Medical Policy

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

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Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • Testing for *EGFR* variants or *ALK* rearrangements	Comparators of interest are: • Management without genetic testing for EGFR variants or ALK rearrangements	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • Testing for *BRAF* variants or *ROS1* rearrangements	Comparators of interest are: • Management without genetic testing for BRAF variants or ROS1 rearrangements	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • Testing for *RET* rearrangements or MET alterations	Comparators of interest are: • Management without genetic testing for RET rearrangements or MET alterations	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: • With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • Testing for *KRAS* or *HER2* variants	Comparators of interest are: • Management without genetic testing for KRAS or HER2 variants	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: With advanced-stage non-small-cell lung cancer who are being considered for targeted therapy	Interventions of interest are: • *NTRK* gene fusion testing	Comparators of interest are: • Management without *NTRK* gene fusion testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: With advanced-stage non-small-cell lung cancer who are being considered for immunotherapy	Interventions of interest are: • *PD-L1* testing	Comparators of interest are: • Management without *PD-L1* testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity
Individuals: With advanced-stage non-small-cell lung cancer who are being considered for immunotherapy	Interventions of interest are: • Tumor mutational burden (TMB) testing	Comparators of interest are: Management without TMB testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test validity • Quality of life • Treatment-related morbidity

DESCRIPTION

Over half of patients with non-small-cell lung cancer (NSCLC) present with advanced and therefore incurable disease. Treatment in this setting has been with platinum-based chemotherapy. The identification of specific, targetable oncogenic "driver mutations" in a subset of NSCLCs has resulted in a reclassification of lung tumors to include molecular subtypes that may direct targeted therapy depending on the presence of specific variants.

OBJECTIVE

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

BACKGROUND

Non-Small-Cell Lung Cancer

Treatment options for 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, cancer has spread locally beyond the lungs at diagnosis, precluding surgical eradication. Also, up to 40% of patients with NSCLC present with metastatic disease.[1,] When treated with standard platinum-based chemotherapy, patients with advanced NSCLC have a median survival of 8 to 11 months and 1-year survival of 30% to 45%.[2,3,] 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.[4,] Most BRAF variants occur more frequently in smokers.

ROS1 Gene
ROS1 codes for a receptor TK of the insulin receptor family and chromosomal rearrangements result in fusion genes. The prevalence of ROS1 fusions in NSCLC varies from 0.9% to 3.7%.[4,] Patients with ROS1 fusions are typically never-smokers with adenocarcinoma.

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

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 U.S. Food and Drug Administration (FDA) approved companion diagnostics.

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. HER2is expressed in approximately 25% of NSCLC. HER2 variants are detected mainly in exon 20 in 1% to 2% of NSCLC, predominantly in adenocarcinomas in nonsmoking women.[4,]

There are currently no targeted therapies specifically approved for this indication.

RET Gene
RET (rearranged during transfection) is a proto-oncogene that encodes a receptor TK growth factor. Translocations that result in fusion genes with several partners have been reported.[4,] RET fusions occur in 0.6% to 2% of NSCLCs and 1.2% to 2% of adenocarcinomas.[4,]

MET Gene
MET amplification alteration is one of the critical events for acquired resistance in EGFR-mutated adenocarcinomas refractory to EGFR TKIs.[4,]

NTRK Gene Fusions
NTRK gene fusions encode tropomyosin receptor kinase fusion proteins that act as oncogenic drivers for solid tumors including lung, salivary gland, thyroid, and sarcoma. It is estimated that NTRK gene fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers.[5,]

PD-1/PD-L1
Programmed cell ligand-1 (PD-L1) is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

Tumor Mutational Burden
Tumor mutational burden, a measure of gene mutations within cancer cells, is an emerging biomarker of outcomes with immunotherapy in multiple tumor types, including lung cancer.[6,]

Targeted Treatment and Immunotherapy
Targeted treatments and immunotherapy for the variants described above are summarized in Table 1.

Table 1. Targeted Treatments and Immunotherapy for NSCLC

Target	FDA-Approved Therapies
EGFR	• Gefitinib (Iressa), • Erlotinib (Tarceva), • Afatinib (Gilotrif) • Osimertinib (Tagrisso) • Dacomitinib (Vizimpro)
ALK	• Crizotinib (Xalkori) • Ceritinib (Zykadia) • Alectinib (Alecensa) • Brigatinib (Alunbrig) • Lorlatinib (Lorbrena)
BRAF	• Dabrafenib and trametinib combination
ROS1	• Crizotinib (Xalkori) • Ceritinib (Zykadia) • Lorlatinib (Lorbrena) • Entrectinib (Rozlytrek)
KRAS	• No FDA-approved targeted treatments
HER2	• No FDA-approved targeted treatments
RET	• Selpercatinib (Retevmo) • Pralsetinib (Gavreto)
MET	• Capmatinib (Tabrecta)
NTRK	• Larotrectinib (Vitrakvi) • Entrectinib (Rozlytrek)
PD-L1	• Pembrolizumab (Keytruda) • Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) • Atezolizumab (Tecentriq)

REGULATORY STATUS
Table 2 summarizes the FDA-approved targeted treatments for patients with NSCLC along with the concurrently approved companion diagnostic tests.[7,8,]

