

Medical Policy



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| Populations | Interventions | Comparators | Outcomes |
|--|---|--|--|
| Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy | Interventions of interest are: • Testing for <i>EGFR</i> variants or <i>ALK</i> rearrangements | Comparators of interest are: • Management without genetic testing | Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity |

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|---|---|---|---|
| Individuals: <ul style="list-style-type: none"> • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy | Interventions of interest are: <ul style="list-style-type: none"> • Testing for <i>BRAF</i> variants or <i>ROS1</i> rearrangements | Comparators of interest are: <ul style="list-style-type: none"> • Management without genetic testing | Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity |
| Individuals: <ul style="list-style-type: none"> • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy | Interventions of interest are: <ul style="list-style-type: none"> • Testing for <i>KRAS</i> or <i>HER2</i> variants, <i>RET</i> rearrangements, or <i>MET</i> amplifications | Comparators of interest are: <ul style="list-style-type: none"> • Management without genetic testing | Relevant outcomes include: <ul style="list-style-type: none"> • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity |

DESCRIPTION

Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease. Treatment in this setting has been with platinum-based chemotherapy. 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 that may direct targeted therapy depending on the presence of specific variants.

OBJECTIVE

The objective of this policy is to examine whether testing for *EGFR*, *BRAF*, *KRAS*, and *HER2* variants; *ALK*, *ROS1*, or *RET* rearrangements; or *MET* amplifications improves the net health outcome in individuals with advanced-stage non-small-cell lung cancer who are being considered for targeted therapy.

BACKGROUND

Non-Small-Cell Lung Cancer

Treatment options for NSCLC depend on disease stage and include various combinations of surgery, radiation therapy, chemotherapy, and best supportive care. Unfortunately, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. In addition, up to 40% of patients with NSCLC present with metastatic disease.¹ 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%.^{2,3} 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 in clinical decision making for the treatment of NSCLC is routine. The use of testing for other variants to direct targeted therapy is not well established and continues to evolve.

EGFR Gene

EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small-molecule 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%.

ALK Gene

ALK is a TK that, in NSCLC, is aberrantly activated because of a chromosomal rearrangement that 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.⁴ 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%.⁴ 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.⁴

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.⁴ *RET* fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.⁴

MET Gene

MET amplification is one of the critical events for acquired resistance in *EGFR*-mutated adenocarcinomas refractory to EGFR TKIs.⁴

PD-1 / PD-L1

PD-1 is a checkpoint protein on T-cells in the immune system and when bound to PD-L1, blocks the recognition of Tcells that the cancer cells are foreign invaders of the body. Some cancer cells will express PD-L1 in greater amounts, which will cause slowing of the immune attack by the T-cells or cause avoidance of the immune attack. Check-point protein inhibitors such as pembrolizumab, block binding of PD-1 with PD-L1 and potentially enhance immune response against cancer cells.

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. Ceritinib is a potent ALK inhibitor that is approved for *ALK*-positive patients 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.

BRAF or MEK inhibition with TKIs (eg, vemurafenib/dabrafenib or trametinib) was originally approved by FDA for treatment of unresectable or metastatic melanoma with *BRAFV600* 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 *BRAFV600* 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.

REGULATORY STATUS

Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved diagnostic tests.⁵⁻¹⁵

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

| Treatment | Indication | FDA Approval of Companion Diagnostic Test |
|-----------------------|---|--|
| Afatinib (Gilotrif) | <ul style="list-style-type: none"> 2013: First line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitutions 2016: Second line for patients with metastatic squamous NSCLC | <ul style="list-style-type: none"> 2013: theascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen) 2017: FoundationOne CDx™ (Foundation Medicine) |
| Alectinib (Alecensa) | <ul style="list-style-type: none"> 2015: Second line for patients with <i>ALK</i>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib 2017: First line for patients with <i>ALK</i>-positive NSCLC who have not received prior systemic therapy for metastatic disease | 2017: FoundationOne CDx™ (Foundation Medicine) |
| Brigatinib (Alunbrig) | <ul style="list-style-type: none"> 2017: Second line for patients with metastatic <i>ALK</i>-positive NSCLC who have progressed on or are intolerant of crizotinib | Test not specified in FDA approval |
| Ceritinib (Zykadia) | <ul style="list-style-type: none"> 2014: Second line for patients with <i>ALK</i>-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib 2017: First line for patients with <i>ALK</i>-positive metastatic NSCLC | <ul style="list-style-type: none"> 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) 2017: FoundationOne CDx™ (Foundation Medicine) |

| Treatment | Indication | FDA Approval of Companion Diagnostic Test |
|--|---|--|
| Crizotinib (Xalkori) | <ul style="list-style-type: none"> 2011: First line for patients with <i>ALK</i>-positive metastatic NSCLC | <ul style="list-style-type: none"> 2011: Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems) 2017: FoundationOne CDx™ (Foundation Medicine) |
| Crizotinib (Xalkori) | <ul style="list-style-type: none"> 2016: Patients with <i>ROS1</i>-positive metastatic NSCLC | <ul style="list-style-type: none"> 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific) |
| Dacomitinib (Vizimpro) | <ul style="list-style-type: none"> 2018: First line for patients with metastatic NSCLC with <i>EGFR</i> exon 19 deletion or exon 21 (L858R) substitutions | Test not specified in FDA approval |
| Dabrafenib (Tafinlar) plus trametinib (Mekinist) | <ul style="list-style-type: none"> 2017: Used in combination for treatment of patients with metastatic NSCLC with <i>BRAF</i>V600E variant | <ul style="list-style-type: none"> 2017: Oncomine™ Dx Target Test 2017: FoundationOne CDx™ (Foundation Medicine) |
| Erlotinib (Tarceva) | <ul style="list-style-type: none"> 2013: First line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitutions 2010: Maintenance for patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based chemotherapy 2004: Second line for patients with locally advanced or metastatic NSCLC | <ul style="list-style-type: none"> 2013: cobas® <i>EGFR</i> Mutation Test (tissue test) (Roche Diagnostics) 2016: cobas® <i>EGFR</i> Mutation Test v2 (tissue or blood test) (Roche Diagnostics) 2017: FoundationOne CDx™ (Foundation Medicine) |
| Gefitinib (Iressa) | <ul style="list-style-type: none"> 2015: First line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 (L858R) substitutions 2003: Second line for patients with locally advanced or metastatic NSCLC | <ul style="list-style-type: none"> 2015: theascreen® <i>EGFR</i> Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit 2017: Oncomine™ Dx Target Test 2017: FoundationOne CDx™ (Foundation Medicine) 2017: cobas® <i>EGFR</i> Mutation Test (tissue test) (Roche Diagnostics) |
| Osimertinib (Tagrisso) | <ul style="list-style-type: none"> 2015: Second line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> T790M variants as detected by FDA-approved test, who have not responded to <i>EGFR</i>-blocking therapy 2018: First line for patients with metastatic NSCLC whose tumors have <i>EGFR</i> exon 19 deletions or exon 21 L858R variants | <ul style="list-style-type: none"> 2015: cobas® <i>EGFR</i> 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.

