td>
<td>1217 patients with stage IIIB/IV NSCLC (261 EGFR-positive)</td>
<td>609 assigned to gefitinib (250 mg/d)</td>
</tr>
<tr>
<td>Mitsudomi (2010)(^{54}); WJTOG3405(^a)</td>
<td>Japan</td>
<td>36</td>
<td>2006-2009</td>
<td>177 patients with stage IIIB/IV or recurrent NSCLC</td>
<td>88 assigned to gefitinib (250 mg/d)</td>
</tr>
<tr>
<td>Maemondo (2010),(^{55}) Inoue (2013)(^{56}); NEJ002</td>
<td>Japan</td>
<td>43</td>
<td>2006-2009</td>
<td>230 patients with stage IIIB/IV NSCLC or postoperative</td>
<td>115 assigned to gefitinib (250 mg/d)</td>
</tr>
</tbody>
</table>
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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; chemo: chemotherapy; 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>Adverse Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NR</td>
<td></td>
<td>Serious</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han et al (2017)</td>
<td>5.7 (5.2 to 6.3)</td>
<td>25.8 (21.3 to 30.2)</td>
<td>Liver dysfunction</td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
<td>Skin rash</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>11.9 (9.1 to 14.6)</td>
<td>24.3 (17.7 to 30.1)</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin rash</td>
</tr>
<tr>
<td>Gefitinib plus</td>
<td>17.5 (15.3 to 19.7)</td>
<td>32.6 (25.5 to 39.8)</td>
<td>Liver dysfunction</td>
</tr>
<tr>
<td>chemotherapy</td>
<td></td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin rash</td>
</tr>
<tr>
<td>TE (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination vs</td>
<td>0.2 (0.1 to 0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination vs</td>
<td>0.5 (0.2 to 0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gefitinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination vs</td>
<td>0.4 (0.2 to 0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gefitinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination vs</td>
<td>1.0 (0.6 to 1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WJTOG3405 (2010)</td>
<td>9.2 (8.0 to 13.9)</td>
<td>34.8 (26.0 to 39.5)</td>
<td>ALT/AST elevation</td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>6.3 (5.8 to 7.8)</td>
<td>37.3 (31.2 to 45.5)</td>
<td>ALT/AST elevation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Leukocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td>TE (95% CI)</td>
<td>HR=0.49 (0.34 to 0.71)</td>
<td>HR=1.25 (0.88 to 1.78)</td>
<td></td>
</tr>
<tr>
<td>NEJ002 (2010, 2013)</td>
<td>10.8</td>
<td>27.7</td>
<td>Rash</td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
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<td>Arthralgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aminotransferase elevation</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5.4</td>
<td>26.6</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Neupathony</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arthralgia</td>
</tr>
</tbody>
</table>
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### Afatinib

Unlike erlotinib and gefitinib, which selectively inhibit EGFR, afatinib inhibits not only EGFR but also human epidermal growth factor receptor 2 (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 including 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 (HR=0.67; 95% CI, 0.51 to 0.89; *p*=0.005).
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 by Wu et al (2014) in a phase 3 trial conducted in 364 Asian patients (Lux-Lung 6), which compared 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 rates were 67% and 23%, respectively.

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 the 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 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).

**Osimertinib**

In 2015, the U.S. Food and Drug Administration (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 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 enrolled 210 patients. The major efficacy outcome measure of both trials was the objective response rate (ORR) assessed by a blinded, independent review committee. The median duration of follow-up of 4.2 months in the first study and 4.0 months in the second. The ORR was similar in the 2 studies. The pooled ORR was 59% (95% CI, 54% to 64%); 0.5% achieved a complete response and 59% achieved a 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 compared osimertinib with chemotherapy and is described in Tables 6 and 7. Osimertinib was associated with clinically and statistically significantly prolonged PFS and higher response rates than chemotherapy and had lower rates of grade 3 and 4 adverse events. However, interstitial lung disease–like adverse events and QT prolongation were more common with osimertinib. Another RCT described in Tables 6 and 7 compared osimertinib with other EGFR TKIs (gefitinib or erlotinib) as first-line therapy. The results suggested a reduced risk for central nervous system progression with osimertinib compared with other TKIs.