Table 2. Targeted Treatments and Immunotherapy for NSCLC and Companion Diagnostic Tests

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
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: therascreen® 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) • 2017: Ventana ALK (D5F3) CDx Assay
Atezolizumab (Tecentriq)	• 2020: First-line treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA approved test, with no EGFR or ALK genomic tumor aberrations. ○ in combination with bevacizumab, paclitaxel, and carboplatin, for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. ○ in combination with paclitaxel protein-bound and carboplatin for the first line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations ○ for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.	• 2020: VENTANA PD-L1
Brigatinib (Alunbrig)	• 2017: Second line for patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant of crizotinib	• 2020: Vysis ALK Break Apart FISH Probe Kit
Capmatinib (Tabrecta)	• 2020: metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to MET exon 14 skipping as detected by an FDA-approved test.	• 2020: FoundationOne CDx

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		(Foundation Medicine)
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) • 2017: VENTANA ALK (D5F3) CDx Assay
Crizotinib (Xalkori)	• 2011: First line for patients with ALK- or ROS1-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) • Oncomine Dx • 2017: VENTANA ALK (D5F3) CDx Assay
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	• 2018: therascreen

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		EGFR RGQ PCR Kit
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)
Entrectinib (Rozlytrek)	• 2019: ○ Adult patients with metastatic NSCLC whose tumors are ROS1-positive ○ Adult and pediatric patients 12 years of age and older with ○ solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, • are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.	• No 8ompanion diagnostic
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) • 2017: FoundationOne CDx™ (Foundation Medicine)
Gefitinib (Iressa)	• 2015: First line for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions 2003: 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

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
		• 2017: FoundationOne CDx™ (Foundation Medicine) • 2017: cobas® EGFR Mutation Test (tissue test) (Roche Diagnostics) • 2017: Oncomine Dx Target Test
Ipilimumab (Yervoy)	Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab. (1.6) • Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum doublet chemotherapy. (1.6)	• PD-L1 IHC 28-8 PharmDx
Larotrectinib (Vitrakvi)	• 2018: Adult and pediatric patients with solid tumors that ○ have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, ○ are metastatic or where surgical resection is likely to result in severe morbidity, and ○ have no satisfactory alternative treatments or that have progressed following treatment.	• FoundationOne CDx (solid tumors, NTRK1/2/3 fusions)
Lorlatinib (Lorbrena)	• 2018: Patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer whose disease has progressed on ○ crizotinib and at least one other ALK inhibitor for metastatic disease; or ○ alectinib as the first ALK inhibitor therapy for metastatic disease; or ○ ceritinib as the first ALK inhibitor therapy for metastatic disease.	• No companion diagnostic
Nivolumab (Opdivo) in combination with	• 2020: ○ adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor	• PD-L1 IHC 28-8 PharmDx

Treatment	Indication	FDA-Approved Companion Diagnostic Tests
Ipilimumab (Yervoy)	aberrations, as first-line treatment in combination with ipilimumab. ○ adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy. ○ patients with metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.	
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 • 2019: EGFR exon 19 deletion and EGFR exon 21 L858R alterations	• 2015: cobas® EGFR Mutation Test v2 (blood test) • 2017: FoundationOne CDx™ (Foundation Medicine) • 2020: Guardant360 CDx
Pembrolizumab (Keytruda)	• Monotherapy for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA	• PD-L1 IHC 22C3 pharmDx
Pralsetinib (Gavreto)	• Adult patients with metastatic RET fusion- positive NSCLC as detected by an FDA approved test	• 2020: Oncomine Dx Target Test
Selpercatinib (Retevmo)	• Adult patients with metastatic RET fusion-positive NSCLC	• No companion diagnostic specified

Sources: U.S. Food and Drug Administration (2020)[7]; U.S. Food and Drug Administration (n.d.)[8]
ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; FISH: fluorescence in situ hybridization; NSCLC: non-small-cell lung cancer; PCR: polymerase chain reaction.

POLICY

EGFR Testing

A. Analysis of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the *EGFR* gene may be considered **medically necessary** to predict treatment response to an *EGFR* tyrosine kinase inhibitor therapy (e.g., erlotinib [Tarceva], gefitinib [Iressa], afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.

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

ALK Testing

C. Analysis of somatic rearrangement variants of the *ALK* gene may be considered **medically necessary** to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori], ceritinib [ZykadiaM], alectinib [Alecensa], or brigatinib [Alunbrig]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.

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

BRAF V600E Testing

E. 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 stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.

F. Analysis of *BRAF* V600E variant is considered **experimental / investigational** in all other situations

ROS1 Testing

G. Analysis of somatic rearrangement variants of the *ROS1* gene may be considered **medically necessary** to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.

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

KRAS Testing

I. Analysis of somatic variants of the *KRAS* gene is considered **experimental / investigational** as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab (Erbitux) in NSCLC.

HER2 Testing

J. Analysis of genetic alterations in the *HER2* gene for targeted therapy in patients with NSCLC is considered **experimental / investigational.**

NTRK Gene Fusion Testing

K. Analysis of *NTRK* gene fusions may be considered **medically necessary** to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified.