POLICY

- A. Analysis of somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the *EGFR* gene may be considered **medically necessary** to predict treatment response to an *EGFR* tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.
- B. Analysis of other *EGFR* variants within exons 22 to 24, or other applications related to NSCLC, is considered **experimental / investigational**.
- C. Analysis of somatic rearrangement variants of the *ALK* gene may be considered **medically necessary** to predict treatment response to *ALK* inhibitor therapy (eg, crizotinib [Xalkori], ceritinib [Zykadia^M], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.
- D. Analysis of somatic rearrangement variants of the *ALK* gene is considered **experimental / investigational** in all other situations.
- E. Analysis of the *BRAF*V600E variant may be considered **medically necessary** to predict treatment response to *BRAF* or *MEK* inhibitor therapy (eg, dabrafenib [Tafinlar] and trametinib [Mekinist]), in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.
- F. Analysis of somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to predict treatment response to *ALK* inhibitor therapy (crizotinib [Xalkori]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.
- G. Analysis of somatic variants of the *KRAS* gene is considered **experimental / investigational** as a technique to predict treatment non-response to anti-*EGFR* therapy with tyrosine kinase inhibitors and for the use of the anti-*EGFR* monoclonal antibody cetuximab in NSCLC.
- H. Analysis for genetic alterations in the genes *RET*, *MET*, and *HER2* for targeted therapy in patients with NSCLC is considered **experimental / investigational**.
- I. Programmed death receptor 1 (PD-1) or its ligand (PD-L1) expression analysis may be considered **medically necessary** as a technique to predict treatment response to drug therapy.

Policy Guidelines

1. These tests are intended for use in patients with advanced NSCLC. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor 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.
2. 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.
3. 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."

RATIONALE

The most recent literature search conducted was conducted through August 6, 2018.

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.

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).¹⁶ 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%.

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.¹⁷ Eberhard et al (2005)¹⁸ observed *EGFR* variants in 6.4% of patients with SCC and Rosell et al (2009)¹⁹ 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.^{20,21}

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.²² 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 theascreen *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 theascreen 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-naïve 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.²³ The positive percent agreement (PPA) of theascreen vs CTA for detection of *EGFR*-sensitizing variants was 98% (95% confidence interval [CI], 95% to 99%) and negative percent agreement (NPA) was 97% (95% CI, 94% to 99%). Overall, a statistically significant efficacy benefit for afatinib vs chemotherapy was reported in the *EGFR*-positive patients as measured by the theascreen *EGFR* RGQ PCR Kit (hazard ratio [HR], 0.49; 95% CI, 0.35 to 0.69) that was similar to the efficacy in the overall population, which was *EGFR*-positive by the CTA (HR=0.58; 95% CI, 0.43 to 0.78).

The clinical validity of the cobas *EGFR* Mutation Test v1 was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT comparing erlotinib with chemotherapy in treatment-naïve 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.²⁴ 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.²⁵ The clinical validity of the cobas *EGFR* Mutation Test v2 was demonstrated in retrospective analyses of patients enrolled in a phase 2, single-arm study of osimertinib for *EGFR*-sensitizing variant-positive metastatic NSCLC who had progressed following prior therapy with an approved *EGFR* TKI. The osimertinib response rate in the patients identified as *EGFR* T790M-positive by the cobas v2 test was 62% (95% CI, 55% to 69%).

The clinical validity of the Oncomine Dx Target Test was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT, which included newly diagnosed patients with stage IIIB or IV or recurrent NSCLC, in which the *EGFR* variant for enrollment was determined using theascreen.¹³ The PPA of Oncomine vs theascreen 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.²⁶ 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.²⁷ 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.²⁸ 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 (2010), with revised conclusions, indicated that *EGFR* variant testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.²⁹

Other meta-analyses have confirmed the PFS and OS results and conclusions for *EGFR*-positive patients have been published.³⁰⁻³⁵

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.³⁶ 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

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|--|------------------------------|-------|-----------|---------------------------------------|---------------------------------------|--|
| | | | | | Erlotinib | Chemotherapy |
| Wu et al (2015) ³⁷ ; ENSURE (NCT01342965) | China, Malaysia, Philippines | 30 | 2011-2012 | 217 patients with stage IIIB/IV NSCLC | 110 assigned to erlotinib (150 mg qd) | 117 assigned to gemcitabine (1250 mg/m ²) and cisplatin (75 mg/m ²) |
| Rosell et al (2012) ³⁸ ; EURTAC (NCT00446225) | France, Italy, Spain | 42 | 2007-2011 | 173 patients with stage IIIB/IV NSCLC | 86 assigned to erlotinib (150 mg qd) | 87 assigned to cisplatin (75mg/m ²), docetaxel (75 mg/m ²), or gemcitabine (1250 mg/m ²) |
| Zhou et al (2011, 2015) ^{39,40} ; OPTIMAL (NCT00874419) | China | 22 | NR | 165 patients with stage IIIB/IV NSCLC | 83 assigned to erlotinib (150 mg qd) | 82 assigned to carboplatin (AUC5) and gemcitabine (1000 mg/m ²) |

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

| Trial | Median PFS, mo | Median OS, mo | Adverse Events, % | | |
|---|---------------------|---------------------|-------------------|-----------------------------|------|
| | | | Serious | Grade 3 or 4 | % |
| ENSURE (2015)³⁷ | | | | | |
| N | 217 | 217 | 214 | 214 | |
| Erlotinib | 11.0 | 26.3 | 2.7 | Overall | 35.5 |
| | | | | Neutropenia | 0.9 |
| | | | | Leukopenia | 0.9 |
| | | | | Anemia | 0.9 |
| | | | | Rash | 6.4 |
| Chemotherapy | 5.5 | 25.5 | 10.6 | Overall | 57.7 |
| | | | | Neutropenia | 25.0 |
| | | | | Leukopenia | 14.4 |
| | | | | Anemia | 12.5 |
| | | | | Rash | 1 |
| 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 | 13 |
| | | | | Neutropenia | 0 |
| | | | | Increased AT concentrations | 2 |
| Chemotherapy | 5.2 (4.4 to 5.8) | 19.5 | 20 | Rash | 0 |
| | | | | Neutropenia | 22 |
| | | | | Increased AT concentrations | 0 |
| 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 | 0 |
| | | | | Thrombocytopenia | 0 |
| Chemotherapy | 4.6 (4.2 to 5.4) | 27.2 | 14 | Neutropenia | 42 |
| | | | | Thrombocytopenia | 40 |
| 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^{18,41-48} were nonconcurrent prospective studies of treatment-naïve 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.^{19,49,50} In patients with wild-type tumors, the objective radiologic response was 3.3%, PFS was 2.1 months, and OS was 9.2 months.⁵¹

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.⁵² 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.⁵³⁻⁵⁵ 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.⁵⁶ 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).⁵⁷ 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

| Study; Trial | Countries | Sites | Dates | Participants | Description of Interventions | | |
|--------------------------------|-----------|-------|-----------|--|-------------------------------------|---|---|
| | | | | | Gefitinib Alone | Chemo Alone | Gefitinib Plus Chemo |
| Han et al (2017) ⁵⁶ | China | 1 | 2011-2015 | 121 patients with advanced lung adenocarcinoma | 41 assigned to gefitinib (250 mg/d) | 40 assigned to pemetrexed (500 mg/m ²) and carboplatin (AUC5) | 40 assigned to pemetrexed (500 mg/m ²) and carboplatin (AUC5) and |

| Study; Trial | Countries | Sites | Dates | Participants | Description of Interventions | |
|--|------------------------|-------|-----------|--|--------------------------------------|--|
| | | | | | gefitinib (250 mg/d) | |
| | | | | | Gefitinib | Chemo |
| Mok (2009) ⁵³ ; IPASS (NCT00322452) | 9 East Asian countries | 87 | 2006-2007 | 1217 patients with stage IIIB/IV NSCLC (261 <i>EGFR</i> -positive) | 609 assigned to gefitinib (250 mg/d) | 608 assigned to paclitaxel (200 mg/m ²) and carboplatin (AUC5 or AUC6) |
| Mitsudomi (2010) ⁵⁴ ; WJTOG3405 ^a | Japan | 36 | 2006-2009 | 177 patients with stage IIIB/IV or recurrent NSCLC | 88 assigned to gefitinib (250 mg/d) | 89 assigned to cisplatin (80 mg/m ²) and docetaxel (60 mg/m ²) |
| Maemondo (2010), ⁵⁵ Inoue (2013) ⁵⁸ ; NEJ002 | Japan | 43 | 2006-2009 | 230 patients with stage IIIB/IV NSCLC or postoperative relapse | 115 assigned to gefitinib (250 mg/d) | 115 assigned to paclitaxel (200 mg/m ²) and carboplatin (AUC6) |

AUC5: area under the concentration time curve of 5.0 mg/mL/min; AUC6: area under the concentration time curve of 6.0 mg/mL/min; chemo: chemotherapy; *EGFR*: epidermal growth factor receptor; NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial.
^a West Japan Oncology Group 172 trial.