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

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reungwetwattana et al (2018)67; FLAURA (NCT02296125)</td>
<td>31 countries in North America, Europe, Australia, Asia</td>
<td>168</td>
<td>2014-2017</td>
<td>128 (of 556) patients with untreated advanced EGFR-positive NSCLC with available brain scans at baseline</td>
<td>61 assigned to osimertinib (80 mg/d) 67 assigned to gefitinib (250 mg/d) or erlotinib (150 mg/d)</td>
</tr>
<tr>
<td>Mok et al (2017)68; AURA3 (NCT02151981)</td>
<td>18 countries in North America, Europe, Australia, Asia</td>
<td>126</td>
<td>2014-2015</td>
<td>419 patients with T790M-positive advanced NSCLC who had disease progression after first-line EGFR-TKI therapy</td>
<td>279 assigned to osimertinib (80 mg/d) 140 to assigned platinum pemetrexed (500 mg/m² of BSA) plus carboplatin (target AUC5 or cisplatin [75 mg/m²])</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS, mo</th>
<th>OS, mo</th>
<th>ORR (95% CI)</th>
<th>Adverse Events, %</th>
<th>Prolongation of QT Interval, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade ≥3</td>
<td>ILD-Like</td>
</tr>
</tbody>
</table>

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Comparative Effectiveness of EGFR TKIs

As the previous sections have shown, erlotinib, gefitinib, afatinib, and osimertinib all have improved efficacy compared with chemotherapy in patients who have NSCLC and EGFR-sensitizing variants and are well tolerated. RCTs, as well as systematic reviews and meta-analyses of the RCTs, directly comparing the EGFR TKIs with each other and with chemotherapy, have been conducted. Several systematic reviews are summarized in Table 8.

Systematic Reviews

The systematic reviews and meta-analyses included overlapping trials. RCTs included in the reviews and analyses differed in study design, treatments compared, and line of treatment (first-, second-, or third-line). In general, patients who are EGFR-positive and treated with TKIs experienced longer PFS than patients treated with chemotherapy. Meta-analyses comparing different TKIs reported inconsistent results, with some analyses finding various TKIs comparable and other analyses finding some TKIs more effective than other TKIs. Safety data were not consistently available among the RCTs, limiting adverse event comparisons among treatments.

Table 8. Summary of Systematic Reviews Comparing EGFR TKIs for the Treatment of NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Dates</th>
<th>Design (No. of Studies)</th>
<th>No. of Patients</th>
<th>Line of Treatment</th>
<th>Treatments Compared</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al (2018)⁹⁰</td>
<td>Nov 2017</td>
<td>RCT (11)</td>
<td>3145</td>
<td>First-line</td>
<td>Chemotherapy, afatinib, dacomitinib, erlotinib, gefitinib, osimertinib</td>
<td>• PFS: TKIs more effective than chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Osimertinib, dacomitinib, and afatinib ranked highest probability of benefit among TKIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Subgroup analyses comparing osimertinib with standard of care showed improvements in</td>
</tr>
</tbody>
</table>

Cl: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; ILD: interstitial lung disease; NC: not calculable; 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.