L. Analysis of *NTRK* gene fusions is considered **experimental / investigational** in all other situations.

RET Rearrangement Testing

M. 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.

N. Analysis of genetic alterations in the *RET* gene is considered **experimental / investigational** in all other situations.

MET Exon 14 Skipping Alteration

O. 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.

P. Analysis of genetic alterations of the *MET* gene is considered **experimental / investigational** in all other situations.

PD-L1 Testing

Q. 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.

R. PD-L1 testing is considered **experimental /investigational** in all other situations

Tumor Mutation Burden Testing

S. Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered **experimental / investigational.**

Policy Guidelines

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

2. 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.
3. The 2018 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology have recommended the following:
   "One set of genes must be offered by all laboratories that test lung cancers, as an absolute minimum: EGFR, ALK, and ROS1. A second group of genes should be included in any expanded panel that is offered for lung cancer patients: BRAF, MET, RET, ERBB2 (HER2), and KRAS, if adequate material is available. KRAS testing may also be offered as a single-gene test to exclude patients from expanded panel testing. All other genes are considered investigational at the time of publication."

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, use of tissue for testing of any/all variants and biomarkers outlined in this policy is recommended, but is not required in all situations. In certain situations, circulating tumor DNA testing (liquid biopsy) may be an option (see BCBSKS medical policy *Circulating Tumor DNA Management of Non-Small-Cell Lung Cancer*).

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 9, 2020.

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

***EGFR* Variant Frequency**
Fang et al (2013) reported *EGFR* variants (all L858R) in 3 (2%) of 146 consecutively treated Chinese patients with early-stage squamous cell carcinoma (SCC).[9,] 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.[10,] Eberhard et al (2005)[11,] observed *EGFR* variants in 6.4% of patients with SCC and Rosell et al (2009)[12,] 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.[13,14,]

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.[15,] 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 also is approved as a companion diagnostic to detect the T790M resistance variant to select patients for treatment with osimertinib.

The clinical validity of the therascreen RGQ PCR kit was demonstrated in a retrospective analysis of patients screened for a phase 3, open-label RCT comparing afatinib with chemotherapy in treatment-naive patients with stage IIIB or IV NSCLC, in which the *EGFR* variants for enrollment were determined using a clinical trial assay (CTA) conducted at central laboratories.[16,] 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.[17,] 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.[18,] 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[19,]. The PPA of Oncomine vstherascreen 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.[20,] 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.[21,] 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.[22,] 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.[23,] Other meta-analyses have confirmed the PFS and OS results and conclusions for *EGFR*-positive patients have been published.[24,23,25,26,27,]

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.[28,] 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

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Erlotinib	Chemotherapy
Wu et al (2015)[29,]; ENSURE (NCT01342965)	China, Malaysia, Philippines	30	2011-2012	217 patients with stage IIIB/IV NSCLC	110 assigned to erlotinib (150 mg qd)	117 assigned to gemcitabine (1250 mg/m^2) and cisplatin (75 mg/m^2)
Rosell et a (2012)[30,]; EURTAC (NCT00446225)	France, Italy, Spain	42	2007-2011	173 patients with stage IIIB/IV NSCLC	86 assigned to erlotinib (150 mg qd)	87 assigned to cisplatin (75mg/m^2), docetaxel (75 mg/m^2), or gemcitabine (1250 mg/m^2)
Zhou et a (2011, 2015)[29,30,]; OPTIMAL (NCT00874419)	China	22	NR	165 patients with stage IIIB/IV NSCLC	83 assigned to erlotinib (150 mg qd)	82 assigned to carboplatin (AUC5) and gemcitabine (1000 mg/m$^{2)}$

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

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

Trial	Median PFS, mo	Median OS, mo	Adverse Events, %		
			Serious	*Grade 3 or 4*	*%*
ENSURE (2015)[29,]					
N	217	217	214	214	
Erlotinib	11.0	26.3	2.7	· Overall · Neutropenia · Leukopenia · Anemia · Rash	· 35.5 · 0.9 · 0.9 · 0.9 · 6.4
Chemotherapy	5.5	25.5	10.6	· Overall · Neutropenia · Leukopenia · Anemia · Rash	· 57.7 · 25.0 · 14.4 · 12.5 · 1
HR (95% CI)	0.34 (0.22 to 0.51)	0.91 (0.63 to 1.31)			

Trial	Median PFS, mo	Median OS, mo	Adverse Events, %		
EURTAC (2012)[30,]					
Erlotinib	9.7 (8.4 to 12.3)	19.3	6	· Rash · Neutropenia · Increased AT concentrations	· 13 · 0 · 2
Chemotherapy	5.2 (4.4 to 5.8)	19.5	20	· Rash · Neutropenia · Increased AT concentrations	· 0 · 22 · 0
HR (95% CI)	0.37 (0.25 to 0.54)	1.04 (0.65 to 1.68)			
OPTIMAL (2011, 2015)[29,30,]					
N	154	154	155	155	
Erlotinib	13.1 (10.6 to 16.5)	22.8	2	· Neutropenia · Thrombocytopenia	· 0 · 0
Chemotherapy	4.6 (4.2 to 5.4)	27.2	14	· Neutropenia · Thrombocytopenia	· 42 · 40
HR (95% CI)	0.16 (0.10 to 0.26)	1.19 (0.83 to 1.71)			