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

| Study | Median PFS, mo | Median OS, mo | Adverse Events, % | | |
|--------------------------------------|--|--|-------------------|-------------------|------|
| | | | Serious | Grade 3 or 4 | % |
| Han et al (2017) ⁵⁶ | | | NR | | |
| Gefitinib | 5.7 (5.2 to 6.3) | 25.8 (21.3 to 30.2) | | Liver dysfunction | 2.4 |
| | | | | Skin rash | 9.8 |
| Chemotherapy | 11.9 (9.1 to 14.6) | 24.3 (17.7 to 30.1) | | Neutropenia | 12.5 |
| | | | | Fatigue | 5.0 |
| | | | | Skin rash | 9.8 |
| Gefitinib plus chemotherapy | 17.5 (15.3 to 19.7) | 32.6 (25.5 to 39.8) | | Liver dysfunction | 10.0 |
| | | | | Neutropenia | 10.0 |
| | | | | Fatigue | 7.5 |
| | | | | Skin rash | 10.0 |
| TE (95% CI) | Combination vs chemotherapy: 0.2 (0.1 to 0.3) Combination vs gefitinib: 0.5 (0.3 to 0.8) Gefitinib vs chemotherapy: 0.3 (0.2 to 0.6) | Combination vs chemotherapy: 0.5 (0.2 to 0.9) Combination vs gefitinib: 0.4 (0.2 to 0.7) Gefitinib vs chemotherapy: 1.0 (0.6 to 1.8) | | | |
| WJTOG3405 (2010) ⁵⁴ | | | | | |
| N | 172 | 172 | NR | 172 | |
| Gefitinib | 9.2 (8.0 to 13.9) | 34.8 (26.0 to 39.5) | | ALT/AST elevation | 27.5 |
| | | | | Rash | 2.3 |
| | | | | Fatigue | 2.3 |
| Chemotherapy | 6.3 (5.8 to 7.8) | 37.3 (31.2 to 45.5) | | ALT/AST elevation | 2.3 |
| | | | | Fatigue | 2.3 |
| | | | | Neutropenia | 84 |
| | | | | Leukocytopenia | 50 |
| | | | | Anemia | 17 |
| TE (95% CI) | HR=0.49 (0.34 to 0.71) | HR=1.25 (0.88 to 1.78) | | | |
| NEJ002 (2010, 2013) ^{55,58} | | | | | |

| Study | Median PFS, mo | Median OS, mo | | Adverse Events, % |
|----------------------------|---------------------|---------------------|-------------------|--|
| N | 224 | | NR | 227 |
| Gefitinib | 10.8 | 27.7 | | Rash 5.3 Arthralgia 0.9 Pneumonitis 2.6 Aminotransferase elevation 26.3 Neutropenia 0.9 |
| Chemotherapy | 5.4 | 26.6 | | Rash 2.7 Neuropathy 6.2 Arthralgia 7.1 Aminotransferase elevation 0.9 Neutropenia 65.5 Anemia 5.3 Thrombocytopenia 3.5 |
| HR (95% CI) | 0.30 (0.22 to 0.41) | 0.89 (0.63 to 1.24) | | |
| IPASS (2009) ⁵³ | | | | |
| N | 259 ^a | 259 ^a | 1196 ^b | |
| Gefitinib | ≈9.6 ^c | NR | 16.3% | Rash 3.1 Diarrhea 3.8 Neurotoxic effects 0.3 Neutropenia 3.7 Anemia 2.2 Leukopenia 1.5 |
| Chemotherapy | ≈5.8 ^c | NR | 15.6% | Rash 0.8 Diarrhea 1.4 Neurotoxic effects 4.9 Neutropenia 67.1 Anemia 10.6 Leukopenia 35.0 |
| HR (95% CI) | 0.48 (0.36 to 0.64) | 0.78 (0.50 to 1.20) | | |

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

^a Analysis includes *EGFR*-positive only.

^b Analysis includes all patients with safety data.

^c Estimated from figure.

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 IIIIB or IV, *EGFR* variant–positive, lung adenocarcinoma who were previously untreated for advanced disease.⁵⁹ Seventy-two percent of patients were Asian, 26% were white, and 90% (308 patients) had common *EGFR* variants (exon 19 deletion or L858R substitution variant in exon 21). Patients received afatinib or chemotherapy (cisplatin plus pemetrexed). In stratified analysis of patients with common *EGFR* variants, the median PFS was 13.6 months for the afatinib group and 6.9 months for the chemotherapy group (HR=0.47; 95% CI, 0.34 to 0.65; p=0.001). The median PFS for the 10% of patients who had other *EGFR* variants was not reported, but the median PFS for the entire patient sample was 11.1 months in the afatinib group and 6.9 months in the chemotherapy group (HR=0.58; 95% CI,

0.43 to 0.78; $p=0.001$). The incidence of objective response in the entire patient sample was 56% in the afatinib group and 23% in the chemotherapy group ($p=0.001$). With a median follow-up of 16.4 months, the median OS was not reached in any group; preliminary analysis indicated no difference in OS between the 2 treatment groups in the entire patient sample (HR=1.12; 95% CI, 0.73 to 1.73; $p=0.60$). Patients in the afatinib group reported greater improvements in dyspnea, cough, and global health status/quality of life than those in the chemotherapy group.⁶⁰ 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.⁵⁹ 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.⁶¹ 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.⁶² Patients had been treated with chemotherapy but not with *EGFR*-targeted therapy; approximately half of the patients (enrolled after a protocol amendment) were chemotherapy-naïve. 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).⁶³ 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.⁶⁴ 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.⁶⁵ 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.⁶⁶

The osimertinib label describes the 2 studies.⁶⁵ 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.⁶⁷ 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

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|---|-------|---------------|---|--|--|
| | | | | | Osimertinib | Standard TKI |
| Reungwetwattan a et al (2018) ⁶⁷ ; FLAURA (NCT02296125) | 31 countries in North America, Europe, Australia, Asia | 168 | 2014- 2017 | 128 (of 556) patients with untreated advanced <i>EGFR</i> -positive NSCLC with available brain scans at baseline | 61 assigned to osimertinib (80 mg/d) | 67 assigned to gefitinib (250 mg/d) or erlotinib (150 mg/d) |
| Mok et al (2017) ⁶⁸ ; AURA3 (NCT02151981) | 18 countries in North America, Europe, Australia, Asia | 126 | 2014- 2015 | 419 patients with T790M-positive advanced NSCLC who had disease progression after first-line <i>EGFR</i> -TKI therapy | 279 assigned to osimertinib (80 mg/d) | 140 to assigned platinum pemetrexed (500 mg/m ² of BSA) plus carboplatin (target AUC5 or cisplatin [75 mg/m ²]) |

