Policy Statement

Molecular analysis (genetic testing) is reserved for advanced (stage III or IV) or metastatic Non-Small-Cell Lung Cancer (NSCLC) including adenocarcinoma, large cell, squamous cell and NSCLC not otherwise specified (see Policy Guidelines). Small panel testing including the following medically necessary genes may be considered as an alternative to individual testing and may be preferred when there is limited tissue available for testing.

**EGFR Testing**
Analysis of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], afatinib [Gilotrif®], or osimertinib [Tagrisso™]) in patients with advanced NSCLC.

Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered investigational.

**ALK Testing**
Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of somatic rearrangement variants of the ALK gene is considered investigational in all other situations.

**BRAF V600E Testing**
Analysis of the BRAF V600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of BRAF V600E variant is considered investigational in all other situations.

**ROS1 Testing**
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 advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of somatic rearrangement variants of the ROS1 gene is considered investigational in all other situations.

**KRAS Testing**
Analysis of somatic variants of the KRAS gene is considered investigational as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors (TKIs) and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC unless included as part of a small panel that otherwise meets medically necessary criteria.
HER2 Testing
Analysis of genetic alterations in the HER2 gene for targeted therapy in patients with NSCLC is considered investigational, unless included as part of a small panel that otherwise meets medically necessary criteria.

NTRK GENE FUSION TESTING
Analysis of NTRK gene fusions may be considered medically necessary to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of NTRK gene fusions is considered investigational in all other situations.

RET Rearrangement Testing
Analysis of genetic alteration in the RET gene may be considered medically necessary to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in patients with metastatic NSCLC.

Analysis of genetic alterations in the RET gene is considered investigational in all other situations.

MET Exon 14 Skipping Alteration
Analysis of genetic alteration that leads to MET exon 14 skipping may be considered medically necessary to predict treatment response to capmatinib (Tabrecta) in patients with metastatic NSCLC.

Analysis of genetic alterations of the MET gene is considered investigational in all other situations.

PD-L1 Testing
Programmed Death-Ligand 1 (PD-L1) testing may be considered medically necessary to predict treatment response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in patients with metastatic NSCLC. PD-L1 is a ligand not a gene, and testing may be requested separately if not part of the panel.

PD-L1 testing is considered investigational in all other situations.

Tumor Mutational Burden Testing
Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered investigational.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines
These gene tests are intended for use in patients with advanced non-small-cell lung cancer (NSCLC). Early stage (I and II) treatments are not dependent on the results of this testing. Tissue testing can be requested for separate genes (as opposed to circulating tumor DNA or liquid biopsy testing that is usually done as a panel). Adenocarcinoma, large cell, squamous cell and NSCLC not otherwise specified, are all subtypes of NSCLC. Squamous cell NSCLC has a lower incidence of genetic variances than adenocarcinoma, so testing is not always needed. Patients with either small deletions in exon 19 or a point mutation in exon 21 (L858R) of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene are considered good candidates for treatment with erlotinib, gefitinib or afatinib. Patients with wild-type variants are unlikely to respond to erlotinib or afatinib; for these patients, other treatment options should be considered.
The 2020 guidelines from the National Comprehensive Cancer Network recommend that EGFR variants and ALK rearrangement testing (category 1) as well as ROS1 and BRAF testing (category 2A) be performed in the workup of non-small-cell lung cancer in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. The guidelines add that testing should be conducted as part of broad molecular profiling and should include the NTRK gene fusion.

NTRK (neurotrophic tyrosine receptor kinase) gene fusions happen when a piece of chromosome containing the NTRK gene breaks off and joins (fuses) with a gene on another chromosome, producing abnormal proteins that can cause cancer cells to grow. It has been associated with cancers of brain, head and neck, thyroid, soft tissue, lung, and colon.

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.”

**Recommended Testing Strategies**

Patients who meet criteria for genetic testing as outlined in the policy statements above should be tested for the variants specified.

- When tumor tissue is available, tissue testing is recommended.
- When tumor tissue is limited or unavailable, circulating tumor DNA (liquid biopsy) is an option only if follow-up tissue-based analysis is planned should a driver mutation not be identified.

**Coding**

The following CPT code is specific for testing for common variants of EGFR:

- **81235**: EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)

If testing is done by immunohistochemical assay, the following CPT code would likely be reported:

- **88342**: Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure

If testing is done by fluorescence in situ hybridization, the following CPT code would likely be reported:

- **88365**: In situ hybridization (e.g., FISH), per specimen; initial single probe stain procedure

The following CPT codes are specific for testing for KRAS:

- **81275**: KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)

- **81276**: KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)

**Effective January 1, 2021**, there is a new Molecular Pathology codes to support Neurotrophic receptor tyrosine kinase (NTRK) gene testing:

- **81191**: NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis
• **81192**: NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis
• **81193**: NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis
• **81194**: NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis

The following CPT code has a listing for **RET** testing:
• **81404**: Molecular Pathology Procedure Level 5
  o RET (ret proto-oncogene) (e.g., multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (e.g., M918T, 2647_2648delinsTT, A883F)

The following CPT code has listings for both **KRAS** and **RET** testing:
• **81405**: Molecular Pathology Procedure Level 6
  o KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., Noonan syndrome), full gene sequence
  o RET (ret proto-oncogene) (e.g., multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (e.g., exons 10, 11, 13-16)

The following CPT code has a listing for **BRAF** testing:
• **81406**: Molecular Pathology Procedure Level 7
  o BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., Noonan syndrome), full gene sequence

Testing for variants in the other genes listed above would be reported with the following code:
• **81479**: Unlisted molecular pathology procedure

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**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.

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**Related Policies**

• Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
• Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies

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**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Table 1 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved diagnostic tests.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>FDA Approval of Companion Diagnostic Test</th>
</tr>
</thead>
</table>
| Afatinib (Gilotrif) | • 2013: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions  
• 2016: Second line for patients with metastatic squamous NSCLC  
• 2018: First line for patients with nonresistant EGFR variants other than exon 19 or exon 21 NSCLC | • 2013: thesrascreen® EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit (Qiagen)  
• 2017: FoundationOne CDx™ (Foundation Medicine)                                                                 |
| Alectinib (Alecensa) | • 2015: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib  
• 2017: First line for patients with ALK-positive NSCLC who have not received prior systemic therapy for metastatic disease | 2017: FoundationOne CDx™ (Foundation Medicine)                                                                 |
| Brigatinib (Alunbrig) | • 2017: Second line for patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant of crizotinib | Test not specified in FDA approval                                                                 |
| Ceritinib (Zykadia) | • 2014: Second line for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib  
• 2017: First line for patients with ALK-positive metastatic NSCLC | • 2015: Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems)  
• 2017: FoundationOne CDx™ (Foundation Medicine)                                                                 |
| Crizotinib (Xalkori) | • 2011: First line for patients with ALK-positive metastatic NSCLC | • 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) | • 2016: Patients with ROS1-positive metastatic NSCLC | • 2017: Oncomine™ Dx Target Test (Thermo Fisher Scientific)                                                                 |
| Dacomitinib (Vizimpro) | • 2018: First line for patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 (L858R) substitutions | Test not specified in FDA approval                                                                 |
| Dabrafenib (Tafinlar) plus trametinib (Mekinist) | • 2017: Used in combination for treatment of patients with metastatic NSCLC with BRAF V600E variant | • 2017: Oncomine™ Dx Target Test  
• 2017: FoundationOne CDx™ (Foundation Medicine)                                                                 |
| Erlotinib (Tarceva) | • 2013: First line for patients with metastatic NSCLC whose tumors have EGFR 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 | • 2013: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics)  
• 2016: cobas® EGFR Mutation Test v2 (tissue or blood test) (Roche Diagnostics)                                                                 |
### Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

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

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

### Rationale

#### Background

**Non-Small-Cell Lung Cancer**

Treatment options for non-small-cell lung cancer (NSCLC) depend on disease stage and include various combinations of surgery, radiotherapy, systemic therapy, and best supportive care. Unfortunately, in up to 85% of cases, the cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease. When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and a 1-year survival of 30% to 45%. 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 epidermal growth factor receptor (EGFR) variants and anaplastic lymphoma kinase (ALK) rearrangements is routine in clinical decision making for the treatment of NSCLC. The use of testing for other variants to direct targeted therapy continues to evolve.

#### EGFR Gene

EGFR, a receptor tyrosine kinase (TK), is frequently overexpressed and activated in NSCLC. Drugs that inhibit EGFR signaling either prevent ligand binding to the extracellular domain (monoclonal antibodies) or inhibit intracellular TK activity (small-molecule tyrosine kinase inhibitors [TKIs]). These targeted therapies dampen signal transduction through pathways downstream to the EGFR, such as the RAS/RAF/MAPK cascade. RAS proteins are G proteins that cycle between active and inactive forms in response to stimulation from cell surface receptors, such as EGFR, acting as binary switches between cell surface EGFR and downstream signaling pathways. These pathways are important in cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

Variants in 2 regions of the EGFR gene (exons 18-24)—small deletions in exon 19 and a point variant in exon 21 (L858R)—appear to predict tumor response to TKIs such as erlotinib. Likewise,
tumors with an acquired exon 20 (T790M) substitution variant appear to respond to osimertinib following the failure of TKI therapy.

The prevalence of EGFR variants in NSCLC varies by population, with the highest prevalence in nonsmoking Asian women with adenocarcinoma, in whom EGFR variants have been reported to be up to 30% to 50%. The reported prevalence in the white population is approximately 10%.

**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. Most BRAF variants occur more frequently in smokers.

**ROS1 Gene**

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

**KRAS Gene**

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

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

**HER2 Gene**

Human epidermal growth factor receptor 2 (HER2) is a member of the HER (EGFR) family of TK receptors and has no specific ligand. When activated, it forms dimers with other EGFR family members. HER2 is expressed in approximately 25% of NSCLC. HER2 variants are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.

**RET Gene**

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

**MET Gene**

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

**Targeted Therapies**

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

Crizotinib is an oral small-molecule TKI that is FDA-approved for patients with locally advanced or metastatic NSCLC who are positive for the ALK or ROS1 gene rearrangements confirmed through a companion diagnostic test. Ceritinib is a potent ALK inhibitor that is approved for ALK-positive patients who whose cancer has progressed while taking crizotinib or who could not tolerate crizotinib. Alectinib is a selective ALK inhibitor with high central nervous system penetration that is active against several secondary resistance variants to crizotinib. Brigatinib is also an ALK inhibitor that may be able to overcome a broad range of the resistance mechanisms in patients who have progressed on or are intolerant to crizotinib.

BRAF or MEK inhibition with TKIs (e.g., vemurafenib/dabrafenib or trametinib) was originally approved by the FDA for treatment of unresectable or metastatic melanoma with BRAF V600 variants confirmed through a companion diagnostic test. The combination of dabrafenib and trametinib was approved for treatment of metastatic NSCLC in 2017 for patients with confirmed BRAF V600 variants.

For the treatment of KRAS-mutated NSCLC, EGFR TKIs and anti-EGFR monoclonal antibodies have been investigated as treatment options. Anti-EGFR monoclonal antibodies include cetuximab and panitumumab. Cetuximab may be used in combination with chemotherapy in patients with advanced or recurrent NSCLC as first-line and maintenance therapy. Panitumumab is not used in NSCLC.