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

Many additional publications have provided data on *EGFR* variants in tumor samples obtained from NSCLC patients treated with erlotinib. Nine of these [9,31,32,33,34,35,36,37,38,] 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.[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.[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.[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.[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.[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).[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

Study; Trial	Countries	Sites	Dates	Participants	Description of Interventions		
					Gefitinib Alone	*Chemo Alone*	*Gefitinib Plus Chemo*
Han et al (2017)[44,]	China	1	2011-2015	121 patients with advanced lung adenocarcinoma	41 assigned to gefitinib (250 mg/d)	40 assigned to pemetrexed (500 mg/m^2) and carboplatin (AUC5)	40 assigned to pemetrexed (500 mg/m^2) and carboplatin (AUC5) and gefitinib (250 mg/d)
					Gefitinib	*Chemo*	
Mok (2009)[43,]; IPASS (NCT00322452)	9 East Asian countries	87	2006-2007	1217 patients with stage IIIB/IV NSCLC (261 *EGFR*-positive)	609 assigned to gefitinib (250 mg/d)	608 assigned to paclitaxel (200 mg/m^2) and carboplatin (AUC5 or AUC6)	
Mitsudomi (2010)[45,]; WJTOG3405[a]	Japan	36	2006-2009	177 patients with stage IIIB/IV or recurrent NSCLC	88 assigned to gefitinib (250 mg/d)	89 assigned to cisplatin (80 mg/m^2) and docetaxel (60 mg/m^2)	

Study; Trial	Countries	Sites	Dates	Participants	Description of Interventions	
Maemondo (2010), [47,] Inoue (2013)[48,]; NEJ002	Japan	43	2006-2009	230 patients with stage IIIB/IV NSCLC or postoperative relapse	115 assigned to gefitinib (250 mg/d)	115 assigned to paclitaxel (200 mg/m^2) and carboplatin (AUC6)

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

Table 6. Results of RCTs of First-Line Gefitinib vs Chemotherapy in *EGFR*-Variant SCLC

Study	Median PFS, mo	Median OS, mo	Adverse Events, %		
			Serious	*Grade 3 or 4*	*%*
Han et al (2017)[44,]			NR		
Gefitinib	5.7 (5.2 to 6.3)	25.8 (21.3 to 30.2)		· Liver dysfunction · Skin rash	· 2.4 · 9.8
Chemotherapy	11.9 (9.1 to 14.6)	24.3 (17.7 to 30.1)		· Neutropenia · Fatigue · Skin rash	· 12.5 · 5.0 · 9.8
Gefitinib plus chemotherapy	17.5 (15.3 to 19.7)	32.6 (25.5 to 39.8)		· Liver dysfunction · Neutropenia · Fatigue · Skin rash	· 10.0 · 10.0 · 7.5 · 10.0
TE (95% CI)	Combination vs chemotherapy: · 0.2 (0.1 to 0.3)Combination vs gefitinib: · 0.5 (0.3 to 0.8)Gefitinib vs chemotherapy: · 0.3 (0.2 to 0.6)	Combination vs chemotherapy: · 0.5 (0.2 to 0.9)Combination vs gefitinib: · 0.4 (0.2 to 0.7)Gefitinib vs chemotherapy: · 1.0 (0.6 to 1.8)			
WJTOG3405 (2010)[45,]					
N	172	172	NR	172	
Gefitinib	9.2 (8.0 to 13.9)	34.8 (26.0 to 39.5)		· ALT/AST elevation · Rash · Fatigue	· 27.5 · 2.3 · 2.3
Chemotherapy	6.3 (5.8 to 7.8)	37.3 (31.2 to 45.5)		· ALT/AST elevation · Fatigue · Neutropenia · Leukocytopenia · Anemia	· 2.3 · 2.3 · 84 · 50 · 17

Study	**Median PFS, mo**	**Median OS, mo**	**Adverse Events, %**		
TE (95% CI)	HR=0.49 (0.34 to 0.71)	HR=1.25 (0.88 to 1.78)			
NEJ002 (2010, 2013)[43,]					
N	224		NR	227	
Gefitinib	10.8	27.7		· Rash · Arthralgia · Pneumonitis · Aminotransferase elevation · Neutropenia	· 5.3 · 0.9 · 2.6 · 26.3 · 0.9
Chemotherapy	5.4	26.6		· Rash · Neuropathy · Arthralgia · Aminotransferase elevation · Neutropenia · Anemia · Thrombocytopenia	· 2.7 · 6.2 · 7.1 · 0.9 · 65.5 · 5.3 · 3.5
HR (95% CI)	0.30 (0.22 to 0.41)	0.89 (0.63 to 1.24)			
IPASS (2009)[43,]					
N	259[a]	259[a]	1196[b]		
Gefitinib	»9.6[c]	NR	16.3%	· Rash · Diarrhea · Neurotoxic effects · Neutropenia · Anemia · Leukopenia	· 3.1 · 3.8 · 0.3 · 3.7 · 2.2 · 1.5
Chemotherapy	»5.8[c]	NR	15.6%	· Rash · Diarrhea · Neurotoxic effects · Neutropenia · Anemia · Leukopenia	· 0.8 · 1.4 · 4.9 · 67.1 · 10.6 · 35.0
HR (95% CI)	0.48 (0.36 to 0.64)	0.78 (0.50 to 1.20)			

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

[a] Analysis includes *EGFR*-positive only.