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

| Study | PFS, mo | OS, mo | ORR (95% CI) | Adverse Events, % | | Prolongation of QT Interval, % |
|---------------------------|------------------------|-----------|------------------------|----------------------|--------------|--------------------------------------|
| | | | | Grade ≥3 | ILD- Like | |
| AURA3(2017) ⁶⁸ | | | | | | |
| N | 419 | | 419 | 415 | 415 | 415 |
| Osimertinib | 10.1 | NR | 71% (65 to 76) | 23 | 4 | 4 |
| Platinum pemetrexed | 4.4 | NR | 31% (24 to 40) | 47 | 1 | 1 |
| TE (95% CI) | HR=0.30 (0.23 to 0.41) | | OR=5.4 (3.5 to 8.5) | | | |
| PFS (N=128) | | | | | | |

| Study | PFS, mo | | OS, mo | ORR (95% CI) | Adverse Events, % | Prolongation of QT Interval, % |
|-----------------------------|------------------|------------------|-------------------|-------------------|-------------------|--------------------------------|
| | Median, mo | 6-Mo (95% CI), % | 12-Mo (95% CI), % | 18-Mo (95% CI), % | 18-Mo (95% CI), % | ORR (95% CI), % |
| FLAURA (2018) ⁶⁷ | | | | | | |
| Osimertinib | (16.5 to NC) | 87 (74 to 94) | 77 (62 to 86) | 58 (40 to 72) | 66 (52 to 77) | |
| Other TKIs ^a | 13.9 (8.3 to NC) | 71 (57 to 81) | 56 (42 to 68) | 40 (25 to 55) | 43 (31 to 56) | |
| TE (95% CI) | | | | | | 2.5 (1.2 to 5.2) |

CI: 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.

^a Erlotinib or gefitinib.

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

| Study | Study Dates | Design (No. of Studies) | No. of Patients | Line of Treatment | Treatments Compared | Conclusions |
|----------------------------------|-------------|-------------------------|-----------------|---------------------------------|--|---|
| Lin et al (2018) ⁶⁹ | Nov 2017 | RCT (11) | 3145 | First-line | Chemotherapy, afatinib, dacomitinib, erlotinib, gefitinib, osimertinib | PFS: TKIs more effective than chemotherapy Osimertinib, dacomitinib, and afatinib ranked highest probability of benefit among TKIs Subgroup analyses comparing osimertinib with standard of care showed improvements in men, non-Asians, smokers, and those with del19 variants Toxicity profiles similar for TKIs |
| Zhang et al (2018) ⁷⁰ | Oct 2017 | RCT (40) | 9376 | First-, second-, and third-line | Erlotinib, gefitinib | PFS: erlotinib and gefitinib comparable Grade 3-5 adverse events more frequent with erlotinib |
| De Mello et | Aug 2016 | RCT (9) | 3179 | First-line | Chemotherapy, afatinib, | PFS: afatinib, erlotinib, and gefitinib more effective than chemotherapy |

| Study | Study Dates | Design (No. of Studies) | No. of Patients | Line of Treatment | Treatments Compared | Conclusions |
|------------------------------------|-------------|-------------------------|-----------------|---------------------------------|---|--|
| al (2018) ⁷¹ | | | | | erlotinib, gefitinib | OS: afatinib, erlotinib, and gefitinib comparable to chemotherapy |
| Crequit et al (2017) ⁷² | Jun 2017 | RCT (102) | 36,058 | Second-line | 61 treatments (combinations of immunotherapy, chemotherapy, and afatinib, cabozantinib, erlotinib, gefitinib) | OS: immunotherapy or pemetrexed plus erlotinib most effective PFS: erlotinib plus cabozantinib most effective Evidence for safety was insufficient |
| Wu et al (2017) ⁷³ | Jan 2017 | RCT (12) | 3341 | Second- and third-line | Chemotherapy, PD-1/PD-L1 antibodies, erlotinib, gefitinib | OS and PFS: PD-1/PD-L1 more effective than chemotherapy and erlotinib and gefitinib OS and PFS: chemotherapy more effective than erlotinib and gefitinib |
| Yang et al (2017) ⁷⁴ | Dec 2016 | Cohort (82) RCT (8) | 17,621 | First- and second-line | Afatinib, erlotinib, gefitinib | PFS: gefitinib and erlotinib comparable regardless of line Afatinib more effective than gefitinib and erlotinib as second- line treatment in for advanced squamous NSCLC Grade 3-4 adverse events comparable with afatinib and erlotinib; gefitinib adverse events lower |
| Zhang et al (2017) ⁷⁵ | Mar 2016 | RCT (6) | 1055 | First-, second-, and third-line | Afatinib, dacomitinib, erlotinib, gefitinib, icotinib | Therapeutic efficacy comparable among all 5 TKIs Rank probabilities showed dacomitinib and afatinib had potentially better efficacy than erlotinib, gefitinib, and icotinib |

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.⁷⁶ 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.⁷⁷ 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.⁷⁸

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.⁷⁹ 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.⁸⁰

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.⁸¹ 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.⁸² 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% (95% 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*-positive by the Vysis assay and *ALK*-negative by the Ventana assay, the relative effect of crizotinib was not clear (HR=1.71; 95% CI, 0.43 to 6.79).

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.¹⁴ 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.⁸³ 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.^{84,85}

Alectinib was associated with response rates of approximately 50% in patients who had progressed on crizotinib in 2 phase 2 studies.^{86,87} 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.⁸⁸⁻⁹⁰

Brigatinib has shown promise in early phase 1 and 2 studies with PFS of almost 13 months in patients with crizotinib-refractory disease.^{91,92} 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.⁹³

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.¹³ 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-naïve 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 79%) 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-naïve 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

The dabrafenib and trametinib product labels describe the results of an open-label, multicenter study of patients enrolled 3 cohorts: cohorts A and B had received at least 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.^{11,12} Trial results for cohorts A,⁹⁴ B,⁹⁵ and C⁹⁶ 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-naïve. 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

| Study; Trial | Study Type | Country | Dates | Participants | Treatment | Median FU, mo |
|---|--------------------------------------|--|-----------|---|--|----------------|
| Planchard et al (2017) ⁹⁶ NCT01336634 | Single-arm, open-label phase 2 trial | 9 countries in North America, Europe, Asia | 2014-2015 | Adults, stage IV, <i>BRAF</i> V600E variant, previously untreated | Dabrafenib (150 mg bid) plus trametinib (2 mg/d) | 15.9 |
| Planchard et al (2016) ⁹⁴ NCT01336634 | Single-arm, open-label phase 2 trial | 9 countries in North America, Europe, Asia | 2011-2014 | Adults, stage IV, <i>BRAF</i> V600E variant, progression after chemotherapy | Dabrafenib (150 mg bid) | 10.7 |
| Planchard et al (2016) ⁹⁵ ; NCT01336634 | Single-arm, open-label phase 2 trial | 9 countries in North America, Europe, Asia | 2013-2015 | Adults, stage IV, <i>BRAF</i> V600E variant, progression after chemotherapy | Dabrafenib (150 mg bid) plus trametinib (2 mg/d) | 11.6 |
| Hyman et al (2015) ⁹⁷ ; NCT01524978 | Single-arm, open-label phase 2 trial | Germany, Spain, U.K., U.S., France | 2012-2014 | <i>BRAF</i> V600 variant-positive nonmelanoma cancers including NSCLC | Vemurafenib (960 mg bid) | 6 ^a |