Targeted therapies currently under investigation and not FDA-approved for the remaining genetic alterations in NSCLC are trastuzumab and afatinib for HER2 variants, crizotinib for MET amplification, and cabozantinib for RET rearrangements.

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, two domains are examined: the relevance, and 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 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, 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; MET amplification, or NTRK gene fusions improve outcomes in individuals with advanced-stage NSCLC who are being considered for targeted therapy?

The following PICO was used to select literature to inform this review.

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

**Interventions**
The intervention of interest is testing for somatic genome alterations known as "driver mutations," specifically EGFR, BRAF, KRAS, HER2 variants; ALK, ROS, or RET rearrangements; MET amplification, or NTRK gene fusions.

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.

**Comparators**
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 QOL 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.

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

**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 long-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, NTRK) 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 TKI experience disease progression. The most common of these secondary variants, called resistance variants, involves the substitution of methionine for threonine at position 790 (T790M) on exon 20.

**EGFR Variant Frequency**

Fang et al (2013) reported EGFR variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (SCC). In a separate cohort of 63 Chinese patients with SCC who received erlotinib or gefitinib as second- or third-line treatment (63% never-smokers, 21% women), EGFR variant prevalence (all exon 19 deletion or L858R) was 23.8%.

In a comprehensive analysis of 14 studies involving 2880 patients, Mitsudomi et al (2006) reported EGFR variants in 10% of men, 7% of non-Asian patients, 7% of current or former smokers, and 2% of patients with nonadenocarcinoma histologies. Eberhard et al (2005) observed EGFR variants in 6.4% of patients with SCC and Rosell et al (2009) observed EGFR variants in 11.5% of patients with large cell carcinomas. Both studies had small sample sizes.

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

U.S. Food and Drug Administration Approved Companion Diagnostic Tests for EGFR Variants

EGFR-sensitizing and -resistance variants can be detected by direct sequencing, polymerase chain reaction (PCR) technologies, or next-generation sequencing (NGS). Gene sequencing is considered an analytic criterion standard. A report by the Canadian Agency for Drugs and Technologies in Health, conducted by Mujoomdar et al (2010) analyzed EGFR variants. Based on 11 observational studies, the report authors concluded that PCR-based approaches identify EGFR variants with a sensitivity equivalent to that of direct sequencing.

Several tests have been approved as companion diagnostics to detect EGFR-resistance variants (exon 19 deletions or exon 21 L858R substitutions) for at least 1 of the EGFR TKIs (afatinib, erlotinib, gefitinib, or osimertinib): the therascreen EGFR Rotor-Gene Q polymerase chain reaction (RGQ PCR) kit, cobas EGFR Mutation Test v1 and v2, Oncomine Dx Target Test, and FoundationOne CDx (see Table 1). The cobas v2 test is also approved as a companion diagnostic to detect the T790M resistance variant to select patients for treatment with osimertinib.

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

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

The clinical validity of the Oncomine Dx Target Test was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT, which included newly diagnosed patients with stage IIIb or IV or recurrent NSCLC, in which the EGFR variant for enrollment was determined using therascreen. The PPA of Oncomine vs therascreen for detection of EGFR-sensitizing variants was 99% (95% CI, 93% to 100%) and NPA was 99% (95% CI, 96% to 100%). No data on the effectiveness of gefitinib in patients identified as EGFR-positive by Oncomine were reported.

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

**Tyrosine Kinase Inhibitors**

**Combined Analyses**

A meta-analysis by Lee et al (2013), which evaluated 23 trials of erlotinib, gefitinib, and afatinib in patients with advanced NSCLC, reported improved progression-free survival (PFS) in EGFR variant-positive patients treated with EGFR TKIs in the first- and second-line settings and for maintenance therapy. Comparators were with chemotherapy, chemotherapy and placebo, and placebo in the first-line, second-line, and maintenance therapy settings, respectively. Among EGFR variant-negative patients, PFS was improved using EGFR TKIs compared with placebo maintenance but not in the first- and second-line settings. Overall survival (OS) did not differ between treatment groups in either variant-positive or variant-negative patients. Statistical heterogeneity was not reported for any outcome.

A TEC Assessment (2007) evaluated EGFR variants and TKI therapy in advanced NSCLC. It concluded that there was insufficient evidence to permit conclusions about the clinical validity or utility of EGFR variant testing to predict erlotinib sensitivity or to guide treatment in patients with NSCLC. An updated Assessment (2010), with revised conclusions, indicated that EGFR variant testing has clinical utility in selecting or deselecting patients for treatment with erlotinib.

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

**Erlotinib**

**Systematic Reviews**

Petrelli et al (2012) reported a meta-analysis (13 randomized trials) of 1260 patients with EGFR-mutated NSCLC who received TKIs for first-line, second-line, or maintenance therapy. The comparator was standard therapy. Overall, reviewers noted that the use of EGFR TKIs increased the chance of obtaining an objective response almost 2-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 3 and 4. 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 3. Characteristics of RCTs of First-Line Erlotinib vs Chemotherapy in EGFR-Variant NSCLC**

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

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

**Table 4. Results of RCTs of First-Line Erlotinib vs Chemotherapy in EGFR-Variant NSCLC**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>Adverse Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENSURE (2015)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>217</td>
<td>217</td>
<td>214</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>11.0</td>
<td>26.3</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Neutropenia</td>
<td>35.5</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>(0.22 to 0.51)</td>
<td>(0.63 to 1.31)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5.5</td>
<td>25.5</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>Neutropenia</td>
<td>57.7</td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td><strong>EURTAC (2012)†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>9.7 (8.4 to 12.3)</td>
<td>19.3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased AT concentrations</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Many additional publications have provided data on EGFR variants in tumor samples obtained from NSCLC patients treated with erlotinib. Nine of these \cite{31,32,33,34,35,36,37,38,39} were nonconcurrent prospective studies of treatment-naive and previously treated patients who received erlotinib and were then tested for the presence or absence of variants. Four others were prospective, single-arm enrichment studies of variant-positive or wild-type patients treated with erlotinib. In 3 studies of EGFR variant-positive patients, the objective radiologic response was 40% to 70%, the median PFS was 8 to 14 months, and the median OS was 16 to 29 months. \cite{10,39,40} In patients with wild-type tumors, the objective radiologic response was 3.3%, PFS was 2.1 months, and OS was 9.2 months. \cite{41}

**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. \cite{42} The literature search was conducted in February 2017 and identified 35 RCTs (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 5 and 6 have compared gefitinib with chemotherapy in the first-line setting. \cite{43,44,45} 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. \cite{44} 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). \cite{46} 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 5. Characteristics of RCTs of First-Line Gefitinib vs Chemotherapy in EGFR-Variant NSCLC

<table>
<thead>
<tr>
<th>Study/Trial</th>
<th>Countries</th>
<th>Sites/Pts</th>
<th>Dates</th>
<th>Participants</th>
<th>Description of Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han et al (2017)</td>
<td>China</td>
<td>1</td>
<td>2011-2015</td>
<td>121 patients with advanced lung adenocarcinoma</td>
<td>Gefitinib 41 assigned to gefitinib (250 mg/d) Chemo 40 assigned to pemetrexed (500 mg/m²) and carboplatin (AUC5) Gefitinib plus Chemo 40 assigned to pemetrexed (500 mg/m²) and carboplatin (AUC5) and gefitinib (250 mg/d)</td>
</tr>
<tr>
<td>Mok (2009) IPASS (NCT00322452)</td>
<td>9 East Asian countries</td>
<td>87</td>
<td>2006-2007</td>
<td>1217 patients with stage III/IV NSCLC (261 EGFR-positive)</td>
<td>Gefitinib 609 assigned to gefitinib (250 mg/d) Chemo 608 assigned to paclitaxel (200 mg/m²) and carboplatin (AUC5 or AUC6)</td>
</tr>
<tr>
<td>Mitsudomi (2010) WJTOG3405</td>
<td>Japan</td>
<td>36</td>
<td>2006-2009</td>
<td>177 patients with stage III/IV or recurrent NSCLC</td>
<td>Gefitinib 88 assigned to gefitinib (250 mg/d) Chemo 89 assigned to cisplatin (80 mg/m²) and docetaxel (60 mg/m²)</td>
</tr>
<tr>
<td>Maemondo (2010), Inoue (2013) NEJ002</td>
<td>Japan</td>
<td>43</td>
<td>2006-2009</td>
<td>230 patients with stage III/IV NSCLC or postoperative relapse</td>
<td>Gefitinib 115 assigned to gefitinib (250 mg/d) Chemo 115 assigned to paclitaxel (200 mg/m²) and carboplatin (AUC6)</td>
</tr>
</tbody>
</table>

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

### Table 6. Results of RCTs of First-Line Gefitinib vs Chemotherapy in EGFR-Variant NSCLC

<table>
<thead>
<tr>
<th>Study/Trial</th>
<th>Median PFS, mo</th>
<th>Median OS, mo</th>
<th>Adverse Events, %</th>
<th>Serious TE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han et al (2017)</td>
<td>5.7 (5.2 to 6.3)</td>
<td>25.8 (21.3 to 30.2)</td>
<td>Liver dysfunction</td>
<td>Combination vs chemotherapy: 0.2 (0.1 to 0.3) Combination vs gefitinib: 0.5 (0.2 to 0.8) Gefitinib vs chemotherapy: 0.3 (0.2 to 0.6)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
<td>Skin rash</td>
<td>Combination vs chemotherapy: 0.4 (0.2 to 0.7) Gefitinib vs chemotherapy: 1.0 (0.6 to 1.8)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>11.9 (9.1 to 14.6)</td>
<td>24.3 (17.7 to 30.1)</td>
<td>Neutropenia</td>
<td>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)</td>
</tr>
<tr>
<td>Gefitinib plus chemotherapy</td>
<td>17.5 (15.3 to 19.7)</td>
<td>32.6 (25.5 to 39.8)</td>
<td>Liver dysfunction</td>
<td>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)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td>Skin rash</td>
<td>Combination vs chemotherapy: 0.4 (0.2 to 0.7) Gefitinib vs chemotherapy: 1.0 (0.6 to 1.8)</td>
</tr>
</tbody>
</table>

WJTOG3405 (2010): 172, 172, NR, 172
### Gefitinib

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>0.30 (0.22 to 0.41)</td>
</tr>
<tr>
<td></td>
<td>0.89 (0.63 to 1.24)</td>
</tr>
</tbody>
</table>

### Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.49 (0.34 to 0.71)</td>
</tr>
<tr>
<td></td>
<td>1.25 (0.88 to 1.78)</td>
</tr>
</tbody>
</table>

### NEJ 002 (2010, 2013)\(^\text{a}\)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>NR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>224</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.8</td>
<td>27.7</td>
<td></td>
</tr>
</tbody>
</table>

### Chemotherapy

|                    | 5.4 | 26.6|                  |

### HR (95% CI)

|                    | 0.30 (0.22 to 0.41) | 0.89 (0.63 to 1.24) |

### IPASS (2009)\(^\text{b}\)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>NR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>259</td>
<td>1196</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Chemotherapy

|                    | PG| 15.6%|                  |

### 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.

\(^\text{a}\) Analysis includes EGFR-positive only.