[b] Analysis includes all patients with safety data.

[c] Estimated from 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 an RCT including 345 patients with stage IIIB or IV, *EGFR* variant-positive, lung adenocarcinoma who were previously untreated for advanced disease.[49,] 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.[50,] 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.[49,] 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.[51,] 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.[52,] Patients had been treated with chemotherapy but not with *EGFR*-targeted therapy; approximately half of the patients (enrolled after a protocol amendment) were chemotherapy-naive. Objective responses (primarily partial responses) were observed in 66% of 106 patients with common *EGFR* variants (exon 19 deletion or L858R) and in 39% of 23 patients with other *EGFR* variants. The median PFS was 13.7 months in patients with common *EGFR* variants and 3.7 months in patients with other *EGFR* variants (p not reported). Results for variant-negative patients were not reported.
- LUX-Lung 1 and LUX-Lung 4 enrolled patients who had progressed on previous treatment with erlotinib, gefitinib, or both for advanced disease. Neither study prospectively genotyped patients. In the LUX-Lung 1 double-blind RCT, 96 (66% Asian, 33% white) of 585 enrolled patients were *EGFR* variant-positive (76 common *EGFR* variant-positive).[53,] 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.[54,] 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.[55,] 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.[56,]

The osimertinib label describes the 2 studies.[55,] 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.[57,] 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

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Osimertinib	Standard TKI
Reungwetwattana et al (2018)[57,];FLAURA (NCT02296125)	31 countries in North America, Europe, Australia, Asia	168	2014-2017	128 (of 556) patients with untreated advanced *EGFR*-positive NSCLC with available brain scans at baseline	61 assigned to osimertinib (80 mg/d)	67 assigned to gefitinib (250 mg/d) or erlotinib (150 mg/d)
					Osimertinib	Chemotherapy

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Mok et al (2017)[58,]; AURA3 (NCT02151981)	18 countries in North America, Europe, Australia, Asia	126	2014-2015	419 patients with T790M-positive advanced NSCLC who had disease progression after first-line EGFR-TKI therapy	279 assigned to osimertinib (80 mg/d)	140 to assigned platinum pemetrexed (500 mg/m^2 of BSA) plus carboplatin (target AUC5 or cisplatin [75 mg/m^2])

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

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

Study	PFS, mo	OS, mo	ORR (95% CI)	Adverse Events, %		Prolongation of QT Interval, %
				Grade ≥3	ILD-Like	
AURA3(2017)[58,]						
N	419		419	415	415	415
Osimertinib	10.1	NR	71% (65 to 76)	23	4	4
Platinum pemetrexed	4.4	NR	31% (24 to 40)	47	1	1
TE (95% CI)	HR=0.30 (0.23 to 0.41)		OR=5.4 (3.5 to 8.5)			
	PFS (N=128)					
	Median, mo	6-Mo (95% CI), %	12-Mo (95% CI), %	18-Mo (95% CI), %		ORR (95% CI), %
FLAURA (2018)[57,]						
Osimertinib	(16.5 to NC)	87 (74 to 94)	77 (62 to 86)	58 (40 to 72)		66 (52 to 77)
Other TKIs[a]	13.9 (8.3 to NC)	71 (57 to 81)	56 (42 to 68)	40 (25 to 55)		43 (31 to 56)
TE (95% CI)						2.5 (1.2 to 5.2)

CI: confidence interval; *EGFR*: epidermal growth factor receptor; HR: hazard ratio; ILD: interstitial lung disease; NC: not calculable; NR: not reported; NSCLC: non-small-cell lung cancer; OR: odds ratio; ORR: objective response rate;OS: overall survival; PFS: progression-free survival; TE: treatment effect.
[a] Erlotinib or gefitinib.

Comparative Effectiveness of *EGFR* TKIs

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

Study	Study Dates	Design (No. of Studies)	No. of Patients	Line of Treatment	Treatments Compared	Conclusions
Lin et al (2018)[59],	Nov 2017	RCT (11)	3145	First-line	Chemotherapy, afatinib, dacomitinib, erlotinib, gefitinib, osimertinib	· PFS: TKIs more effective than chemotherapy · Osimertinib, dacomitinib, and afatinib ranked highest probability of benefit among TKIs · Subgroup analyses comparing osimertinib with standard of care showed improvements in men, non-Asians, smokers, and those with del19 variants · Toxicity profiles similar for TKIs
Zhang et al (2018)[60],	Oct 2017	RCT (40)	9376	First-, second-, and third-line	Erlotinib, gefitinib	· PFS: erlotinib and gefitinib comparable · Grade 3-5 adverse events more frequent with erlotinib
De Mello et al (2018)[61],	Aug 2016	RCT (9)	3179	First-line	Chemotherapy, afatinib, erlotinib, gefitinib	· PFS: afatinib, erlotinib, and gefitinib more effective than chemotherapy · OS: afatinib, erlotinib, and gefitinib comparable to chemotherapy
Crequit et al (2017)[62],	Jun 2017	RCT (102)	36,058	Second-line	61 treatments (combinations of immunotherapy, chemotherapy, and afatinib, cabozantinib, erlotinib, gefitinib)	· OS: immunotherapy or pemetrexed plus erlotinib most effective · PFS: erlotinib plus cabozantinib most effective · Evidence for safety was insufficient
Wu et al (2017)[63],	Jan 2017	RCT (12)	3341	Second- and third-line	Chemotherapy, PD-1/PD-L1 antibodies, erlotinib, gefitinib	· OS and PFS: PD-1/PD-L1 more effective than chemotherapy and erlotinib and gefitinib