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

| Study | Response (95% CI), % | PFS (95% CI), mo | Overall Survival (95% CI) | Adverse Events, % | | | |
|--------------------------------------|---------------------------------------|---|--|---|---------------------|---------|--------------------|
| | | | | Grade 3 or 4 | % | Serious | % |
| Planchard et al (2017) ⁹⁶ | N=36 64 (46 to 79) | N=36 10.9 (7.0 to 16.6) ^c | N=36 At data cutoff: 24.6 mo At 2-y: 51% (33% to 67%) | Overall Pyrexia Hypertension | 7 11 11 | | |
| Planchard et al (2016) ⁹⁴ | N=78 33 (23 to 45) ^a | N=78 5.5 (3.4 to 7.3) | N=78 Median, 12.7 mo | N=78 Overall Cutaneous SCC Asthenia BCC | 39 12 5 5 | Overall | 42 |
| Planchard et al (2016) ⁹⁵ | N=57 63 (49 to 76) | N=57 9.7 (6.9 to 19.6) | N=57 At 6 mo, 82% | N=57 Overall Neutropenia Hyponatremia | 49 9 7 | Overall | 56 16 5 4 |
| Hyman et al (2015) ⁹⁷ | N=19 At 8 wk, 42 (20 to 67) | N=20 Median, 7.3 (3.5 to 10.8) | N=20 At 12 mo, 66% (36% to 85%) | N=95 ^b Overall Rash Fatigue Arthralgia | 73 16 12 4 | | |

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.⁹⁸⁻¹⁰⁰

Section Summary: *BRAF* Gene Variants

FDA has approved a companion diagnostic for detecting *BRAF* variants to aid in selecting NSCLC patients for treatment with combination BRAF and MEK inhibitors, dabrafenib and trametinib. The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. FDA expanded the indication for dabrafenib and trametinib to include the treatment of NSCLC patients whose tumors have a *BRAF*V600E variant based on a multicenter, single-arm study that included a cohort of 57 patients who had progressed on prior therapy and a cohort of 36 treatment-naïve patients. Dabrafenib and trametinib combination therapy 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 test is an NGS oncology panel that detects, among other variants, fusions in *ROS1* from RNA isolated from FFPE tumor tissue samples.¹³ 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.¹⁰¹ 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

| Study | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|---------------------------------|---------------------------------------|---------|-----------|---|----------------------|---------------|
| Lim et al (2017) ¹⁰² | Open-label, single-arm, phase 2 study | Korea | 2013-2016 | Adults with <i>ROS1</i> rearrangement who had progressed on prior | Ceritinib (750 mg/d) | 14.0 |

| Study | Study Type | Country | Dates | Participants | Treatment | Follow-Up, mo |
|--------------------------------------|---|------------------------|-----------|--|-------------------------|---------------|
| Mazieres et al (2015) ¹⁰³ | Retrospective | Six European countries | NR | therapy, 94% crizotinib-naive <i>ROS1</i> rearrangement, 97% had received previous chemotherapy | Crizotinib (250 mg bid) | NR |
| Shaw et al (2014) ¹⁰¹ | Open-label, single-arm, expansion cohort of phase 1 study | Australia, Korea, U.S. | 2010-2013 | Adults with <i>ROS1</i> rearrangement, 86% had received prior therapy | Crizotinib (250 mg bid) | 16.4 |

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

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

| Study | Response (95% CI), % | Median PFS (95% CI), mo | OS (95% CI) | Adverse Events | | | |
|--------------------------------------|--------------------------|---------------------------------------|---------------------------------------|------------------|----|----------------------|----|
| | | | | Grade 3 or 4 | % | All Grades | % |
| Lim et al (2017) ¹⁰² | n=28 62 (45 to 77) | N=32 9.3 (0 to 22) | N=32 24 mo (5 to 43) | N=32 | | N=32 | |
| | | | | Overall | 37 | Diarrhea | 78 |
| | | | | Fatigue | 16 | Nausea | 59 |
| | | | | Pneumonia | 6 | Anorexia | 56 |
| | | | | Hyperglycemia | 9 | Vomiting | 53 |
| | | | | Increased AST | 9 | Cough | 47 |
| | | | | Increased ALT | 6 | Abdominal pain | 41 |
| | | | | | | Musculoskeletal pain | 41 |
| Mazieres et al (2015) ¹⁰³ | n=29 80 (NR) | N=30 9.1 (NR) | NR | N=30 | | NR | |
| | | | | Grade 3 | NR | | |
| | | | | Grade 4 or 5 | 0 | | |
| Shaw et al (2014) ¹⁰¹ | N=50 72 (58 to 84) | N=50 19.2 (14.4 to not reached) | N=50 At 12 mo: 85% (72% to 93%) | N=50 | | N=50 | |
| | | | | Hypophosphatemia | 10 | Visual impairment | 82 |
| | | | | Neutropenia | 10 | Diarrhea | 44 |
| | | | | Elevated ALT | 4 | Nausea | 40 |
| | | | | | | Peripheral edema | 40 |
| | | | | | | Constipation | 34 |
| | | | | | | Vomiting | 34 |

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.¹⁰⁴ *ALK* rearrangements and *EGFR* variants were concurrently analyzed. The patients had clinical stages ranging from I to IV, but most were stage IV (41.3%). Of the 208 tumors, 3.4% (n=7) were *ROS1* rearranged. *ROS1* rearrangement was mutually exclusive from *ALK* rearrangement, but 1 of 7 *ROS1*-positive patients had a concurrent *EGFR* variant. Patients with *ROS1* rearrangement had a higher ORR and longer median PFS on pemetrexed than those without a rearrangement. In patients with *ROS1* rearrangement, PFS with EGFR TKIs was shorter than those patients without the rearrangement. None of the *ROS1*-positive patients received ALK inhibitors (eg, crizotinib), which is the recommended targeted therapy for patients with NSCLC and this genetic alteration.

Section Summary: ROS1 Gene Rearrangements

FDA has approved a companion diagnostic for detecting *ROS1* gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori). The clinical validity of the companion diagnostic was established in the Summary of Safety and Effectiveness Data document. FDA expanded the indication for crizotinib to include the treatment of patients whose tumors have a *ROS1* rearrangement based on a multicenter, single-arm study including 50 patients, the majority of whom had progressed on prior therapy. 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.¹⁰⁵ 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.¹⁰⁶ 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.¹⁰⁷ 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.¹⁰⁸ 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 multitargeted signal transduction inhibitor that inhibits raf-kinases, vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor-B, and c-kit. Only 186 evaluable patients were included in analyses. The 8-week disease control rate was 20%, 25%, 62%, and 44% for the 4 treatment groups, respectively, in the *KRAS* variant–positive patients. For *KRAS* 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.¹⁰⁹ TAILOR enrolled patients from 52 Italian hospitals and genotyped patients for *KRAS* and *EGFR* variant status. Wild-type *EGFR* patients (n=218) received first-line platinum-based chemotherapy and then were 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.⁴⁴ 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.⁴⁸ 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.¹¹⁰ 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-naïve patients 70 years of age or older who had advanced NSCLC.⁴⁷ 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-naïve patients with advanced NSCLC.⁴⁶ 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.¹¹¹ 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)¹⁸ 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)¹¹² 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* (phosphatidylinositide-3-kinase catalytic subunit- α) variant testing.¹¹³ 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.¹¹⁴ 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.¹¹⁵ *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).⁴⁵ 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-naïve patients with stage IIIB or IV NSCLC were assigned to taxane and carboplatin with or without cetuximab.¹¹⁶ 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.¹¹⁷ 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).¹¹⁸ 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.¹¹⁹ *KRAS* variants were detected in 75 (19%) tumors. Among patients with mutated *KRAS*, the median OS in the cetuximab-containing (n=38) and chemotherapy-alone arms (n=37) was similar (8.9 months vs 11.1 months, respectively; HR=1.00; 95% CI, 0.60 to 1.66; p=1.0). Among patients with wild-type *KRAS*, the median OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (11.4 months vs 10.3 months, respectively; HR=0.96; 95% CI, 0.75 to 1.23; p=0.74). PFS also was similar in the cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR=0.97; 95% CI, 0.76 to 1.24) and wild-type (HR=0.84; 95% CI, 0.50 to 1.40) *KRAS*. Response rates in the cetuximab-containing arm in patients with *KRAS*-mutated and wild-type tumors were 36.8% and 37.3%, respectively (p=0.96). Overall, there was no indication that *KRAS* variant status was predictive of cetuximab effect in NSCLC.