\(^\text{b}\) Analysis includes all patients with safety data.

\(^\text{c}\) Estimated from the 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 a RCT including 345 patients with stage IIIb or IV, EGFR variant-positive, lung adenocarcinoma who were previously untreated for advanced disease.\(^\text{a}\) 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 a 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/QOL than those in the chemotherapy group.44 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.45 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.46 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.51 Patients had been treated with chemotherapy but not with EGFR-targeted therapy; approximately half of the patients (enrolled after a protocol amendment) were chemotherapy-naive. Objective responses (primarily partial responses) were observed in 66% of 106 patients with common EGFR variants (exon 19 deletion or L858R) and in 39% of 23 patients with other EGFR variants. The median PFS was 13.7 months in patients with common EGFR variants and 3.7 months in patients with other EGFR variants (p not reported). Results for variant-negative patients were not reported. 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).52 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.53 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.54 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.55

The osimertinib label describes the 2 studies.56 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 7 and 8. Osimertinib was associated with clinically and statistically significantly prolonged PFS and higher response rates than chemotherapy and had lower rates of grade 3 and 4 adverse events. However, interstitial lung disease-like adverse events and QT prolongation were more common with osimertinib. Another RCT described in Tables 6 and 7 compared osimertinib with other EGFR TKIs (gefitinib or erlotinib) as first-line therapy. The results suggested a reduced risk for central nervous system progression with osimertinib compared with other TKIs.

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

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reungwetwattana et al (2018)fl; FLAURA (NCT02296125)</td>
<td>31 countries in North America, Europe, Australia, Asia</td>
<td>168</td>
<td>2014-2017</td>
<td>128 (of 556) patients with untreated advanced EGFR-positive NSCLC with available brain scans at baseline</td>
<td>Osimertinib 61 assigned to osimertinib (80 mg/d)</td>
</tr>
<tr>
<td>Mok et al (2017)fl; AURA3 (NCT02151981)</td>
<td>18 countries in North America, Europe, Australia, Asia</td>
<td>126</td>
<td>2014-2015</td>
<td>419 patients with T790M-positive advanced NSCLC who had disease progression after first-line EGFR-TKI therapy</td>
<td>Osimertinib 279 assigned to osimertinib (80 mg/d)</td>
</tr>
</tbody>
</table>

### Table 8. Osimertinib Randomized Controlled Trial Results in EGFR-Variant NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS, mo</th>
<th>OS, mo</th>
<th>ORR (95% CI)</th>
<th>Adverse Events, %</th>
<th>Prolongation of QT Interval, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AURA3 (2017)fl</td>
<td>67</td>
<td>NR</td>
<td>71% (65 to 76)</td>
<td>31% (24 to 40)</td>
<td>31%</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>16.5 (to NC)</td>
<td>87 (to 94)</td>
<td>77 (62 to 86)</td>
<td>58 (40 to 72)</td>
<td>66 (52 to 77)</td>
</tr>
<tr>
<td>Platinum pemetrexed TE (95% CI)</td>
<td>4.4</td>
<td>NR</td>
<td>31% (24 to 40)</td>
<td>47</td>
<td>1</td>
</tr>
<tr>
<td>FlAURA (2018)fl</td>
<td>Median, mo</td>
<td>6-Mo (95% CI), %</td>
<td>12-Mo (95% CI), %</td>
<td>18-Mo (95% CI), %</td>
<td>ORR (95% CI), %</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>13.9 (8.3 to NC)</td>
<td>87 (to 94)</td>
<td>77 (62 to 86)</td>
<td>58 (40 to 72)</td>
<td>66 (52 to 77)</td>
</tr>
<tr>
<td>Other TKIsa</td>
<td>13.9 (8.3 to NC)</td>
<td>71 (57 to 81)</td>
<td>56 (42 to 68)</td>
<td>40 (25 to 55)</td>
<td>43 (31 to 56)</td>
</tr>
</tbody>
</table>

AUC5: area under the concentration-time curve of 5.0 mg/mL/min; BSA: body surface area; EGFR: epidermal growth factor receptor; NSCLC: non-small-cell lung cancer; TKI: tyrosine kinase inhibitor.
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 9.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Dates</th>
<th>Design (No. of Studies)</th>
<th>No. of Patients</th>
<th>Line of Treatment</th>
<th>Treatments Compared</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al (2018)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Nov 2017</td>
<td>RCT (11)</td>
<td>3145</td>
<td>First-line</td>
<td>Chemotherapy, afatinib, dacomitinib, erlotinib, gefitinib, osimertinib</td>
<td>· PFS: TKIs more effective than chemotherapy · Osimertinib, dacomitinib, and afatinib ranked highest probability of benefit among TKIs · Subgroup analyses comparing osimertinib with standard of care showed improvements in men, non-Asian, smokers, and those with del19 variants · Toxicity profiles similar for TKIs</td>
</tr>
<tr>
<td>Zhang et al (2018)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Oct 2017</td>
<td>RCT (40)</td>
<td>9376</td>
<td>First-, second-, and third-line</td>
<td>Erlotinib, gefitinib</td>
<td>· PFS: erlotinib and gefitinib comparable · Grade 3-5 adverse events more frequent with erlotinib</td>
</tr>
<tr>
<td>De Mello et al (2018)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Aug 2016</td>
<td>RCT (9)</td>
<td>3179</td>
<td>First-line</td>
<td>Chemotherapy, afatinib, erlotinib, gefitinib</td>
<td>· PFS: afatinib, erlotinib, and gefitinib more effective than chemotherapy · OS: afatinib, erlotinib, and gefitinib comparable to chemotherapy</td>
</tr>
<tr>
<td>Crequit et al (2017)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Jun 2017</td>
<td>RCT (102)</td>
<td>36,058</td>
<td>Second-line</td>
<td>61 treatments (combinations of immunotherapy, chemotherapy, and afatinib, cabozantinib, erlotinib, gefitinib)</td>
<td>· OS: immunotherapy or pemetrexed plus erlotinib most effective · PFS: erlotinib plus cabozantinib most effective · Evidence for safety was insufficient</td>
</tr>
<tr>
<td>Wu et al (2017)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Jan 2017</td>
<td>RCT (12)</td>
<td>3341</td>
<td>Second- and third-line</td>
<td>Chemotherapy, PD-1/PD-L1 antibodies, erlotinib, gefitinib</td>
<td>· OS and PFS: PD-1/PD-L1 more effective than chemotherapy and</td>
</tr>
</tbody>
</table>
Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Cohort</th>
<th>Sample Size</th>
<th>Treatment Group</th>
<th>OS and PFS</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al (2017)</td>
<td>Dec 2016</td>
<td>Cohort (82) RCT (8)</td>
<td>17,621</td>
<td>Afatinib, erlotinib, gefitinib</td>
<td>chemotherapy more effective than erlotinib and gefitinib</td>
<td>OS and PFS: gefitinib and erlotinib comparable regardless of line</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Afatinib more effective than gefitinib and erlotinib as second-line treatment in advanced squamous NSCLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3-4 adverse events comparable with afatinib and erlotinib; gefitinib adverse events lower</td>
</tr>
<tr>
<td>Zhang et al (2017)</td>
<td>Mar 2016</td>
<td>RCT (6)</td>
<td>1055</td>
<td>Afatinib, dacomitinib, erlotinib, gefitinib, icotinib</td>
<td>therapeutic efficacy comparable among all 5 TKIs</td>
<td>Rank probabilities showed dacomitinib and afatinib had potentially better efficacy than erlotinib, gefitinib, and icotinib</td>
</tr>
</tbody>
</table>

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

**Randomized Controlled Trials**

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

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

LUX-7 was a phase 2b, head-to-head trial of afatinib vs gefitinib for the treatment of first-line EGFR variant-positive (del19 and L858R) adenocarcinoma of the lung. LUX-7 randomized 319 patients in a 1:1 ratio to afatinib 40 mg/d or gefitinib 250 mg/d, stratified by variant type (del19 and L858R) and brain metastases (present vs absent). In the overall population, PFS was significantly improved with afatinib than with gefitinib (HR=0.73; 95% CI, 0.57 to 0.95; p=0.02). Time-to-treatment failure also showed improvement in favor of afatinib (HR=0.73; 95% CI, 0.58 to 0.92; p=0.01). The ORR was significantly higher in the afatinib group (70% vs 56%; p=0.01). Several grade 3 or 4 adverse events were more common with afatinib than with gefitinib including diarrhea (13% vs 1%) and rash (9% vs 3%); liver enzyme elevations were more common with gefitinib (0% vs 9%). Serious events occurred in 11% of patients in the afatinib group and 4% in the gefitinib group.
Section Summary: EGFR Gene Variants
Several RCTs, nonconcurrent prospective studies, single-arm enrichment studies, and meta-analyses of RCTs have demonstrated that patients with EGFR-sensitivity variants benefit from erlotinib, gefitinib, or afatinib therapy and patients with EGFR-resistance variant (T790M) benefit from osimertinib. Patient populations in these studies primarily had adenocarcinoma. Currently, there is little evidence to indicate that EGFR variant testing can guide treatment selection in patients with squamous cell histology. The 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.\(^70\).

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 the FDA as companion diagnostics to detect ALK rearrangements for treatment with crizotinib: the Vysis ALK Break Apart FISH Probe Kit and Ventana ALK (D5F3) CDx Assay.

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

The Ventana assay is an immunohistochemical-based assay. The clinical validity of the Ventana ALK (D5F3) CDx Assay was demonstrated in a retrospective analysis of patients screened for an open-label RCT of crizotinib vs platinum-doublet chemotherapy in patients with stage IIIb or IV NSCLC. The concordance between the Ventana and Vysis tests were calculated using patient samples analyzed at an independent, central laboratory. The PPA was 86.0% (95% CI, 80.2% to 90.4%) and the NPA was 96.3% (99% CI, 94.7% to 97.4%). Overall, in 343 patients who were ALK-positive by the Vysis assay, crizotinib was associated with longer PFS compared with chemotherapy (HR=0.45; 95% CI, 0.36 to 0.60). In the subset of 141 patients who were also ALK-positive by the Ventana assay, the results were similar (HR=0.40; 95% CI, 0.25 to 0.64). In the 25 patients who were ALK-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 the FDA was based on phase 1 and 2 trials in which crizotinib showed marked antitumor activity in patients with ALK-positive advanced NSCLC, with an ORR of 60% and PFS range from 7 to 10 months.\(^71\). 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 one 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 endpoint was PFS. Patients in the chemotherapy group who experienced progressive disease were allowed to crossover 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 QOL with crizotinib than with chemotherapy.

A phase 3, open-label trial compared crizotinib and chemotherapy in 343 previously untreated patients with ALK-positive advanced nonsquamous NSCLC. Patients were randomized to oral crizotinib twice daily or pemetrexed plus cisplatin or carboplatin every 3 weeks for up to 6 cycles. If there was disease progression for patients receiving chemotherapy, crossover to crizotinib was allowed. PFS was the primary endpoint. 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 QOL.