⁹⁰ Erlotinib or gefitinib.
<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Design</th>
<th>Sample Size</th>
<th>Line</th>
<th>Treatment(s)</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3-5 adverse events more frequent with erlotinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS: afatinib, erlotinib, and gefitinib comparable to chemotherapy</td>
</tr>
<tr>
<td>Crequit et al (2017)</td>
<td>Jun 2017</td>
<td>RCT (102)</td>
<td>36,058</td>
<td>Second-line</td>
<td>61 treatments (combinations of immunotherapy, chemotherapy, and afatinib, cabozantinib, erlotinib, gefitinib)</td>
<td>OS: immunotherapy or pemetrexed plus erlotinib most effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS: erlotinib plus cabozantinib most effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Evidence for safety was insufficient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS and PFS: chemotherapy more effective than erlotinib and gefitinib</td>
</tr>
<tr>
<td>Yang et al (2017)</td>
<td>Dec 2016</td>
<td>Cohort (82)</td>
<td>17,621</td>
<td>First- and second-line</td>
<td>Afatinib, erlotinib, gefitinib</td>
<td>PFS: gefitinib and erlotinib comparable regardless of line</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCT (8)</td>
<td></td>
<td></td>
<td></td>
<td>Afatinib more effective than gefitinib and erlotinib as second- line treatment in for advanced squamous NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3-4 adverse events comparable with afatinib and erlotinib; gefitinib adverse events lower</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rank probabilities showed dacomitinib and afatinib had potentially better efficacy than erlotinib, gefitinib, and icotinib</td>
</tr>
</tbody>
</table>

**EGFR:** epidermal growth factor receptor; **NSCLC:** non-small-cell lung cancer; **OS:** overall survival; **PD-1:** programmed death-1; **PD-L1:** programmed death ligand-1; **PFS:** progression free survival; **RCT:** randomized controlled trial; **TKI:** tyrosine kinase inhibitors.
Randomized Controlled Trials

Soria et al (2018) conducted a double-blind phase 3 trial comparing osimertinib with other TKIs (gefitinib or erlotinib) for the first-line treatment of patients with EGFR-positive advanced NSCLC. Median PFS was longer with osimertinib (18.9 months; 95% CI, 15.2 to 21.4 months) than with the other TKIs (10.2 months, 95% CI, 9.6 to 11.1 months; HR=0.5, 95% CI, 0.4 to 0.6). ORR did not differ significantly between osimertinib and the other TKIs. Follow-up was not long enough to adequately determine OS.

Two RCTs 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 (95% CI, 8.5 to 11.2 months) for those receiving erlotinib. 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 months 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 randomized 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 ORR was significantly higher in the afatinib group (70% vs 56%; p=0.01). Several grade 3 or 4 adverse events were more common with afatinib than 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.

Section Summary: EGFR Gene Variants

Several RCTs, nonconcurrent prospective studies, single-arm enrichment studies, and meta-analyses of RCTs 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. Patient populations in these studies primarily had adenocarcinoma. 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. These 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.

ALK Rearrangement Frequency

ALK rearrangements occur in 3% to 6% of NSCLC.

FDA-Approved Companion Diagnostic Tests for ALK Rearrangements

Several methods are available to detect ALK gene rearrangements or the resulting fusion proteins in tumor specimens including FISH, immunohistochemistry, reverse transcription polymerase chain reaction 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 weeks). The response rate for 19 ALK-negative patients was 26% (95% CI, 9% to 51%).

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% (99% CI, 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 who were ALK-negative 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).

Tyrosine Kinase Inhibitors

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 and 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%) and 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 in the crizotinib group and 12.1 months in the chemotherapy group. 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 groups that received crizotinib and 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 chemotherapy. Crizotinib was associated with greater patient-reported reductions in lung cancer symptoms and greater improvements in quality of life.

Other ALK Inhibitors
Several 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 2 studies with PFS of almost 13 months in patients with crizotinib-refractory disease. FDA approval was granted to brigatinib in 2017 for the treatment of patients with ALK-positive NSCLC who have progressed on or are intolerant of crizotinib. Approval was based on an open-label, multicenter clinical trial that reported a durable overall response rate.
Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer

Policy #: 00452  
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Current Effective Date: 12/19/2018

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 or detecting ALK gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib.

BRAF GENE VARIANTS
FDA-Approved Companion Diagnostic Tests for BRAF Variants
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 formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples. The detection of BRAF V600E variants by the test was evaluated by retrospective analyses of a phase 2, multicenter, nonrandomized study that included 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 enrollment site. 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) 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 who were BRAF-positive by local lab test was 67% (95% CI, 53% to 77%) compared with 73% (95% CI, 50% to 89%) for the 22 patients who 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.