Study	Study Dates	Design (No. of Studies)	No. of Patients	Line of Treatment	Treatments Compared	Conclusions
						· OS and PFS: chemotherapy more effective than erlotinib and gefitinib
Yang et al (2017)[64]	Dec 2016	Cohort (82)RCT (8)	17,621	First- and second-line	Afatinib, erlotinib, gefitinib	· PFS: gefitinib and erlotinib comparable regardless of line · Afatinib more effective than gefitinib and erlotinib as second- line treatment in for advanced squamous NSCLC · Grade 3-4 adverse events comparable with afatinib and erlotinib; gefitinib adverse events lower
Zhang et al (2017)[65]	Mar 2016	RCT (6)	1055	First-, second-, and third-line	Afatinib, dacomitinib, erlotinib, gefitinib, icotinib	· Therapeutic efficacy comparable among all 5 TKIs · Rank probabilities showed dacomitinib and afatinib had potentially better efficacy than erlotinib, gefitinib, and icotinib

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

Randomized Controlled Trials

Soria et al (2018) conducted a double-blind phase 3 trial comparing osimertinib with other TKIs (gefitinib or erlotinib) for the first-line treatment of patients with *EGFR*-positive advanced NSCLC.[66] 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.[67] 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.[68]

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.[69] 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% (9%% 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 cross over to crizotinib as part of a separate study. The median PFS was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; p<0.001). Partial response rates with crizotinib were 65% (95% CI, 58% to 72%) and 20% (95% CI, 14% to 26%) with chemotherapy (p<0.001). Interim analysis of OS showed no significant improvement with crizotinib compared with chemotherapy (HR for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; p=0.54). The median follow-up for OS was 12.2 in the crizotinib group and 12.1 months in the chemotherapy group. Patients reported greater reductions in lung cancer symptoms and greater improvement in global 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.[72,] 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.[73,72,]

Alectinib was associated with response rates of approximately 50% in patients who had progressed on crizotinib in 2, phase 2 studies.[74,75,] 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.[76,77,]

Brigatinib has shown promise in early phase 1 and 2 studies with PFS of almost 13 months in patients with the crizotinib-refractory disease.[78,79,] 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.[80,]

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

BRAF GENE VARIANTS

FDA-Approved Companion Diagnostic Tests for *BRAF* Variants

BRAF variants are detected by PCR sequencing or NGS methods. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect *BRAF* V600E variants to aid in selecting NSCLC patients for treatment with combination dabrafenib (Tafinlar) and trametinib (Mekinist) therapy. The Oncomine test is an NGS oncology panel that detects, among other variants, *BRAF* V600E variants from DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples. The detection of *BRAF* V600E variants by the test was evaluated by retrospective analyses of a phase 2, multicenter, nonrandomized study that included patients with a *BRAF* V600E variant who had progressed on prior treatment or were treatment-naive who were treated with dabrafenib in combination with trametinib in the study. Patients were screened for a *BRAF* V600E variant based on local lab tests used at each enrollment site. No FDA-approved test was available for detection of *BRAF* V600E variants in FFPE NSCLC specimens so a validated PCR assay (BRAF V600 PCR Mutation Test) was used to estimate concordance. The concordance between the Oncomine test and the BRAF V600 PCR Mutation Test was 100% for PPA (95% CI, 95% to 100%) and 100% for NPA (95% CI, 97% to 100%). The response rate in the 57 previously treated patients in the study who were *BRAF*-positive by local lab test was 67% (95% CI, 53% to 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 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.[81,82,] Trial results for cohorts A,[83,] B,[84,] and C[85,] 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% at8 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 10. Characteristics of Key Nonrandomized Trials of BRAF or MEK Inhibitors in *BRAF*-Variant NSCLC

Study; Trial	Study Type	Country	Dates	Participants	Treatment	Median FU, mo
Planchard et al (2017)[85,]NCT01336634	Single-arm, open-label phase 2 trial	9 countries in North America, Europe, Asia	2014-2015	Adults, stage IV, *BRAF* V600E variant, previously untreated	Dabrafenib (150 mg bid) plus trametinib (2 mg/d)	15.9
Planchardet al (2016)[83,] NCT01336634	Single-arm, open-label phase 2 trial	9 countries in North America, Europe, Asia	2011-2014	Adults, stage IV, *BRAF* V600E variant, progression after chemotherapy	Dabrafenib (150 mg bid)	10.7
Planchard et al (2016)[84,]; NCT01336634	Single-arm, open-label phase 2 trial	9 countries in North America, Europe, Asia	2013-2015	Adults, stage IV, *BRAF* V600E variant, progression after chemotherapy	Dabrafenib (150 mg bid) plus trametinib (2 mg/d)	11.6
Hyman et al (2015)[86,]; NCT01524978	Single-arm, open-label phase 2 trial	Germany, Spain, U.K., U.S., France	2012-2014	*BRAF* V600 variant-positive nonmelanoma cancers including NSCLC	Vemurafenib (960 mg bid)	6[a]

bid: twice a day; FU: follow-up; NSCLC: non-small-cell lung cancer.
[a] Estimated from a figure.