**Other ALK Inhibitors**

Ceritinib has demonstrated superior efficacy concerning PFS when compared with chemotherapy in both the first-line and second-line (following crizotinib) settings in the ASCEND-4 and ASCEND-5 RCTs. Alectinib was associated with response rates of approximately 50% in patients who had progressed on crizotinib in 2, phase 2 studies. Alectinib has also shown superior efficacy and lower toxicity when compared with crizotinib in the first-line setting in the ALEX and J-ALEX phase 3 RCTs.

Brigatinib has shown promise in early phase 1 and 2 studies with PFS of almost 13 months in patients with the crizotinib-refractory disease. The 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.

**Section Summary: ALK Gene Rearrangements**

Crizotinib was granted accelerated approval by the 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 QOL in patients with crizotinib vs chemotherapy, in both previously untreated and untreated ALK-positive advanced NSCLC. The FDA has approved 2 companion diagnostics for detecting ALK gene rearrangements to aid in selecting NSCLC patients for treatment with crizotinib.
**BRAF Gene Variants**

**FDA-Approved Companion Diagnostic Tests for BRAF Variants**

BRAF variants are detected by PCR sequencing or NGS methods. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect BRAF V600E variants to aid in selecting NSCLC patients for treatment with combination dabrafenib (Tafinlar) and trametinib (Mekinist) therapy. The Oncomine test is an NGS oncology panel that detects, among other variants, BRAF V600E variants from DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples. The detection of BRAF V600E variants by the test was evaluated by retrospective analyses of a phase 2, multicenter, nonrandomized study that included patients with a BRAF V600E variant who had progressed on prior treatment or were treatment-naive who were treated with dabrafenib in combination with trametinib in the study. Patients were screened for a BRAF V600E variant based on local lab tests used at each enrollment site. No FDA-approved test was available for detection of BRAF V600E variants in FFPE NSCLC specimens so a validated PCR assay (BRAF V600 PCR Mutation Test) was used to estimate concordance.

The concordance between the Oncomine test and the BRAF V600 PCR Mutation Test was 100% for PPA (95% CI, 95% to 100%) and 100% for NPA (95% CI, 97% to 100%). The response rate in the 57 previously treated patients in the study who were BRAF-positive by local lab test was 67% (95% CI, 53% to 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-naive patients who were BRAF-positive by local lab test was 61% (95% CI, 44% to 77%) compared with 61% (95% CI, 39% to 80%) in the 23 patients who were also BRAF-positive by Oncomine.

In June 2017, the FDA approved an additional indication for use of dabrafenib and trametinib combination therapy in patients with NSCLC with the 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 in 3 cohorts: cohorts A and B had received at least one previous platinum-based chemotherapy regimen with demonstrated disease progression but no more than 3 prior systemic regimens; cohort C could not have received prior systemic therapy for metastatic disease.\(^8^1, ^8^2\) Trial results for cohorts A,\(^8^3\) B,\(^8^4\) and C\(^8^5\) were reported by Planchard et al (2016, 2017) and are shown in Tables 10 and 11. Cohort A (n=78) received dabrafenib; cohorts B (n=57) and C (n=36) received dabrafenib and trametinib combination therapy.

The characteristics and results of key nonrandomized trials of BRAF or MEK inhibitors in NSCLC are described in Tables 9 and 10. In summary, the response rate for dabrafenib monotherapy in 78 patients who had progressed on chemotherapy was 33% at 11 months median follow-up while the response rate for 19 patients (17 of whom had progressed on chemotherapy) treated with vemurafenib monotherapy was 42% at 8 weeks. Response rates for dabrafenib and trametinib combination therapy were higher than 60% in patients who had progressed on prior treatment and those who were treatment-naive. Toxicities were similar to those seen in melanoma patients taking BRAF or MEK inhibitors. SCCs and other dermatological side effects were reported.

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Median FU, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planchard et al (2017)(^8^5) NCT01336634</td>
<td>Single-arm, open-label phase 2 trial</td>
<td>9 countries in North America, Europe, Asia</td>
<td>2014-2015</td>
<td>Adults, stage IV, BRAF V600E variant, previously untreated</td>
<td>Dabrafenib (150 mg bid) plus trametinib (2 mg/d)</td>
<td>15.9</td>
</tr>
<tr>
<td>Study</td>
<td>Response (95% CI), %</td>
<td>PFS (95% CI), mo</td>
<td>Overall Survival (95% CI)</td>
<td>Adverse Events, %</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3 or 4 %</td>
<td>Serious %</td>
<td></td>
</tr>
<tr>
<td>Planchard et al (2016) NCT01336634</td>
<td>Single-arm, open-label phase 2 trial</td>
<td>9 countries in North America, Europe, Asia</td>
<td>2011-2014</td>
<td>Adults, stage IV, BRAF V600E variant, progression after chemotherapy</td>
<td>Dabrafenib (150 mg bid)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64 (46 to 79)</td>
<td>10.9 (7.0 to 16.6)c</td>
<td>At data cutoff: 24.6 mo</td>
<td>At 2-y: 51% (33% to 67%)</td>
<td>· Overall · Pyrexia · Hypertension</td>
<td></td>
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<tr>
<td></td>
<td>11.6</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hyman et al (2015) NCT01524978</td>
<td>Single-arm, open-label phase 2 trial</td>
<td>Germany, Spain, U.K., U.S., France</td>
<td>2012-2014</td>
<td>BRAF V600 variant-positive nonmelanoma cancers including NSCLC</td>
<td>Vemurafenib (960 mg bid)</td>
<td></td>
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<tr>
<td></td>
<td>33 (23 to 45)a</td>
<td>5.5 (3.4 to 7.3)</td>
<td>Median, 12.7 mo</td>
<td>· Overall · Cutaneous SCC · Asthenia · BCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=78</td>
<td>N=78</td>
<td>N=78</td>
<td>N=78</td>
<td>N=78</td>
<td></td>
</tr>
<tr>
<td></td>
<td>63 (49 to 76)</td>
<td>9.7 (6.9 to 19.6)</td>
<td>At 6 mo, 82%</td>
<td>· Overall · Neutropenia · Hyponatremia</td>
<td>· Overall · Pyrexia · Anemia · Cutaneous SCC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=57</td>
<td>N=57</td>
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</tr>
<tr>
<td></td>
<td>42 (20 to 67)</td>
<td>Median, 7.3 (3.5 to 10.8)</td>
<td>At 12 mo, 66% (36% to 85%)</td>
<td>· Overall · Rash · Fatigue · Arthralgia</td>
<td>· Overall · 73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=19</td>
<td>N=20</td>
<td>N=20</td>
<td>N=95b</td>
<td>N=95b</td>
<td></td>
</tr>
</tbody>
</table>

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 U.S. 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 response to vemurafenib in patients with NSCLC and a BRAF variant.87,86.

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**Section Summary: **BRAF Gene Variants

The 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. The FDA expanded the indication for dabrafenib and trametinib to include the treatment of NSCLC patients whose tumors have a BRAF V600E variant based on a multicenter, single-arm study that included a cohort of 57 patients who had progressed on prior therapy and a cohort of 36 treatment-naive patients. Dabrafenib and trametinib combination therapy were effective in patients with a BRAF V600E variant, with a response rate of about 60% in both cohorts. Lower response rates were reported in other nonrandomized studies of BRAF inhibitor monotherapy in patients who had previously progressed on prior treatments.

**ROS1 Gene Rearrangements**

**FDA-Approved Companion Diagnostic Tests for ROS1 Rearrangements**

Several methods are available to detect ROS1 translocations including FISH, 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. 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, the FDA expanded the indication for crizotinib to include the treatment of patients whose metastatic NSCLC tumors have a ROS1 rearrangement. The approval was based on a 2014 multicenter, single-arm study that enrolled 50 patients with advanced NSCLC who tested positive for ROS1 rearrangement. The study 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 12 and 13. 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 12. Characteristics of Key Nonrandomized Studies of Crizotinib or Ceritinib for ROS1 Rearrangements in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim et al 2017</td>
<td>Open-label, single-arm, phase 2 study</td>
<td>Korea</td>
<td>2013-2016</td>
<td>Adults with ROS1 rearrangement who had progressed on prior therapy, 94% crizotinib-naive</td>
<td>Ceritinib (750 mg/d)</td>
<td>14.0</td>
</tr>
<tr>
<td>Mazieres et al 2015</td>
<td>Retrospective</td>
<td>6 European countries</td>
<td>NR</td>
<td>ROS1 rearrangement, 97% had received previous chemotherapy</td>
<td>Crizotinib (250 mg bid)</td>
<td>NR</td>
</tr>
<tr>
<td>Shaw et al 2014</td>
<td>Open-label, single-arm, expansion cohort of phase 1 study</td>
<td>Australia, Korea, U.S.</td>
<td>2010-2013</td>
<td>Adults with ROS1 rearrangement, 86% had received prior therapy</td>
<td>Crizotinib (250 mg bid)</td>
<td>16.4</td>
</tr>
</tbody>
</table>

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

Table 13. Results of Key Nonrandomized Studies of Crizotinib or Ceritinib for ROS1 Rearrangements in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Response (95% CI), %</th>
<th>Median PFS (95% CI), mo</th>
<th>OS (95% CI)</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3 or 4 %</td>
</tr>
<tr>
<td>Lim et al 2017</td>
<td>62 (45 to 77)</td>
<td>9.3 (0 to 22)</td>
<td>24 mo (5 to 43)</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td></td>
<td></td>
<td>N=32</td>
</tr>
<tr>
<td>Mazieres et al 2015</td>
<td>80 (NR)</td>
<td>9.1 (NR)</td>
<td>NR</td>
<td>Grade 3: 30</td>
</tr>
<tr>
<td>Shaw et al 2014</td>
<td>72 (58 to 84)</td>
<td>19.2 (14.4 to 22)</td>
<td>At 12 mo: 85% (72% to 93%)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td>N=50</td>
</tr>
</tbody>
</table>

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

Kim et al (2013) reported on clinical outcomes in 208 never-smokers with NSCLC adenocarcinoma, according to ROS1-rearrangement status. ALK rearrangements and EGFR variants were concurrently analyzed. The patients had clinical stages ranging from I to IV, but most were stage IV (41.3%). Of the 208 tumors, 3.4% (n=7) were ROS1 rearranged. ROS1 rearrangement was mutually exclusive from ALK rearrangement, but 1 of 7 ROS1-positive patients had a concurrent EGFR variant. Patients with ROS1 rearrangement had a higher ORR and longer median PFS on pemetrexed than those without a 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 (e.g., crizotinib), which is the recommended targeted therapy for patients with NSCLC and this genetic alteration.
Entrectinib
Drilon et al (2020) conducted an analysis of 53 patients with ROS-1 fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib. At median followup of 15.5 months (interquartile range 13.4 to 20.2), 41 of 53 patients had an objective response (77%; 95% CI 64% to 88%), with a median duration of response of 24.6 months (95% CI 11.4 to 34.8). In the safety-evaluable population 46 (34%) of 134 patients had grade 3 or 4 treatment-related adverse events. There were no treatment-related deaths. There is currently no FDA-approved companion diagnostic test for entrectinib.

Section Summary: ROS1 Gene Rearrangements
The 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. The 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. In an analysis of 53 patients with ROS-1 fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib, the objective response rate was 77%, with a median duration of response of 24.6 months. There is currently no FDA-approved companion diagnostic test for entrectinib.