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.

BRAF Inhibitors
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 1 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, B, and C
were reported by Planchard et al (2016, 2017) and are shown in Tables 9 and 10. Cohort A (n=78) received dabrafenib; cohorts B (n=57) and C (n=36) received dabrafenib and trametinib combination therapy.

The characteristics and results of key nonrandomized trials of BRAF or MEK inhibitors in NSCLC are described in Tables 9 and 10. 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 who 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 9. Characteristics of Key Nonrandomized Trials of BRAF or MEK Inhibitors in BRAF-Variant NSCLC**

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Median FU, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planchard et al (2017); NCT01336634</td>
<td>Single-arm, open-label phase 2 trial</td>
<td>9 countries in North America, Europe, Asia</td>
<td>2014-2015</td>
<td>Adults, stage IV, BRAF V600E variant, previously untreated</td>
<td>Dabrafenib (150 mg bid) plus trametinib (2 mg/d)</td>
<td>15.9</td>
</tr>
<tr>
<td>Planchard et al (2016); NCT01336634</td>
<td>Single-arm, open-label phase 2 trial</td>
<td>9 countries in North America, Europe, Asia</td>
<td>2011-2014</td>
<td>Adults, stage IV, BRAF V600E variant, progression after chemotherapy</td>
<td>Dabrafenib (150 mg bid)</td>
<td>10.7</td>
</tr>
<tr>
<td>Planchard et al (2016); NCT01336634</td>
<td>Single-arm, open-label phase 2 trial</td>
<td>9 countries in North America, Europe, Asia</td>
<td>2013-2015</td>
<td>Adults, stage IV, BRAF V600E variant, progression after chemotherapy</td>
<td>Dabrafenib (150 mg bid) plus trametinib (2 mg/d)</td>
<td>11.6</td>
</tr>
<tr>
<td>Hyman et al (2015); NCT01524978</td>
<td>Single-arm, open-label phase 2 trial</td>
<td>Germany, Spain, U.K., U.S., France</td>
<td>2012-2014</td>
<td>BRAF V600 variant–positive nonmelanoma cancers including NSCLC</td>
<td>Vemurafenib (960 mg bid)</td>
<td>6a</td>
</tr>
</tbody>
</table>

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

a Estimated from a figure.

**Table 10. Results of Key Nonrandomized Trials of BRAF or MEK Inhibitors in BRAF-Variant NSCLC**

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Response (95% CI), %</th>
<th>PFS (95% CI), mo</th>
<th>Overall Survival (95% CI)</th>
<th>Adverse Events, %</th>
<th>Grade 3 or 4</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64 (46 to 79)</td>
<td>10.9</td>
<td>At data cutoff: 24.6 mo</td>
<td>Overall</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7.0 to 16.6)</td>
<td></td>
<td>At 2-y: 51% (33% to 67%)</td>
<td>Pyrexia</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Planchard et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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N=78  N=78  N=78  N=78  N=78
33 (23 to 45)  5.5  Median, 12.7 mo  • Overall  • 39  • Overall  • 42
(3.4 to 7.3)

Planchard et al (2016)

N=57  N=57  N=57  N=57  N=57
63 (49 to 76)  9.7  At 6 mo, 82%  • Overall  • 49  • Overall  • 56
(6.9 to 19.6)

Hyman et al (2015)

N=19  N=20  N=20  N=95b
At 8 wk, 42 (20 to 67)  Median, 7.3  At 12 mo, 66%  • Overall  • 73  • Overall  • 4
(3.5 to 10.8)  (36% to 85%)

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

a The response rate in the Food and Drug Administration product label for this cohort was 27% (18% to 38%).
b Only reported for entire cohort including all cancer types.
c Investigator-assessed estimates. An independent committee assessment of PFS reported 14.6 months (9% CI, 7.0 to 22.1 months).