MEK Inhibitors

Two RCTs have compared a MEK inhibitor (with or without chemotherapy) with chemotherapy alone in patients with *KRAS*-positive advanced NSCLC after progression with first-line therapy.^{120,121} 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.

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

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|--|-------|-----------|--|---|---|
| | | | | | MEK Inhibitor | Chemotherapy |
| Janne et al (2017) ¹²⁰ ; SELECT1 (NCT01933932) | 25 countries in North and South America, | 202 | 2013-2016 | 510 patients with advanced NSCLC and progression | 254 assigned to selumetinib (75 mg bid) | 256 assigned to docetaxel (75 mg/m ²) |

| Study; Trial | Countries | Sites | Dates | Participants | Interventions |
|--|--|-------|-----------|--|--|
| Blumenschein et al (2015) ¹²¹ ; NCT01362296 | Australia, Europe U.S., Korea, 6 European countries | 60 | 2011-2012 | 129 patients with stage IV NSCLC and progression following first-line platinum-containing chemotherapy | plus docetaxel (75 mg/m ²) 86 assigned to trametinib (2 mg/d) 43 assigned to docetaxel (75 mg/m ²) |

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

Table 14. RCT Results for MEK Inhibitors for *KRAS*-Variant NSCLC

| Study | PFS (95% CI%) | OS (95% CI%) | ORR (95% CI), % | Adverse Events, % | | |
|--|------------------------|------------------------|------------------------|-----------------------|----|---------|
| | | | | Grade ≥3 | % | Serious |
| SELECT1 (2017) ¹²⁰ | | | | | | |
| N | 510 | 510 | 510 | 505 | | |
| Selumetinib plus docetaxel | 3.9 mo | 8.7 mo | 20.1 | Overall | 67 | 49 |
| | | | | Diarrhea | 7 | |
| | | | | Asthenia | 9 | |
| | | | | Dyspnea | 8 | |
| | | | | Anemia | 5 | |
| | | | | Neutropenia | 7 | |
| Docetaxel | 2.8 mo | 7.9 mo | 13.7 | Overall | 45 | 32 |
| | | | | Diarrhea | 3 | |
| | | | | Asthenia | 3 | |
| | | | | Dyspnea | 2 | |
| | | | | Anemia | 4 | |
| | | | | Neutropenia | 4 | |
| TE (95% CI) | HR=0.93 (0.77 to 1.12) | HR=1.05 (0.85 to 1.30) | OR=1.61 (1.00 to 2.62) | | | |
| Blumenschein et al (2015) ¹²¹ | | | | | | |
| N | 129 | 129 | 129 | 130 | | |
| Trametinib | 12 wk | 8 mo | 12 | Overall | 41 | 37 |
| | | | | Rash | 6 | |
| | | | | Diarrhea | 5 | |
| | | | | Asthenia | 5 | |
| | | | | Hypertension | 9 | |
| | | | | Neutropenia | 0 | |
| | | | | Decreased neutrophils | 0 | |
| Docetaxel | 11 wk | Not reached | 12 | Overall | 37 | 21 |
| | | | | Rash | 0 | |
| | | | | Diarrhea | 2 | |
| | | | | Asthenia | 0 | |
| | | | | Hypertension | 0 | |
| | | | | Neutropenia | 14 | |
| | | | | Decreased neutrophils | 7 | |
| HR (95% CI) | 1.14 (0.75 to 1.75) | 0.97 (0.52 to 1.83) | | | | |

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.¹²² 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.¹²³ *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.¹²⁴ 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.¹²⁵ 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.¹²⁶

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.¹²⁷

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.

PD-1 / PD-L1

As a primary immunosuppressive driver, PD-L1 overexpression may be an important facilitator for tumor growth and metastasis. PD-L1 has been detected in up to 50% of human cancers, making the PD-L1 pathway a focus of cancer research. NCCN recommends IHC testing for PD-L1 expression before first-line treatment in patients with metastatic NSCLC with negative or unknown test results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements. Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for pembrolizumab. PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses. The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.

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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network Guidelines

EGFR Testing

The National Comprehensive Cancer Network (NCCN) guidelines (v.6.2018) for the treatment of metastatic non-small-cell lung cancer (NSCLC) recommend the following on epidermal growth factor receptor (*EGFR*) testing¹²⁸:

- *EGFR* mutation testing is recommended (category 1) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified, because erlotinib or afatinib (category 1 for both) is recommended for patients who are positive for *EGFR* variants.
- When an *EGFR* variant is discovered prior to first-line chemotherapy, erlotinib (category 1), afatinib (category 1), gefitinib (category 1), or osimertinib (category 1) are recommended.
- When an *EGFR* variant is discovered during first-line chemotherapy, interrupt or continue chemotherapy, then follow with erlotinib, afatinib, or gefitinib.
- If progression occurs following first-line treatment, *EGFR* T790M testing is recommended (category 2A). If T790M-positive, osimertinib (category 1), local therapy, or continuing with erlotinib, afatinib, or gefitinib are recommended (depending on symptoms, the location of metastases, and a number of lesions).
- Tyrosine kinase inhibitors are not recommended as first-line therapy or subsequent therapy following progression for patients negative for *EGFR* variants or with unknown *EGFR* status.
- In patients with squamous cell carcinoma (SCC), *EGFR* variant testing should be considered in never-smokers; when histology is assessed using small biopsy specimens (rather than surgically resected samples); or when histology is mixed adenosquamous (category 2A).

ALK Testing

NCCN guidelines (v.6.2018) state the following on anaplastic lymphoma kinase (*ALK*) rearrangement testing¹²⁸:

- *ALK*-rearrangement testing is recommended (category 1) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- If *ALK*-positive status is discovered before first-line chemotherapy, alectinib (category 1; preferred), crizotinib (category 1), or ceritinib (category 1) is recommended.
- If *ALK* rearrangement is discovered during first-line chemotherapy, interrupt or complete planned chemotherapy and start alectinib, crizotinib or ceritinib.
- If there is progression on first-line therapy, continue alectinib, crizotinib, or ceritinib, switch to ceritinib, alectinib, or brigatinib, or consider local therapies are recommended (depending on symptoms, the location of metastases, and number of lesions).
- In patients with SCC, *ALK*-rearrangement testing should be considered in never-smokers; when histology is assessed using small biopsy specimens (rather than surgically resected samples); or when histology is mixed adenosquamous (category 2A).
- Flare phenomenon has been seen in a subset of patients who discontinue *ALK* inhibitors. If disease flare occurs, restart *ALK* inhibitor.