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 = 13103 patients) of prognostic and predictive values of a KRAS variant in NSCLC. Having a KRAS variant was significantly associated with poorer OS (HR=1.6; 95% CI, 1.4 to 1.8) and DFS (HR=1.57; 95% CI, 1.2 to 2.1) in early-stage resected NSCLC, and with inferior outcomes of EGFR TKI treatment (relative risk, 0.21; 95% CI, 0.1 to 0.4) in advanced NSCLC. Having a KRAS variant was still significantly associated with poorer OS (HR=1.4; 95% CI, 1.2 to 1.6) and PFS (HR=1.4; 95% CI, 1.1 to 1.6) of EGFR TKIs when patients with EGFR variants were excluded.

Mao et al (2010) performed a meta-analysis of 22 studies in 1470 patients with NSCLC (1335 [91%] evaluable for response), 231 (17%) of whom had KRAS variants. Studies were heterogeneous in patient populations (smoking history, tumor histology, stage, ethnicity, treatment received) and response criteria. The primary endpoint was ORR, defined as the sum of complete and partial response. ORRs for patients with KRAS and wild-type KRAS variants were 3% and 26%, respectively. Incomplete reporting of survival data precluded meaningful assessment of the effect of KRAS status on survival in NSCLC patients treated with EGFR TKIs. Data for PFS and OS stratified by KRAS status were available in 8 studies. The median PFS in KRAS-mutated and wild-type patients was 3.0 months and 3.9 months, respectively. The median OS in KRAS-mutated and
wild-type patients was 4.7 months and 10.7 months, respectively. However, only 2 studies presented HRs with 95% CIs for PFS and OS and, therefore, a pooled analysis to derive an overall HR was not performed.

Linardou et al (2008) performed a meta-analysis of 17 studies with 1008 patients, 165 (16.4%) of whom had a KRAS variant. Eligible studies reported response (complete or partial) stratified by KRAS variant status. Primary endpoints 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 (e.g., lack of individual patient data, heterogeneity of response endpoints, treatment regimens, patient selection criteria, retrospective design of included studies). Furthermore, incomplete reporting of survival data precluded meaningful assessment of the effect of the KRAS variant on survival.

Retrospective Studies

Papadimitrakopoulou et al (2016) reported on the results of the A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer (BATTLE-2) phase 2 study. The BATTLE-2 program is an umbrella study evaluating the effects of targeted therapies focusing on KRAS-mutated cancers. Two hundred patients with advanced NSCLC tumors who did not have EGFR variants or ALK gene fusions whose cancer was refractory to more than 1 prior therapy were assigned to 1 of 4 arms using adaptive randomization: erlotinib (n=22), erlotinib plus MK-2206 (n=42), MK-2206 plus AZD6244 (n=75), or sorafenib (n=61), stratified by KRAS status. AZD6244 and MK2206 are targeted small-molecule drugs that inhibit MEK and AKT, respectively. Sorafenib is a 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 Tarceva Italian Lung Optimization trial (TAILOR) trial. TAILOR enrolled patients from 52 Italian hospitals and genotyped patients for KRAS and EGFR variant status. Wild-type EGFR patients (n=218) received first-line platinum-based chemotherapy and then were randomized at progression to erlotinib or docetaxel. KRAS variants were present in 23% of randomized patients. The presence of a KRAS variant was not associated with PFS (HR=1.01; 95% CI, 0.71 to 1.41; p=0.98) or OS (HR=1.24; 95% CI, 0.87 to 1.77; p=0.23). The treatment effect did not differ by KRAS status (test for interaction: OS p=0.97; PFS p=0.42).

In a phase 2 trial, Miller et al (2008) assessed response to erlotinib in 101 patients with lung bronchioloalveolar carcinoma (n=12) or adenocarcinoma, bronchioloalveolar subtype (n=89), according to KRAS variant status. Eighteen (18%) patients had KRAS-mutated tumors, and none responded to erlotinib (95% CI, 0% to 19%; p<0.01). In patients without a KRAS variant, the response rate was 32%. The median OS in patients with KRAS-mutated tumor was 13 months and 21 months in patients with KRAS wild-type tumor (p=0.30).

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

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

Pao et al (2005) were the first to suggest that patients with KRAS-mutated lung tumors were nonresponsive to treatment with EGFR TKIs. Thirty-six patients with bronchioloalveolar carcinoma underwent KRAS variant analysis; 9 (25%) were found to harbor KRAS variants. The response was by a single radiologist, blinded to patient outcome, using RECIST criteria. None of 9 patients with KRAS-mutated tumors responded to erlotinib (p=0.553).

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

Observational Studies

Fiala et al (2013) retrospectively analyzed patients with NSCLC who underwent EGFR, KRAS, and PIK3CA (phosphatidylinositol-3-kinase catalytic subunit-alpha) variant testing. Of 215 patients tested, 16 (7.4%) had a KRAS variant. Of 174 patients treated with an EGFR TKI (erlotinib or gefitinib), median PFS in 14 KRAS-mutated patients was 1.3 months vs 2.0 months in KRAS wild-type patients (n=160 [92%]); the difference was not statistically significant (p=0.120). Median OS in this treated group was 5.7 months in KRAS-mutated patients and 8.2 months in KRAS wild-type patients, a statistically significant difference (p=0.039). The authors concluded that KRAS variant status might have a negative prognostic role but a predictive role was not confirmed.

Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single-institution in China. Patients with KRAS variants were randomized by the tumor, node, metastasis stage, time of the first visit within 1 year, and histology, to both EGFR variant-positive and KRAS/EGFR wild-type patients. Seventy (4%) patients received EGFR TKI therapy. In this group, median PFS was 11.8 months and 2.0 months in patients with EGFR and KRAS variants,
respectively, and 1.9 months in wild-type patients; compared with wild-type patients, PFS was statistically longer in patients with EGFR variants (p<0.001) but no different in patients with KRAS variants (p=0.48). The authors observed that “the presence of an EGFR variant, but not a KRAS variant, was predictive of responsiveness to EGFR TKI treatment.”

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

Schneider et al (2008) reported on the relationship between clinical benefit and putative tumor markers in a subgroup of patients in a global open-label, single-arm study of erlotinib in advanced NSCLC, involving 7043 patients in 52 countries (the TRUST study). The subgroup was from German centers and comprised 311 patients with stage IIIb or IV disease who were treated using erlotinib because they had failed or were not medically suitable for standard first-line chemotherapy. Tumor response was assessed using RECIST. Seventeen (15%) patients had KRAS variants, and none responded to erlotinib; 2 patients had stable disease. The impact of KRAS variant status on OS (p=0.06) and PFS (p not reported) was of borderline statistical significance. The authors concluded that their data did not support the selection of patients for treatment with erlotinib on the basis of tumor molecular characteristics.

**Anti-EGFR Monoclonal Antibodies**

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

In the multicenter, phase 3 BMS099 trial (2010), 676 chemotherapy-naive patients with stage IIIb or IV NSCLC were assigned to taxane and carboplatin with or without cetuximab. The primary endpoint was PFS; secondary endpoints were overall response rate, OS, QOL, and safety. The addition of cetuximab did not significantly improve PFS; however, there was a statistically significant improvement in overall response rate in the cetuximab group. The trend in OS favoring cetuximab was not statistically significant. A post hoc correlative analysis was conducted to identify molecular markers for the selection of patients most likely to benefit from cetuximab. Of the original 676 enrolled patients, 202 (29.9%) had tumor samples available for KRAS testing. KRAS variants were present in 35 (17%) patients. Among patients with wild-type KRAS, OS was similar for the cetuximab-containing arm (n=85) and the chemotherapy-alone arm (n=82) (HR=0.93; 95% CI, 0.67 to 1.30; p=0.68; median survival, 9.7 months and 9.9 months, respectively). Among patients with KRAS variants, OS was similar between the cetuximab-containing arm (n=13) and the chemotherapy-alone arm (n=22) (HR=0.91; 95% CI, 0.45 to 2.07; p=0.93; median survival, 16.8 months and 10.8 months, respectively). Overall, the study showed no significant treatment-specific interactions for the presence of KRAS variants and outcomes evaluated; treatment differences favoring the addition of cetuximab in the KRAS-mutated subgroup were consistent with those observed in the wild-type KRAS subgroup and in the overall study population. The authors concluded that the results did not support an association between KRAS variant status and lack of cetuximab benefit. However, the results should be interpreted with caution due to small subgroup sample sizes and the retrospective nature of the analysis.

In the open-label, randomized, phase 3 FLEX trial (2009), 1125 chemotherapy-naive patients with stage III or IV, NSCLC were randomized to chemotherapy plus cetuximab (n=557) or chemotherapy alone (n=568). The primary endpoint was OS. Patients who received
chemotherapy plus cetuximab survived longer than those who received chemotherapy only (median OS, 11.3 months vs 10.1 months, respectively; HR for death, 0.87; 95% CI, 0.76 to 1.00; p=0.04). Subsequently, KRAS variant testing was performed on archived tumor tissue of 395 (35%) of 1125 patients. KRAS variants were detected in 75 (19%) tumors. 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 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. Trial characteristics and results are shown in Tables 14 and 15. 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 14. RCT Characteristics of MEK Inhibitors for KRAS-Variant NSCLC

<table>
<thead>
<tr>
<th>Study, Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janne et al (2017); SELECT1 (NCT01933932)</td>
<td>25 countries in North and South America, Australia, Europe</td>
<td>202</td>
<td>2013-2016</td>
<td>510 patients with advanced NSCLC and progression following first-line therapy</td>
<td>254 assigned to selumetinib (75 mg bid) plus docetaxel (75 mg/m²)</td>
</tr>
<tr>
<td>Blumenschein et al (2015); NCT01362296</td>
<td>U.S., Korea, 6 European countries</td>
<td>60</td>
<td>2011-2012</td>
<td>129 patients with stage IV NSCLC and progression following first-line platinum-containing chemotherapy</td>
<td>86 assigned to trametinib (2 mg/d) plus docetaxel (75 mg/m²)</td>
</tr>
</tbody>
</table>

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

### Table 15. RCT Results for MEK Inhibitors for KRAS-Variant NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>PFS (95% CI%), OS (95% CI%), ORR (95% CI), %</th>
<th>Adverse Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade ≥3</td>
<td>%</td>
</tr>
<tr>
<td>SELECT1 (2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>510</td>
<td>510</td>
</tr>
<tr>
<td>Selumetinib plus docetaxel</td>
<td>3.9 mo</td>
<td>8.7 mo</td>
</tr>
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<td></td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>2.8 mo</td>
<td>7.9 mo</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>
**Section Summary: KRAS Gene Variants**

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

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

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

**HER2 Gene Variants**

Mok et al (2016) reported on the biomarker subgroup analyses from the FASTACT-2 study. FASTACT-2 is a multicenter, randomized, placebo-controlled, double-blind, phase 3 study of intercalated first-line erlotinib or placebo with gemcitabine and platinum, followed by maintenance therapy with erlotinib or placebo, for Asian patients with stage IIIIB 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.