Case reports have also 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-naive patients. Dabrafenib and trametinib combination therapy were 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
FDA-Approved Companion Diagnostic Tests for ROS1 Rearrangements
Several methods are available to detect ROS1 translocations including FISH, immunohistochemistry, quantitative real-time reverse transcription-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...
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test is an NGS oncology panel that detects, among other variants, fusions in ROS1 from RNA isolated from 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 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%).

Tyrosine Kinase Inhibitors

Crizotinib
In 2016, after an expedited review, 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 assessed 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 11 and 12. 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 whom had progressed on prior therapy.

Ceritinib
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 11. Characteristics of Key Nonrandomized Studies of Crizotinib or Ceritinib for ROS1 Rearrangements in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al(2017)</td>
<td>Open-label, single-arm, phase</td>
<td>Korea</td>
<td>2013-2016</td>
<td>Adults with ROS1 rearrangement who had ceritinib (750 mg/d)</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

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

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Table 12. Results of Key Nonrandomized Studies of Crizotinib or Ceritinib for ROS1 Rearrangements in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Response (95% CI), %</th>
<th>Median PFS (95% CI), mo</th>
<th>OS (95% CI)</th>
<th>Grade 3 or 4 %</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al (2017)102</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=28</td>
<td>N=32</td>
<td>N=32</td>
<td></td>
<td>N=32</td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>(45 to 77)</td>
<td>9.3 (0 to 22)</td>
<td>24 mo (5 to 43)</td>
<td>37</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>Cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td>Mazieres et al (2015)103</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=29</td>
<td>N=30</td>
<td>N=30</td>
<td></td>
<td>N=30</td>
<td></td>
</tr>
<tr>
<td>80 (NR)</td>
<td>9.1 (NR)</td>
<td>NR</td>
<td></td>
<td>Grade 3 NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 4 or 5</td>
<td>0</td>
</tr>
<tr>
<td>Shaw et al (2014)101</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=50</td>
<td>N=50</td>
<td>N=50</td>
<td></td>
<td>N=50</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>(58 to 84)</td>
<td>19.2 (14.4 to not reached)</td>
<td>At 12 mo: 85% (72% to 93%)</td>
<td>10</td>
<td>Visual impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
</tbody>
</table>

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; NR: not reported; NSCLC: non-small-cell lung cancer; OS: overall survival; PFS: progression-free 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
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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. Crizotinib was 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
FDA-Approved Companion Diagnostic Tests for KRAS Variants
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 this indication and, therefore, no FDA-approved companion diagnostics.

Tyrosine Kinase Inhibitors
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
Pooled data on the relation between KRAS variants and response to EGFR TKI therapy are insufficient to determine an association between KRAS variant status and treatment effects on PFS or OS. Pan et al (2016) published a meta-analysis of 41 studies (total N=13,103 patients) of prognostic and predictive values of a KRAS variant in NSCLC. Having a 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 TKI treatment (relative risk, 0.21; 95% CI, 0.1 to 0.4) in advanced NSCLC. Having a 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.

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 with KRAS and wild-type KRAS variants 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.

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 was tentative due to limitations of selected studies (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.

Retrospective Studies
Papadimitrakopoulou et al (2016) reported on results of the BATTLE-2 phase 2 study. The BATTLE-2 program is an umbrella study evaluating the 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 multtargeted 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 wild-type patients, disease control rate was 36%, 57%, 49%, and 47%, respectively. The median PFS did not differ by KRAS status.

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
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patients (n=218) received first-line platinum-based chemotherapy and then were randomized 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).

In a phase 2 trial, Miller et al (2008) 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 and 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) 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 a KRAS variant, 1 (5.0%) patient responded (HR [erlotinib vs placebo] in patients with a KRAS variant, 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).