Table 11. Results of Key Nonrandomized Trials of BRAF or MEK Inhibitors in *BRAF*-Variant NSCLC

Study	Response (95% CI), %	PFS (95% CI), mo	Overall Survival (95% CI)	Adverse Events, %			
				Grade 3 or 4	%	Serious	%
Planchard et al (2017)[85,]							
	N=36	N=36	N=36				
	64 (46 to 79)	10.9 (7.0 to 16.6)[c]	At data cutoff: 24.6 mo At 2-y: 51% (33% to 67%)	· Overall · Pyrexia · Hypertension	· 7 · 11 · 11		
Planchard et al (2016)[83,]							
	N=78	N=78	N=78	N=78		N=78	
	33 (23 to 45)[a]	5.5 (3.4 to 7.3)	Median, 12.7 mo	· Overall · Cutaneous SCC · Asthenia · BCC	· 39 · 12 · 5 · 5	· Overall	· 42
Planchard et al (2016)[84,]							
	N=57	N=57	N=57	N=57		N=57	
	63 (49 to 76)	9.7 (6.9 to 19.6)	At 6 mo, 82%	· Overall · Neutropenia · Hyponatremia	· 49 · 9 · 7	· Overall · Pyrexia · Anemia · Cutaneous SCC	· 56 · 16 · 5 · 4
Hyman et al (2015)[86,]							
	N=19	N=20	N=20	N=95[b]			
	At 8 wk, 42 (20 to 67)	Median, 7.3 (3.5 to 10.8)	At 12 mo, 66% (36% to 85%)	· Overall · Rash · Fatigue · Arthralgia	· 73 · 16 · 12 · 4		

BCC: basal cell carcinoma; CI: confidence interval; NSCLC: non-small-cell lung cancer; PFS: progression-free survival; SCC: squamous cell carcinoma.
[a] The response rate in the 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,]

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, immunohistochemistry, quantitative real-time reverse transcription-PCR, and some NGS panels. FISH is considered the standard method. The Oncomine Dx Target Test was FDA-approved in 2017 as a companion diagnostic to detect fusions in *ROS1* to aid in selecting NSCLC patients for treatment with crizotinib (Xalkori). The Oncomine test is an NGS oncology panel that detects, among other variants, fusions in *ROS1* from RNA isolated from FFPE tumor tissue samples. 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.[88,] 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 *ROS*1 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

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up, mo
Lim et al (2017)[89],	Open-label, single-arm, phase 2 study	Korea	2013-2016	Adults with *ROS1* rearrangement who had progressed on prior therapy, 94% crizotinib-naive	Ceritinib (750 mg/d)	14.0
Mazieres et al (2015)[90],	Retrospective	6 European countries	NR	*ROS1* rearrangement, 97% had received previous chemotherapy	Crizotinib (250 mg bid)	NR
Shaw et al (2014)[88],	Open-label, single-arm, expansion cohort of phase 1 study	Australia, Korea, U.S.	2010-2013	Adults with *ROS1* rearrangement, 86% had received prior therapy	Crizotinib (250 mg bid)	16.4

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

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

Study	Response (95% CI), %	Median PFS (95% CI), mo	OS (95% CI)	Adverse Events			
				Grade 3 or 4	%	All Grades	%
Lim et al (2017)[89],							
	n=28	N=32	N=32	N=32		N=32	
	62 (45 to 77)	9.3 (0 to 22)	24 mo (5 to 43)	· Overall · Fatigue · Pneumonia · Hyperglycemia · Increased AST · Increased ALT	· 37 · 16 · 6 · 9 · 9 · 6	· Diarrhea · Nausea · Anorexia · Vomiting · Cough · Abdominal pain · Musculoskeletal pain	· 78 · 59 · 56 · 53 · 47 · 41 · 41
Mazieres et al (2015)[90],							
	n=29	N=30		N=30			

Study	Response (95% CI), %	Median PFS (95% CI), mo	OS (95% CI)	Adverse Events			
	80 (NR)	9.1 (NR)	NR	· Grade 3 NR · Grade 4 or 5	· NR · 0	NR	
Shaw et al (2014)[88,]							
	N=50	N=50	N=50	N=50		N=50	
	72 (58 to 84)	19.2 (14.4 to not reached)	At 12 mo: 85% (72% to 93%)	·Hypophosphatemia · Neutropenia · Elevated ALT	· 10 · 10 · 4	· Visual impairment · Diarrhea · Nausea · Peripheral edema · Constipation · Vomiting	· 82 · 44 · 40 · 40 · 34 · 34

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

Kim et al (2013) reported on clinical outcomes in 208 never-smokers with NSCLC adenocarcinoma, according to *ROS1*-rearrangement status.[91,] *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.[92,] At median follow-up 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.