**Table**

<table>
<thead>
<tr>
<th>TE (95% CI)</th>
<th>HR=0.93 (0.77 to 1.12)</th>
<th>HR=1.05 (0.85 to 1.30)</th>
<th>OR=1.61 (1.00 to 2.62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>4</td>
<td>Neutropenia</td>
<td>4</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>N</th>
<th>129</th>
<th>129</th>
<th>129</th>
<th>130</th>
<th>130</th>
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</thead>
<tbody>
<tr>
<td>Trametinib</td>
<td>12 wk</td>
<td>8 mo</td>
<td>12</td>
<td>Overall</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rash</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
<td>5</td>
</tr>
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<td></td>
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<td></td>
<td>Asthenia</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neutropenia</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased neutrophils</td>
<td>0</td>
</tr>
</tbody>
</table>

Docetaxel

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>1.14 (0.75 to 1.75)</th>
<th>0.97 (0.52 to 1.83)</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

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.
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.111 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 an HER2 variant, and they assessed clinicopathologic characteristics and patient outcomes by variant status.112 A HER2 variant was identified in 65 (1.7%) of 3800 patients, and was mutually exclusive of other driver mutations (EGFR, ALK, BRAF), with the exception of a case in which both a 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.

**Section Summary: HER2 Gene Variants**

Studies of HER2 variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions.

**RET Gene Testing**

**FDA-Approved Companion Diagnostic Tests for RET Gene Testing**

Oncomine DxTarget is FDA approved as a companion diagnostic for pralsetinib for the treatment of metastatic RET-fusion-positive NSCLC.7

**Kinase Inhibitors**

In May 2020, FDA granted accelerated approval for selpercatinib for the treatment of adult patients with metastatic RET-fusion-positive NSCLC. Approval was based on the overall response observed in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO) in patients whose tumors had RET alterations (Tables 16 and 17).92 There is currently no FDA-approved companion diagnostic test for selpercatinib.

In September 2020, FDA approved pralsetinib for treatment of metastatic RET-fusion positive NSCLC along with the Oncomine Dx Target Test companion diagnostic. This indication was approved under the FDA’s Accelerated Approval program, based on data from the phase I/II ARROW study (Tables 16 and 17). The ARROW study is ongoing and not yet published in a peer review journal, but trial results are available in the FDA multi-discipline review of pralsetinib.113 The FDA reviewers noted that for NSCLC, overall response rates may be considered an endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable.

**Table 16. Characteristics of Key Nonrandomized Trials of Kinase Inhibitors in RET-Fusion Positive NSCLC**

<table>
<thead>
<tr>
<th>Study; Citation</th>
<th>Study Type</th>
<th>Sites, Countries</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Median FU, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIBRETTO NCT03157128 Drilon et al 202092</td>
<td>Single-arm, open-label phase 1-2 trial</td>
<td>65 centers in 12 countries</td>
<td>2017-2018</td>
<td>Patients with advanced RET fusion-positive NSCLC • 105 who had previously received platinum-based chemotherapy</td>
<td>Selpercatinib</td>
<td>12.1</td>
</tr>
</tbody>
</table>
Table 17. Results of Key Nonrandomized Trials of Kinase Inhibitors in RET-Fusion Positive NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Response (95% CI), %</th>
<th>PFS (95% CI), mo</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| LIBRETTOLIBRETTONCT03157128Drilon et al 202066 | Previously treated: 64% (54% to 73%)  
Previously untreated: 85% (70% to 94%) | 16.5 months (13.7 to NE) | Grade 3 or 4:  
- Hypertension (14%)  
- Increased ALA: (13%)  
- Hyponatrema (6%)  
- Lymphopenia (6%)  

Grade 5 (6 events in 4% of patients):  
- sepsis (n=2)  
- cardiac arrest,  
- multiple organ dysfunction syndrome,  
- pneumonia, and  
- respiratory failure (1 patient each)  |
| ARROWARROWNCT03037385FDA (2020)113 | Previously treated: 57% (46% to 68%)  
Previously untreated: 70% (50% to 86%) | 12.7 months (95% CI: 9.1 to NE) | Serious adverse reactions occurred in 45% of patients.  
Permanent discontinuation due to an adverse reaction occurred in 15% of patients.  
Grades 3-4 AEs:  
- Fatigue (2.3%),  
- constipation (1%),  
- diarrhea (3.2%),  
- hypertension (14%),  
- cough (0.5%),  
- pneumonia (8%) |

Section Summary: RET Gene Testing
The FDA has approved a companion diagnostic (Oncomine Dx Target Test) for treating metastatic RET-fusion positive NSCLC with pralsetinib under accelerate approval based on studies of effect particularly among treatment naive patients (70% [95% CI, 50%-86%]). The FDA has also approved selpercatinib for the treatment of adult patients with metastatic RET fusion-positive NSCLC based on a multicenter, open-label, multicohort clinical trial in patients whose tumors had RET alterations, with high treatment naive effect (85% [95% CI, 70%-94%]).
MET Gene Testing
FDA-Approved Companion Diagnostic Tests for MET Gene Testing
FoundationOne CDx is FDA approved as a companion diagnostic for capmatinib for the treatment of NSCLC harboring MET with an exon 14 skipping mutation.7

Capmatinib
In 2020, FDA approved the MET inhibitor capmatinib for treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping. Approval was accelerated based on overall response rate and duration of response in the GEOMETRY mono-1 trial (NCT02414139).114 Tables 18 and 19 summarize characteristics and results of this trial.

Table 18. Characteristics of Key Nonrandomized Trials of Capmatinib in MET amplifications or MET Exon 14 skipping Alteration

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEOMETRY mono-1 NCT02414139 Wolf et al 2020114</td>
<td>Multiple-cohort, phase 2 trial</td>
<td>364 patients with NSCLC</td>
<td>• 97 patients had a MET exon 14 skipping mutation&lt;br&gt;• 210 had MET amplification</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 19. Results of Key Nonrandomized Trials of Capmatinib in MET amplifications or MET exon 14 skipping alteration

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Response</th>
<th>PFS (95% CI), mo</th>
<th>Median Duration of Response</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEOMETRY mono-1 NCT02414139 Wolf et al 2020114</td>
<td>Patients with MET exon 14 skipping mutation:&lt;br&gt;• 41% (29 to 53) of 69 patients who had received 1 or 2 lines of therapy previously&lt;br&gt;• 68% (48 to 84) of 28 patients who had not received treatment previously</td>
<td>Previously treated: 4.1 months (95% CI, 2.9 to 4.8)&lt;br&gt;No previous treatment: 4.2 months (95% CI, 1.4 to 6.9)</td>
<td>9.7 months</td>
<td>Grade 3 or 4: 67% of patients. Most frequent were peripheral edema, nausea, vomiting, and increased blood creatinine level. Treatment-related adverse events leading to discontinuation of treatment occurred in 39 patients (11%)</td>
</tr>
</tbody>
</table>

Patients with MET amplification:<br>• Limited efficacy was observed in previously treated patients with MET amplification who had a gene copy number of less than 10 (overall response in 7% to 12% of patients)<br>• Among patients with MET amplification and a gene copy number of 10 or higher, overall response was observed in 29% (95% CI, 19 to 41) of
Section Summary: MET Gene Testing
The GEOMETRY Mono-1 trial showed efficacy of capmatinib in patients with advanced NSCLC with a MET exon 14 skipping mutation, especially in treatment-naive patients (68% [95% CI, 48% to 84%]). Efficacy was higher in tumors with a gene copy of 10 or higher. Median duration of response was 9.7 months.

NTRK Gene Fusions
FDA-Approved Companion Diagnostic Tests for NTRK Gene Fusions
There are currently no FDA-approved companion diagnostic tests for NTRK gene fusions.

Larotrectinib
Drilon et al (2018) evaluated the effectiveness of larotrectinib in 55 patients with consecutively and prospectively identified tropomyosin receptor kinase (TRK) fusion-positive solid tumors, including 4 patients with lung tumors. The overall response rate was 80% (95% CI, 67 to 90). The median PFS had not been reached after a median follow-up duration of 9.9 months (range, 0.7 to 25.9). Responses were observed regardless of tumor type or age of the patient. The FDA approved larotrectinib for patients with TRK fusion-positive solid tumors based on these results. An updated analysis of 153 patients from this data set was consistent with the earlier analysis.

Entrectinib
Doebele et al (2020) published an analysis of 3 phase 1-2 trials of entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumors. Of 54 patients, 10 (19%) had NSCLC. At a median follow-up of 12.9 months, 31 of 54 patients had an objective response (57% [95% CI 43.2–70.8]). Median duration of response was 10 months (95% CI 7·1 to not estimable). The most common grade 3 or 4 treatment-related adverse events in both safety populations were increased weight (7 [10%] of 68 patients in the NTRK fusion-positive safety population and in 18 [5%] of 355 patients in the overall safety-evaluable population) and anemia (8 [12%] and 16 [5%]). The most common serious treatment-related adverse events were nervous system disorders (3 [4%] of 68 patients and 10 [3%] of 355 patients). No treatment-related deaths occurred.

Section Summary: NTRK Gene Fusions
Studies of 55 patients with consecutively and prospectively identified NTRK fusion-positive solid tumors, including 4 patients with lung tumors, the overall response rate was 80% (95% CI, 67 to 90). The median PFS had not been reached after a median follow-up duration of 9.9 months (range, 0.7 to 25.9). Responses were observed regardless of tumor type or age of the patient. In an integrated analysis of 3 phase 1-2 trials in patients with NTRK solid tumors, 10 of whom had NSCLC, response was 57% (95% CI 43.2% to 70.8%) with an acceptable safety profile.

Immunotherapy for Advanced Non-Small-Cell Lung Cancer
Clinical Context and Test Purpose
The purpose of identifying PD-L1 expression and tumor mutational burden (TMB) in patients who have advanced NSCLC is to inform a decision whether patients should receive a immunotherapy vs another systemic therapy. Patients who present with advanced disease or recurrence following initial definitive treatment typically receive systemic therapy. Traditionally, systemic therapy was cytotoxic chemotherapy. Targeted treatments are ineffective in patients whose tumors lack genetic alterations such as EGFR, ALK, BRAF, and ROS1 variants (driver mutations). However, a subset of these patients may be good candidates for treatment with immunotherapy. The goal of immunotherapy 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 PD-L1 and TMB improve the net health outcome in individuals with advanced-stage NSCLC who are being considered for immunotherapy?

The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest are individuals with advanced NSCLC who are being considered for immunotherapy.

**Interventions**
The interventions of interest are testing for PD-L1 and TMB.

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.

**Comparators**
The following practice is currently being used to target therapy for advanced-stage NSCLC: standard management without testing for PD-L1 or TMB. Standard management consists primarily of chemotherapy.

**Outcomes**
Beneficial outcomes resulting from a true-positive test result are prolonged survival, reduced toxicity, and improved QOL associated with receiving a more effective and less cytotoxic targeted therapy than chemotherapy. Beneficial outcomes from a true negative result are prolonged survival associated with receiving chemotherapy in those whose tumors do not express PD-L1.

Harmful outcomes resulting from a false-negative test result include shorter survival from receiving less effective and more cytotoxic chemotherapy in those whose tumors express PD-L1; possible harmful outcomes resulting from a false-positive test result are a shorter survival from receiving potentially ineffective immunotherapy and delay in initiation of chemotherapy in those whose tumors do not express PD-L1.