In a phase 2, multicenter, open-label study, Jackman et al (2007) evaluated treatment response to erlotinib in chemotherapy-naive patients 70 years of age or older who had advanced NSCLC. Of 80 patients eligible for 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 phase 2 trial, Giaccone et al (2006) studied the response to erlotinib in 53 chemotherapy-naive patients with advanced NSCLC. Histologic samples were available to assess KRAS variant status from 29 patients, 10 (34%) of whom had variants. All 10 were nonresponders to erlotinib (p=0.125).

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 in the phase 3 trial (TRIBUTE) to chemotherapy with or without erlotinib. Of the original 1079 patients, tumor DNA samples from 274 (25%) patients were 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. 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).

**Observational Studies**

Fiala et al (2013) retrospectively analyzed patients with NSCLC who underwent *EGFR, KRAS,* and *PIK3CA* (phosphatidylinositol-3-kinase catalytic subunit-alpha) variant testing. Of 215 patients tested, 16 (7.4%) had a *KRAS* variant. Of 174 tested patients 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 and 8.2 months in *KRAS* wild-type patients, a statistically significant difference (p=0.039). The authors concluded that *KRAS* variant status might have a negative prognostic role but a predictive role was not confirmed.

Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single institution in China. Patients with *KRAS* variants were randomized by the tumor, node, metastasis stage, time of the 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.”

Boldrini et al (2009) 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 a partial response, 4 (21%) had stable disease, and 7 (37%) had progressive disease. Two patients with *KRAS* variants had progressive disease.
Schneider et al (2008) reported on the relation between clinical benefit and putative tumor markers in a subgroup of patients 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 using 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 their data did not support the selection of patients for treatment with erlotinib on the basis of tumor molecular characteristics.

**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, quality of life, and safety. The addition of cetuximab did not significantly improve PFS; however, there was a statistically significant improvement in overall response rate in the cetuximab group. The trend in OS favoring cetuximab 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 for 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 for 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 status and lack of cetuximab benefit. However, the results should be interpreted with caution due to small subgroup sample sizes and the 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 plus cetuximab (n=557) or chemotherapy alone (n=568). The primary endpoint 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 archived tumor tissue of 395 (35%) of 1125 patients. KRAS variants were detected in 75 (19%) tumors.
patients with mutated \textit{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 \textit{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 wild-type (HR=0.84; 95% CI, 0.50 to 1.40) \textit{KRAS}. Response rates in the cetuximab-containing arm in patients with \textit{KRAS}-mutated and wild-type tumors were 36.8% and 37.3%, respectively (p=0.96). Overall, there was no indication that \textit{KRAS} variant status was predictive of cetuximab effect in NSCLC.

\textbf{MEK Inhibitors}

Two RCTs have compared a MEK inhibitor (with or without chemotherapy) with chemotherapy alone in patients with \textit{KRAS}-positive advanced NSCLC after progression with first-line therapy. Trial characteristics and results are shown in Tables 13 and 14. 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.

\textbf{Table 13. RCT Characteristics of MEK Inhibitors for \textit{KRAS}-Variant NSCLC}

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>MEK Inhibitor</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janne et al (2017); SELECT1 (NCT01933932)</td>
<td>25 countries in North and South America, Australia, Europe</td>
<td>202</td>
<td>2013-2016</td>
<td>510 patients with advanced NSCLC and progression following first-line therapy</td>
<td>254 assigned to selumetinib (75 mg bid) plus docetaxel (75 mg/m\textsuperscript{2})</td>
<td>256 assigned to docetaxel (75 mg/m\textsuperscript{2})</td>
</tr>
<tr>
<td>Blumenschein et al (2015); NCT01362296</td>
<td>U.S., Korea, 6 European countries</td>
<td>60</td>
<td>2011-2012</td>
<td>129 patients with stage IV NSCLC and progression following first-line platinum-containing chemotherapy</td>
<td>86 assigned to trametinib (2 mg/d)</td>
<td>43 assigned to docetaxel (75 mg/m\textsuperscript{2})</td>
</tr>
</tbody>
</table>

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

\textbf{Table 14. RCT Results for MEK Inhibitors for \textit{KRAS}-Variant NSCLC}