ROS1 Testing

NCCN guidelines (v.6.2018) state the following on *ROS1*-rearrangement testing¹²⁸:

- *ROS1*-rearrangement testing is recommended (category 2A) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- *ROS1*-rearrangement testing may be considered in patients with SCC.
- If *ROS1*-positive status is discovered, crizotinib (preferred) or ceritinib is recommended.

BRAF Testing

NCCN guidelines (v.6.2018) state the following on *BRAF* testing¹²⁸:

- *BRAF* testing is recommended (category 2A) in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- *BRAF* testing may be considered in patients with SCC.
- If *BRAF* V600E variant-positive status is discovered, combination dabrafenib and trametinib or other first-line cytotoxic therapy options are recommended.

KRAS Gene

NCCN guidelines (v.6.2018) state that "*KRAS* mutations are associated with intrinsic TKI [tyrosine kinase inhibitor] resistance, and *KRAS* gene sequencing could be useful for the selection of patients as candidates for TKI therapy."¹²⁸ Targeted therapy for patients with the *KRAS* variants is currently unavailable.

Other Genes

NCCN guidelines (v.6.2018) do not give specific recommendations for testing for genetic alterations in the genes *HER2*, *RET*, or *MET* in NSCLC. However, the guidelines state that the following emerging targeted agents are available for patients with one of these specific genetic alterations¹²⁸:

- High-level *MET* amplification or *MET* exon 14 skipping mutation: crizotinib (category 2A)
- *HER2* variants: ado-trastuzumab emtansine (category 2B)
- *RET* rearrangements: cabozantinib or vandetanib (category 2A).

College of American Pathologists et al

The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (2013) published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR and ALK TKI therapy.¹²⁹ Based on excellent quality evidence (category A), the guidelines recommended *EGFR* variant and *ALK* rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, smoking history).

In 2018, updated guidelines were published and added new *EGFR* and *ALK* recommendations.¹³⁰ *ROS1* testing is recommended for all patients with lung adenocarcinoma irrespective of clinical characteristics (strong recommendation). *BRAF*, *RET*, *HER2*, *KRAS*, and *MET* testing are not recommended as routine stand-alone tests but may be considered as part of a larger testing panel or if *EGFR*, *ALK*, and *ROS1* are negative (expert consensus opinion).

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO; 2014) reviewed and endorsed the 2013 College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology guidelines, and highlighted 3 evolving areas: advances in *ALK* testing methodology, considerations for selecting appropriate populations for molecular testing, and the emergence of other targeted molecular alterations.¹³¹ ASCO recommendations stated that testing for *EGFR* should be prioritized over other molecular markers in lung adenocarcinoma, and that, after *EGFR* testing, testing for *ALK* should be prioritized over other proposed molecular markers in lung adenocarcinomas, for which published evidence is insufficient to support testing guideline development at the present time.

ASCO (2018) reviewed and endorsed, with minor modifications, the 2018 guidelines from College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (see above).¹³² ASCO differed from the guidelines in its recommendation of stand-alone *BRAF* testing in patients with advanced lung adenocarcinoma, irrespective of clinical characteristics (expert consensus opinion).

ASCO (2017) also updated its evidence-based recommendations on systemic therapy for patients with stage IV NSCLC.¹³³ Table 15 summarizes the recommendations and associated quality and strength of evidence.

Table 15. Recommendations on Systemic Therapy for Stage IV NSCLC

| Recommendation | QOE | SOR |
|--|--------------|----------|
| First-line therapy | | |
| Sensitizing <i>EGFR</i> variants: afatinib, erlotinib, or gefitinib | High | Strong |
| <i>ALK</i> rearrangements: crizotinib | Intermediate | Moderate |
| <i>ROS1</i> rearrangement: crizotinib | Low | Weak |
| Second-line therapy | | |
| Sensitizing <i>EGFR</i> variants and T790M resistance variant: osimertinib | High | Strong |
| <i>ROS1</i> rearrangement who have not received prior crizotinib: crizotinib | Low | Moderate |
| <i>BRAF</i> variants who have received prior immune checkpoint therapy: dabrafenib alone or in combination with trametinib | Insufficient | Moderate |

NSCLC: non-small-cell lung cancer; QOE: quality of evidence; SOR: strength of recommendation.

American College of Chest Physicians Guidelines

The American College of Chest Physicians (2013) updated its evidence-based practice guidelines on the treatment of stage IV NSCLC.¹³⁴ Based on a review of the literature, the College reported improved response rates, progression-free survival, and toxicity profiles with first-line erlotinib or gefitinib compared with first-line platinum-based therapy in patients with *EGFR* variants, especially exon 19 deletion and L858R. The College recommended “testing patients with NSCLC for *EGFR* mutations at the time of diagnosis whenever feasible, and treating with first-line EGFR TKIs if mutation-positive.”

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Currently unpublished trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|---|--------------------|-----------------|
| Ongoing | | | |
| NCT01248247 ^a | BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer | 334 | Jun 2019 |
| NCT01306045 | Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies | 600 | Dec 2019 |
| NCT02894853 ^a | Lung Cancer Early Molecular Assessment Trial (LEMA) | 1297 | Dec 2019 |
| NCT03225664 ^a | BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer | 217 | Sep 2020 |
| NCT02622581 ^a | Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP) | 5000 | Dec 2020 |
| NCT02117167 ^a | Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIRO2_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-small Cell Lung Cancer | 650 | Feb 2022 |
| NCT02465060 | Molecular Analysis for Therapy Choice (MATCH) | 6452 | Jun 2022 |

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- 81235 EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion L858R, T790M, G719A, G719S, L861Q)
- 81275 KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis, variants in exon 2 (eg, codons 12 and 13)

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| 81276 | KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146) |
| 81404 | Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) |
| 81405 | Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) |
| 81406 | Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia) |
| 81479 | Unlisted molecular pathology procedure |
| 88342 | Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure |
| 88365 | In situ hybridization (eg, FISH), per specimen; initial single probe stain procedure |
| 0022U | Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider |

- There is a specific CPT code for testing for common variants of *EGFR*: 81235.
- If testing is done by immunohistochemical assay, CPT code 88342 would likely be reported. If testing is done by fluorescence in situ hybridization (FISH), CPT code 88365 would likely be reported.
- There are specific CPT codes for testing for *KRAS*: 81275, 81276.
- CPT code 81404 has a listing for *RET* testing.
- CPT code 81405 has listings for both *KRAS* and *RET* testing.
- CPT code 81406 has a listing for *BRAF* testing.
- Testing for variants in the other genes listed above would be reported with the unlisted molecular pathology code 81479.

ICD-10 Diagnoses

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| C34.01 | Malignant neoplasm of right main bronchus |
| C34.02 | Malignant neoplasm of left main bronchus |
| C34.11 | Malignant neoplasm of upper lobe, right bronchus or lung |
| C34.12 | Malignant neoplasm of upper lobe, left bronchus or lung |
| C34.2 | Malignant neoplasm of middle lobe, bronchus or lung |
| C34.31 | Malignant neoplasm of lower lobe, right bronchus or lung |
| C34.32 | Malignant neoplasm of lower lobe, left bronchus or lung |
| C34.81 | Malignant neoplasm of overlapping sites of right bronchus and lung |
| C34.82 | Malignant neoplasm of overlapping sites of left bronchus and lung |

- ICD-10-CM does not have specific coding for non-small-cell lung cancer. The malignant neoplasm of lung codes above would be used.