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

**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 long-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.

**PD-L1 Testing**
**FDA Companion Diagnostic Tests for PD-L1**
Companion diagnostic tests have been FDA-approved for PD-L1 testing for immunotherapy with atezolizumab, pembrolizumab, and the combination of nivolumab plus ipilimumab in patients with NSCLC.
Atezolizumab
Herbst et al (2020) published results of a phase 3, open label RCT of atezolizumab compared to platinum-based chemotherapy in 572 patients with NSCLC who had not previously received chemotherapy and who had PD-L1 expression on at least 1% of tumor cells or at least 1% of tumor-infiltrating immune cells (NCT02409342). In the subgroup of patients with tumors who had the highest expression of PD-L1 (205 patients), the median overall survival was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months vs. 13.1 months; hazard ratio for death, 0.59; P = 0.01). Atezolizumab treatment resulted in significantly longer overall survival than platinum-based chemotherapy among patients with NSCLC with high PD-L1 expression, regardless of histologic type, was consistent with that observed in previous studies of atezolizumab monotherapy. Grade 3 or 4 adverse events occurred in 30.1% and 52.5% of the patients in the atezolizumab group and the chemotherapy group, respectively.

Pembrolizumab
Reck et al (2016) published results of the KEYNOTE-024 Trial (NCT02142738), which compared pembrolizumab to platinum-based chemotherapy in 305 patients with NSCLC and PD-L1 expression on at least 50% of tumor cells. At a median follow-up of 11.2 months, PFS was longer with pembrolizumab compared with chemotherapy (median PFS, 10.3 versus 6 months; HR 0.50, 95% CI 0.37-0.68). The median duration of response was not reached in the pembrolizumab group and was 6.3 months in the chemotherapy group.

Nivolumab in Combination with Ipilimumab
In the CHECKMATE 227 Trial (NCT02477826) reported in Hellmann et al (2019), among the patients with a PD-L1 expression level of 1% or more, the median duration of overall survival was 17.1 months (95% confidence interval [CI], 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (P = 0.007), with 2-year overall survival rates of 40.0% and 32.8%, respectively. The median duration of response was 23.2 months with nivolumab plus ipilimumab and 6.2 months with chemotherapy. First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.

Section Summary: PD-L1 Testing
In RCTs, patients with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.

Tumor Mutational Burden Testing
FDA-Approved Companion Diagnostic Tests
FoundationOne CDx is FDA approved as a companion diagnostic for use with pembrolizumab in patients with TMB-high (≥ 10 mutations per megabase) solid tumors.

Immunotherapy
In a subgroup analysis of the CHECKMATE 227 trial (NCT02477826), PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational burden (≥10 mutations per megabase).

In exploratory analyses, retrospective observational studies have reported an association between higher tumor mutational burden (TMB) and longer PFS and OS in patients receiving immunotherapy.

Table 20. Characteristics of RCT of Nivolumab Plus Ipilimumab in Patients with NSCLC and High Tumor Mutational Burden

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
</table>

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

Table 21. Results of RCT of Nivolumab Plus Ipilimumab in Patients with NSCLC and High Tumor Mutational Burden

<table>
<thead>
<tr>
<th>Study</th>
<th>1-year PFS</th>
<th>Median PFS (95% CI)</th>
<th>ORR (95% CI), %</th>
<th>Adverse Events, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab plus ipilimumab</td>
<td>42.6%</td>
<td>7.2 months (5.5 to 13.2)</td>
<td>45.3 (36.9 to 54.0)</td>
<td>Any event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any serious event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any event leading to discontinuation</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>5.5%</td>
<td>5.5 months (4.4 to 5.8)</td>
<td>26.9 (20.2 to 34.4)</td>
<td>Any event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any serious event</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any event leading to discontinuation</td>
</tr>
<tr>
<td>TE (95% CI)</td>
<td>HR=0.58; 97.5% CI, 0.41 to 0.81; P&lt;0.001</td>
<td>Difference 18.4 (7.6-28.8)</td>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>

NSCLC: non-small-cell lung cancer; RCT: randomized controlled trial.

**Section Summary: Tumor Mutational Burden Testing**

In a subgroup analysis of an RCT, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational burden (>10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies.

**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 tyrosine kinase inhibitors (TKIs) (e.g., afatinib, erlotinib, gefitinib, osimertinib, et al) with chemotherapy. Relevant outcomes are overall survival (OS), disease-specific survival, test validity, quality of life (QOL), and treatment-related morbidity. Studies have shown that TKIs are superior to chemotherapy regarding tumor response rate and progression-
free survival (PFS), with a reduction in toxicity and improvement in QOL. 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 OS, disease-specific survival, test validity, QOL, 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. In an analysis of 53 patients with ROS-1 fusion-positive NSCLC enrolled in 3 ongoing clinical trials of entrectinib, the objective response rate was 77%, with a median duration of response of 24.6 months and acceptable toxicity. 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 RET or MET gene testing, the evidence includes nonrandomized trials of kinase inhibitors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. Studies have shown efficacy in PFS and duration of response for selpercatinib and pralsetinib in patients with RET-fusion positive NSCLC, and for capmatinib in patients with MET Exon 14 skipping alterations, with acceptable toxicity. 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, the evidence includes post hoc analysis of trials, observational studies, and meta-analyses. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. 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. 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. Studies for HER2 variant testing have reported response rates and PFS in numbers of patients too small from which to draw conclusions. The evidence is insufficient 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 NTRK gene fusion testing, the evidence includes nonrandomized trials of larotrectinib and entrectinib in patients with solid tumors. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and treatment-related morbidity. In 55 patients with consecutively and prospectively identified tropomyosin receptor kinase fusion-positive solid tumors who received larotrectinib, including 4 patients with lung tumors, the overall response rate was 80% (95% CI, 67 to 90). The median PFS had not been reached after a median follow-up duration of 9.9 months (range, 0.7 to 25.9). Responses were observed regardless of tumor type or age of the patient. In an integrated analysis of 3 phase 1-2 trials in patients with NTRK solid tumors who received entrectinib, 10 of whom had NSCLC, response was 57% (95% CI 43.2% to 70.8%) with an acceptable safety profile. 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 immunotherapy who receive PD-L1 testing, the evidence includes RCTs comparing immunotherapy to chemotherapy. Relevant outcomes are OS, disease-specific survival, test validity, QOL, and
2.04.45  Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

Page 40 of 56

For individuals who have advanced-stage NSCLC who are being considered for immunotherapy who receive tumor mutational burden (TMB) testing, the evidence includes a RCT and retrospective observational studies. In a subgroup analysis of the KEYNOTE trial, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high TMB (>10 mutations per megabase). In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy. These results need to be confirmed in additional, well-designed prospective studies. Additionally, there is no consensus on how to measure TMB. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American College of Chest Physicians Guidelines**

In 2013, the American College of Chest Physicians updated its evidence-based practice guidelines on the treatment of stage IV NSCLC. 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.”

**American Society of Clinical Oncology**

In 2014, the American Society of Clinical Oncology (ASCO) reviewed and endorsed the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (2013) 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. The 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.

In 2018, the ASCO reviewed and endorsed, with minor modifications, the guidelines from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology (2018; see above). The 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). In 2017, the ASCO also updated its evidence-based recommendations on systemic therapy for patients with stage IV NSCLC. Table 17 summarizes the recommendations and associated quality and strength of evidence.

**Table 17. Recommendations on Systemic Therapy for Stage IV NSCLC**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>QOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitizing EGFR variants: afatinib, erlotinib, or gefitinib</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>ALK rearrangements: crizotinib</td>
<td>Intermediate</td>
<td>Moderate</td>
</tr>
<tr>
<td>ROS1 rearrangement: crizotinib</td>
<td>Low</td>
<td>Weak</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.04.45  Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer

| Sensitizing EGFR variants and T790M resistance variant: osimertinib | High | Strong |
| ROSE rearrangement who have not received prior crizotinib: crizotinib | Low | Moderate |
| BRAF rearrangement who have received prior immune checkpoint therapy: dabrafenib alone or in combination with trametinib | Insufficient | Moderate |


College of American Pathologists et al

In 2013, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology published evidence-based guidelines for molecular testing to select patients with lung cancer for treatment with EGFR and ALK TKI therapy. 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 (e.g., smoking history).

In 2018, updated guidelines were published and added new EGFR and ALK recommendation). BRAF, RET, HER2, KRAS, and MET testing recommendations. ROS1 testing is recommended for all patients with lung adenocarcinoma irrespective of clinical characteristics (strong 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).

National Comprehensive Cancer Network Guidelines

EGFR Testing

The NCCN guidelines (v.8.2020) for the treatment of metastatic non-small-cell lung cancer (NSCLC) recommend the following on epidermal growth factor receptor (EGFR) testing:

- EGFR mutation testing is recommended (category 1) in patients with nonsquamous NSCLC (i.e., 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), dacomitinib (category 1), gefitinib (category 1), or osimertinib (category 1, preferred) 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

The NCCN guidelines (v.8.2020) state the following on anaplastic lymphoma kinase (ALK) rearrangement testing:

- ALK-rearrangement testing is recommended (category 1) in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- If ALK-positive status is discovered before first-line chemotherapy, alectinib (category 1; preferred), brigatinib (category 1), 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 (preferred), brigatinib, crizotinib or ceritinib.
• If there is progression on first-line therapy, continue alectinib, crizotinib, or ceritinib, switch to ceritinib, alectinib, lorlatinib, or brigatinib, or consider local therapies are recommended (depending on symptoms, the location of metastases, and the 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.

**BRAF Testing**

The NCCN guidelines (v.8.2020) state the following on BRAF testing:

- BRAF testing is recommended (category 2A) in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell carcinoma) or in NSCLC not otherwise specified.
- BRAF testing may be considered in patients with SCC.
- If BRAFV600E variant-positive status is discovered, combination dabrafenib and trametinib or other first-line cytotoxic therapy options are recommended.

**ROS1 Testing**

The NCCN guidelines (v.8.2020) state the following on ROS1-rearrangement testing:

- ROS1-rearrangement testing is recommended (category 2A) in patients with nonsquamous NSCLC (i.e., 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), entrectinib (preferred) or ceritinib is recommended.

**KRAS Testing**

The NCCN guidelines (v.8.2020) state that “The presence of a KRAS mutation is prognostic of poor survival when compared to patients with tumors without KRAS mutation. Mutations in KRAS have been associated with reduced responsiveness to EGFR TKI [tyrosine kinase inhibitor] therapy. Owing to the low probability of overlapping targetable alterations, the presence of a mutation in KRAS may identify patients who will not benefit from further molecular testing.” Targeted therapy for patients with the KRAS variants is currently unavailable.

**RET Testing**

The NCCN guidelines (v.8.2020) recommend testing for RET rearrangements (category 2A) in eligible patients with metastatic NSCLC.

**MET Exon 14 Skipping Alterations**

The NCCN guidelines (v.8.2020) recommend testing for MET Exon 14 skipping mutations (category 2A) in eligible patients with metastatic NSCLC.

**NTRK Testing**

NCCN guidelines (v.8.2020) recommend NTRK gene fusion testing in patients with metastatic NSCLC. The Panel recommends larotrectinib and entrectinib (category 2A) as either first-line or subsequent therapy options for patients with NTRK gene fusion-positive metastatic NSCLC based on data and the U.S. Food and Drug Administration approvals.