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS (95% CI%), mo</th>
<th>OS (95% CI%), mo</th>
<th>ORR (95% CI), %</th>
<th>Adverse Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade \geq 3</td>
<td></td>
<td></td>
<td>Serious</td>
</tr>
<tr>
<td>SELECT1 (2017)</td>
<td>510</td>
<td>510</td>
<td>510</td>
<td>505</td>
</tr>
<tr>
<td>Selumetinib plus docetaxel</td>
<td>3.9</td>
<td>8.7</td>
<td>20.1</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asthenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>2.8</td>
<td>7.9</td>
<td>13.7</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Study</th>
<th>TE (95% CI)</th>
<th>PFS (95% CI)</th>
<th>OS (95% CI)</th>
<th>ORR (95% CI), %</th>
<th>Adverse Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trametinib</td>
<td>HR=0.93</td>
<td>(0.77 to 1.12)</td>
<td>HR=1.05</td>
<td>(0.85 to 1.30)</td>
<td>OR=1.61 (1.00 to 2.62)</td>
</tr>
<tr>
<td>N</td>
<td>129</td>
<td>129</td>
<td>129</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>12 wk</td>
<td>8 mo</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>3</td>
<td></td>
<td>Asthenia</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>3</td>
<td></td>
<td>Dyspnea</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>4</td>
<td></td>
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</tr>
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<td>Docetaxel</td>
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<td>HR=0.97</td>
<td>(0.52 to 1.83)</td>
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<td></td>
<td>Rash</td>
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<tr>
<td></td>
<td>Rash</td>
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<td></td>
<td>Diarrhea</td>
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<tr>
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<td></td>
<td>Decreased neutrophils</td>
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 CI: confidence interval; HR: hazard ratio; NSCLC: non-small-cell lung cancer; OR: odds ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; 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 the 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-positive 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**

Mok et al (2016) reported on the biomarker subgroup analyses from the FASTACT-2 study. 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.

Shen et al (2015) retrospectively reviewed 111 patients from a Uygur population who received gefitinib 250 mg once daily and were evaluated for HER2 expression. HER2 overexpression was detected in 24 patients. The ORRs in patients with and without HER2 overexpression were 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).

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 mutation (EGFR, ALK, BRAF), with the exception of a case in which both an HER2 and a KRAS 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 evaluable individual anti-HER2 treatments). Four patients had progressive disease, 7 had disease stabilization, and 11 with partial response. PFS for patients with HER2 therapies was 5.1 months.

**RET GENE REARRANGEMENTS**

Yoh et al (2017) presented results of an open-label phase 2 trial (LURET) in which patients with NSCLC with RET rearrangements who had received at least 1 previous chemotherapy treatment, received vandetanib therapy. Nine of the 17 patients achieved an objective response.

In a phase 2, prospective trial for patients with RET fusion–positive tumors, Drilon et al (2013) reported 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 of MET-positive NSCLC by Sadiq and Salgin (2013), which patients treated with an anti-MET antibody plus erlotinib, reported improved PFS and OS.
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Current Effective Date:  12/19/2018

Section Summary: HER2 Gene Variants, RET Gene Rearrangements, and MET Gene Amplifications
Studies for HER2, RET, and MET variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions.

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 (eg, afatinib, erlotinib, gefitinib, osimertinib) with chemotherapy. Relevant outcomes are overall survival, disease-specific survival, test 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 and observational studies of BRAF and MEK inhibitors and crizotinib or ceritinib, respectively. Relevant outcomes are overall survival, disease-specific survival, test 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 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 2 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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69. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): Vysis ALK Break Apart FISH Probe PMCID 3257. PMID 27022112


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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.
12/06/2018 Medical Policy Committee review
12/19/2018 Medical Policy Implementation Committee approval. The policy section on EGFR Testing was changed given the new evidence in support of testing for additional variants in the EGFR gene.

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02/22/2019 Coding update
Next Scheduled Review Date: 12/2019

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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:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.
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A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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