REVISIONS

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| 09-28-2014 | Policy added to the bcbsks.com web site on 08-29-2014. Effective on 09-28-2014, 30 days after posting. |
| 02-08-2015 | Title of policy changed from "Epidermal Growth Factor Receptor Mutation Analysis for Patients with Non-Small Cell Lung Cancer" |
| | Updated Description section. |
| | In Policy section: <ul style="list-style-type: none"> ▪ Added "D. Analysis of somatic mutations of the KRAS gene is considered experimental / investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC." ▪ Added "E. Testing for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2, for targeted therapy in patients with NSCLC, is considered experimental / investigational." |
| | Updated Rationale section. |
| 05-14-2015 | In Coding section: <ul style="list-style-type: none"> ▪ The following CPT codes were added: 81275, 81404, 81405, 81406, 81479, 88342, 88365. |
| | Updated References section. |
| | Updated Description section. |
| 05-14-2015 | In Policy section: <ul style="list-style-type: none"> ▪ Added Item D, "Analysis of somatic rearrangement mutations of the ALK gene may be considered medically necessary to predict treatment response to crizotinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)." ▪ Added Item E, " Analysis of somatic rearrangement mutations of the ALK gene is considered experimental / investigational in all other clinical situations." ▪ In Item G, added "Analysis" and removed "Testing", to read " Analysis for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2, for targeted therapy in patients with NSCLC, is considered experimental / investigational." ▪ In Policy Guidelines, Item 2, added "The 2015", "as a category 1 recommendation that", and "and ALK rearrangement testing be performed in the workup of NSCLC in patients with histologic subtypes adenocarcinoma, large-cell carcinoma, and NSCLC not otherwise specified," and removed "a) for patients with advanced lung cancer, nonsquamous cell type, or b) when biopsy specimens are small and histology is mixed," to read, "2. The 2015 guidelines from the National Comprehensive Cancer Network recommend as a category 1 recommendation that EGFR mutation testing and ALK rearrangement testing be performed in the workup of NSCLC in patients with histologic subtypes adenocarcinoma, large-cell carcinoma, and NSCLC not otherwise specified." ▪ In Policy Guidelines, Item 3, added "The", "and ALK rearrangement" and "and ALK", and removed "Current", to read, "The 2014 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend: a) EGFR mutation and ALK rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (eg, smoking history); b) In the setting of fully excised lung cancer specimens, EGFR and ALK mutation testing is not recommended in lung cancers when an adenocarcinoma component is lacking (such as pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and c) In the setting of more limited lung cancer specimens (eg, biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous cell histology. Clinical criteria (eg, |

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| | <p>young age, lack of smoking history) may be useful to select a subset of these samples for testing."</p> <p>Updated Rationale section.</p> <p>Updated References section.</p> |
| 01-01-2016 | <p>Updated Description section.</p> <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Revised nomenclature to CPT code: 81275. ▪ Revised bullets under CPT/HCPCS coding. <p>Updated References section.</p> <p>Added Appendix section.</p> |
| 11-22-2016 | <p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A, added "an EGFR tyrosine kinase inhibitor (TKI) therapy (eg, "[Tarceva®], gefitinib [Iressa®],", and "[Gilotrif®])" to read, "Except as noted below, analysis of 2 types of somatic mutation within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (eg, erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)." ▪ Added new Item B, "Analysis for the T790M mutation in the gene for the EGFR is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy." ▪ In Policy Guidelines, revised guideline dates for Items 2 and 3 and added "Genetic Counseling." <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT code: 81276. ▪ Updated coding bullets. <p>Updated References section.</p> |
| 10-01-2017 | <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Removed Genetic Counseling information from Policy Guidelines. <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT code: 0022U. |
| 03-14-2018 | <p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A, removed "mutation", "point mutation", and "with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)" and added "variants", "single-nucleotide variant", and "with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified" to read, "Except as noted below, analysis of 2 types of somatic variants within the EGFR gene – small deletions in exon 19 and a single-nucleotide variant in exon 21 (L8514) – may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (eg, erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item B, removed "mutation" and added "variants" to read, "Analysis of the T790M variants in the EGFR gene is considered medically necessary as a technique to predict |

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| | <p>treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy."</p> <ul style="list-style-type: none"> ▪ In Item C, removed "mutation" and added "variants" to read, "Analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—is considered experimental / investigational for patients with advanced squamous cell NSCLC." ▪ In Item D, removed "mutations" and added "variants" to read, "Analysis of other EGFR variants within exons 18 to 24, or other applications related to NSCLC, is considered experimental / investigational." ▪ In Item E, removed "mutations" and "with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)" and added "variants", "ALK inhibitor therapy (eg, "[Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™])", and "with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified" to read, "Analysis of somatic rearrangement variants of the ALK gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item F, removed "mutations" and "clinical" and added "variants" to read, "Analysis of somatic rearrangement variants of the ALK gene is considered experimental / investigational in all other situations." ▪ Added new Item G, "Analysis of the BRAFV600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ Added new Item H, "Analysis of somatic rearrangement variants of the ROS1 gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori®]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In previous Item G (now Item I), removed "mutations" and added "variants" to read, "Analysis of somatic variants of the KRAS gene is considered experimental / investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC." ▪ In Previous Item H (now Item J), removed "ROS" and "BRAF" to read, "Analysis for genetic alterations in the genes RET, MET, and HER2 for targeted therapy in patients with NSCLC is considered experimental / investigational." ▪ Added new Item K, "Programmed death receptor 1 (PD-1) or its ligand (PD-L1) expression analysis may be considered medically necessary as a technique to predict treatment response to drug therapy." ▪ Updated Policy Guidelines. <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated nomenclature for CPT codes: 88342, 88365. ▪ Updated coding bullets. ▪ Removed ICD-9 codes. <p>Updated References section.</p> |
| 09-12-2018 | In Policy section: |

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| | <ul style="list-style-type: none"> ▪ In Item A, removed "metastatic" and added "stage III or IV" to read, "Except as noted below, analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a single-nucleotide variant in exon 21 (L858R)—may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (eg, erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item E, removed "metastatic" and added "stage III or IV" to read, "Analysis of somatic rearrangement variants of the ALK gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (eg, crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item G, removed "metastatic" and added "stage III or IV" to read, "Analysis of the BRAF V600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (eg, dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with stage III or IV metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item H, removed "metastatic" and added "stage III or IV" to read, "Analysis of somatic rearrangement variants of the ROS1 gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori®]) in patients with stage III or IV metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." |
| | Updated References section. |
| 02-01-2019 | Policy posted 01-04-2019 with an effective date of 02-01-2019. |
| | Updated Description section. |
| | <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A, removed "Except as noted below," "2 types of," "small deletions in exon 19 and a single nucleotide variant in exon 21 (L858R)" and added "in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q)" and "osimertinib [Tagrisso]" to read, "Analysis of somatic variants in exons 18 through 21 (eg, G719X, L858R, T790M, S6781, L861Q) within the EGFR gene may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (eg, erlotinib [Tarceva], gefitinib [Iressa}, afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ Removed Item B, "Analysis of the T790M variants in the EGFR gene is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy." ▪ Removed Item C, "Analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—is considered experimental / investigational for patients with advanced squamous cell NSCLC." ▪ In previous Item D, now Item B, removed "18" and added "22" to read, "Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered experimental / investigational." ▪ Updated Policy Guidelines. |
| | Updated Rationale section. |
| | Updated References section. |
| | Removed Appendix section. |

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