**Immunotherapy and Tumor Mutational Burden**

In the NCCN guideline (v.2020), nivolumab/ipilimumab is recommended for patients with metastatic NSCLC, regardless of PD-L1 levels or histology; negative test results for EGFR, ALK, ROS1, MET Exon 14 skipping, RET, or BRAF variants, and no contraindications to immunotherapy. The guidelines state that first line therapy with nivolumab/ipilimumab is useful in certain circumstances (e.g., renal impairment) for patients with PD-L1 levels of 1% or more and is an "other recommended" first-line therapy option for patients with PD-L1 levels less than 1%.
TMB is considered to be an emerging biomarker that may be useful in selecting patients for nivolumab with or without ipilimumab; however, there is no consensus on how to measure TMB.

Other Biomarkers
The NCCN guidelines (v.8.2020) identify high-level MET amplification, ERBB2 (HER2) mutations, and tumor mutational burden as emerging biomarkers to identify novel therapies for patients with metastatic NSCLC:

Plasma Cell-Free/Circulating Tumor DNA Testing:
The NCCN guidelines (v.8.2020) support limited use of liquid biopsy.
- Plasma cell-free/circulating tumor DNA testing should not be used in lieu of a histologic tissue diagnosis.
- The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, including: in the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 18.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
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<tr>
<td>NCT01306045</td>
<td>Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies</td>
<td>469</td>
<td>Dec 2021</td>
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<tr>
<td>NCT03225664</td>
<td>BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer</td>
<td>102</td>
<td>Sep 2020</td>
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<tr>
<td>NCT02622581</td>
<td>Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)</td>
<td>7500</td>
<td>Dec 2025</td>
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<tr>
<td>NCT02117167</td>
<td>Intergroup Trial UNICANCER UC 0105-1305/ IFCT 1301: SAFIR02_Lung - Evaluation of the Efficacy of High Throughput Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Non-Small Cell Lung Cancer</td>
<td>999</td>
<td>Feb 2021</td>
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<tr>
<td>NCT02465060</td>
<td>Molecular Analysis for Therapy Choice (MATCH)</td>
<td>6452</td>
<td>Jun 2022</td>
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<tr>
<td>NCT02756431</td>
<td>A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-positive Tumors</td>
<td>203</td>
<td>May 2025</td>
</tr>
<tr>
<td>NCT02568267</td>
<td>An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements</td>
<td>300</td>
<td>Dec 2024</td>
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<tr>
<td>NCT01639508</td>
<td>A Phase II Study of Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity</td>
<td>68</td>
<td>Jul 2021</td>
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<tr>
<td>NCT03469960</td>
<td>A Randomized Phase 3 Trial Comparing Continuation Nivolumab-Ipilimumab Doublet Immunotherapy Until Progression Versus Observation in Treatment-naive Patients</td>
<td>1360</td>
<td>May 2023</td>
</tr>
</tbody>
</table>
### References


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

Page 51 of 56


Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Diagnosis and cancer stage
  - Previous treatment plan(s) and response(s)
  - Current treatment plan
  - Clinical justification for analysis testing

Post Service (in addition to the above, please include the following):

- Analysis testing results

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.
<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td></td>
<td>81191</td>
<td>NTRK1 (neurotrophic receptor tyrosine kinase 1) (e.g., solid tumors) translocation analysis <em>(Code added effective 1/1/2021)</em></td>
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<td>81192</td>
<td>NTRK2 (neurotrophic receptor tyrosine kinase 2) (e.g., solid tumors) translocation analysis <em>(Code added effective 1/1/2021)</em></td>
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<td>81193</td>
<td>NTRK3 (neurotrophic receptor tyrosine kinase 3) (e.g., solid tumors) translocation analysis <em>(Code added effective 1/1/2021)</em></td>
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<td>81194</td>
<td>NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3) (e.g., solid tumors) translocation analysis <em>(Code added effective 1/1/2021)</em></td>
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<td></td>
<td>0239U</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations <em>(Code added effective 1/1/2021)</em></td>
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<tr>
<td>CPT®</td>
<td>81235</td>
<td>EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)</td>
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<td>81275</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)</td>
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<td>81276</td>
<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)</td>
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<td>81404</td>
<td>Molecular Pathology Procedure Level 5 <em>(Code revision effective 1/1/2021)</em></td>
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<td>81405</td>
<td>Molecular Pathology Procedure Level 6 <em>(Code revision effective 1/1/2021)</em></td>
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<td>81406</td>
<td>Molecular Pathology Procedure Level 7 <em>(Code revision effective 1/1/2021)</em></td>
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<td></td>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td></td>
<td>88342</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure</td>
</tr>
<tr>
<td></td>
<td>88365</td>
<td>In situ hybridization (e.g., FISH), per specimen; initial single probe stain procedure</td>
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**HCPCS**

None

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>11/26/2014</td>
<td>BCBSA Medical Policy adoption</td>
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<tr>
<td>08/31/2015</td>
<td>Policy title change from Molecular Analysis for Targeted Therapy for Non-Small-Cell Lung Cancer Policy revision without position change</td>
</tr>
<tr>
<td>06/01/2016</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>12/01/2016</td>
<td>Policy revision without position change</td>
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<tr>
<td>12/01/2017</td>
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<td>12/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>12/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>12/01/2020</td>
<td>Annual review. Policy statement updated</td>
</tr>
</tbody>
</table>
**Effective Date** | **Action**
--- | ---

**Definitions of Decision Determinations**

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member’s illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.
## Policy Statement

**Before**

Molecular analysis (genetic testing) is reserved for advanced (stage III or IV) or metastatic Non-Small-Cell Lung Cancer (NSCLC) including adenocarcinoma, large cell, squamous cell and NSCLC not otherwise specified (see Policy Guidelines). Small panel testing including the following medically necessary genes may be considered as an alternative to individual testing.

### EGFR Testing

Analysis of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], afatinib [Gilotrif®], or osimertinib [Tagrisso™]) in patients with advanced NSCLC.

Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered investigational.

### ALK Testing

Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of somatic rearrangement variants of the ALK gene is considered investigational in all other situations.

### BRAF V600E Testing

**After**

Molecular analysis (genetic testing) is reserved for advanced (stage III or IV) or metastatic Non-Small-Cell Lung Cancer (NSCLC) including adenocarcinoma, large cell, squamous cell and NSCLC not otherwise specified (see Policy Guidelines). Small panel testing including the following medically necessary genes may be considered as an alternative to individual testing and may be preferred when there is limited tissue available for testing.

### EGFR Testing

Analysis of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the epidermal growth factor receptor (EGFR), may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], afatinib [Gilotrif®], or osimertinib [Tagrisso™]) in patients with advanced NSCLC.

Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered investigational.

### ALK Testing

Analysis of somatic rearrangement variants of the anaplastic lymphoma kinase (ALK) gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).

Analysis of somatic rearrangement variants of the ALK gene is considered investigational in all other situations.
## POLICY STATEMENT

<table>
<thead>
<tr>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF V600E Testing</strong></td>
<td>Analysis of the BRAF V600E variant may be considered <em>medically necessary</em> to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).</td>
</tr>
<tr>
<td>Analysis of BRAF V600E variant is considered <em>investigational</em> in all other situations.</td>
<td></td>
</tr>
<tr>
<td><strong>ROS1 Testing</strong></td>
<td>Analysis of somatic rearrangement variants of the ROS1 gene may be considered <em>medically necessary</em> to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines section).</td>
</tr>
<tr>
<td>Analysis of somatic rearrangement variants of the ROS1 gene is considered <em>investigational</em> in all other situations.</td>
<td></td>
</tr>
<tr>
<td><strong>KRAS Testing</strong></td>
<td>Analysis of somatic variants of the KRAS gene is considered <em>investigational</em> as a technique to predict treatment nonresponse to anti-EGFR therapy with tyrosine kinase inhibitors (TKIs) and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC.</td>
</tr>
<tr>
<td>Analysis of genetic alterations in the KRAS gene for targeted therapy in patients with NSCLC is considered <em>investigational</em>, unless included as part of a small panel that otherwise meets medically necessary criteria.</td>
<td></td>
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<tr>
<td><strong>HER2 Testing</strong></td>
<td>Analysis of genetic alterations in the HER2 gene for targeted therapy in patients with NSCLC is considered <em>investigational</em>, unless included as part of a small panel that otherwise meets medically necessary criteria.</td>
</tr>
<tr>
<td><strong>NTRK GENE FUSION TESTING</strong></td>
<td>Analysis of NTRK gene fusions may be considered <em>medically necessary</em> to predict treatment response to larotrectinib (Rozlytrek) or entrectinib (Rozlytrek) or larotrectinib</td>
</tr>
<tr>
<td>Analysis of NTRK gene fusions is considered <em>investigational</em> in all other situations.</td>
<td></td>
</tr>
<tr>
<td><strong>Other Genes</strong></td>
<td>Analysis of genetic alterations in the genes HER2, RET, and MET for targeted therapy in patients with NSCLC is considered <em>investigational</em>.</td>
</tr>
<tr>
<td>Large or pan-cancer panels used for targeting non-small cell lung cancer treatments are considered <em>investigational</em>.</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>POLICY STATEMENT</th>
<th>BEFORE</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-L1 Testing</strong></td>
<td>Programmed Death-Ligand 1 (PD-L1) testing may be considered <strong>medically necessary</strong> in patients with NSCLC in addition to gene testing. PD-L1 is a ligand not a gene, and testing may be requested separately.</td>
<td>(Vitrakvi) in patients with advanced lung adenocarcinoma or in whom an adenocarcinomacomponent cannot be excluded (see Policy Guidelines section). Analysis of NTRK gene fusions is considered <strong>investigational</strong> in all other situations.</td>
</tr>
<tr>
<td><strong>RET Rearrangement Testing</strong></td>
<td>Analysis of genetic alteration in the RET gene may be considered <strong>medically necessary</strong> to predict treatment response to pralsetinib (Gavreto) or selpercatinib (Retevmo) in patients with metastatic NSCLC. Analysis of genetic alterations in the RET gene is considered <strong>investigational</strong> in all other situations.</td>
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<tr>
<td><strong>MET Exon 14 Skipping Alteration</strong></td>
<td>Analysis of genetic alteration that leads to MET exon 14 skipping may be considered <strong>medically necessary</strong> to predict treatment response to capmatinib (Tabrecta) in patients with metastatic NSCLC. Analysis of genetic alterations of the MET gene is considered <strong>investigational</strong> in all other situations.</td>
<td></td>
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<tr>
<td><strong>PD-L1 Testing</strong></td>
<td>Programmed Death-Ligand 1 (PD-L1) testing may be considered <strong>medically necessary</strong> to predict treatment response to atezolizumab (Tecentriq), nivolumab (Opdivo) in combination with ipilimumab (Yervoy), or pembrolizumab (Keytruda) in patients with metastatic NSCLC. PD-L1 is a ligand not a gene, and testing may be requested separately if not part of the panel. PD-L1 testing is considered <strong>investigational</strong> in all other situations.</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor Mutational Burden Testing</strong></td>
<td>Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered <strong>investigational</strong>.</td>
<td></td>
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