KRAS GENE VARIANTS

FDA-Approved Companion Diagnostic Tests for *KRAS* Variants

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

Tyrosine Kinase Inhibitors

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

Systematic Reviews

Pooled data on the relation between *KRAS* variants and response to EGFR TKI therapy are insufficient to determine an association between *KRAS* variant status and treatment effects on PFS or OS.

Pan et al (2016) published a meta-analysis of 41 studies (total N = 13103 patients) of prognostic and predictive values of a *KRAS* variant in NSCLC.[93,] 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.[94,] 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.[95,] 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.[96,] 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.[97,] 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.[36,] 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.[40,] 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.[98,] 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.[39,] Of 80 patients eligible for treatment, 41 (51%) had *KRAS* variant analysis; 6 (15%) patients were variant-positive, none of whom responded to erlotinib. Five (14%) of 35 patients with wild-type *KRAS* had a partial response.

In a phase 2 trial, Giaccone et al (2006) studied the response to erlotinib in 53 chemotherapy-naive patients with advanced NSCLC.[38,]Histologic samples were available to assess *KRAS* variant status from 29 patients, 10 (34%) of whom had variants. All 10 were nonresponders to erlotinib (p=0.125).

Pao et al (2005) were the first to suggest that patients with *KRAS*-mutated lung tumors were nonresponsive to treatment with EGFR TKIs.[99,] 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)[11,] 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)[100,] to chemotherapy with or without erlotinib. Of the original 1079 patients, tumor DNA samples from 274 (25%) patients were sequenced for *KRAS* variants. Baseline demographics between patients with available tumor DNA and those without were balanced. *KRAS* variants were detected in 55 (21%) of 274 patients. The response rate for patients with wild-type *KRAS* was 26%, regardless of treatment. In patients with *KRAS*-mutated tumors, the response rate was 8% for those receiving chemotherapy with erlotinib and 23% for those receiving chemotherapy alone (p=0.16; 95% CI for difference, -5% to 35%); the median OS was 4.4 months (95% CI, 3.4 to 12.9 months) in patients who received erlotinib and 13.5 months (95% CI, 11.1 to 15.9 months) in those who received chemotherapy alone (p=0.019).

Observational Studies

Fiala et al (2013) retrospectively analyzed patients with NSCLC who underwent *EGFR*, *KRAS*, and *PIK3CA* (phosphatidylinositide-3-kinase catalytic subunit-alpha) variant testing.[101,] Of 215 patients tested, 16 (7.4%) had a *KRAS* variant. Of 174 tested patients treated with an EGFR TKI (erlotinib or gefitinib), median PFS in 14 *KRAS*-mutated patients was 1.3 months vs 2.0 months in *KRAS* wild-type patients (n=160 [92%]); the difference was not statistically significant

(p=0.120). Median OS in this treated group was 5.7 months in *KRAS*-mutated patients and 8.2 months in *KRAS* wild-type patients, a statistically significant difference (p=0.039). The authors concluded that *KRAS* variant status might have a negative prognostic role but a predictive role was not confirmed.

Guan et al (2013) reported on 1935 consecutive patients with NSCLC who were treated at a single-institution in China.[102,] 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.[103,] *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).[37,] 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.[104,] 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.[105,] 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).[106,] 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.[107,] *KRAS* variants were detected in 75 (19%) tumors. Among patients with mutated *KRAS*, the median OS in the cetuximab-containing (n=38) and chemotherapy-alone arms (n=37) was similar (8.9 months vs 11.1 months, respectively; HR=1.00; 95% CI, 0.60 to 1.66; p=1.0). Among patients with wild-type *KRAS*, the median OS in the cetuximab-containing (n=161) and chemotherapy-alone arms (n=159) was similar (11.4 months vs 10.3 months, respectively; HR=0.96; 95% CI, 0.75 to 1.23; p=0.74). PFS also was similar in the cetuximab-containing and chemotherapy-alone arms in patients with mutated (HR=0.97; 95% CI, 0.76 to 1.24) and wild-type (HR=0.84; 95% CI, 0.50 to 1.40) *KRAS*. Response rates in the cetuximab-containing arm in patients with *KRAS*-mutated and wild-type tumors were 36.8% and 37.3%, respectively (p=0.96). Overall, there was no indication that *KRAS* variant status was predictive of cetuximab effect in NSCLC.

MEK Inhibitors

Two RCTs have compared a MEK inhibitor (with or without chemotherapy) with chemotherapy alone in patients with *KRAS*-positive advanced NSCLC after progression with first-line therapy.[107,108,] 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

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					MEK Inhibitor	Chemotherapy
Janne et al (2017)[108]; SELECT1 (NCT01933932)	25 countries in North and South America, Australia, Europe	202	2013-2016	510 patients with advanced NSCLC and progression following first-line therapy	254 assigned to selumetinib (75 mg bid) plus docetaxel (75 mg/m^2)	256 assigned to docetaxel (75 mg/m^2)
Blumenschein et al (2015)[109]; NCT01362296	U.S., Korea, 6 European countries	60	2011-2012	129 patients with stage IV NSCLC and progression following first-line platinum-containing chemotherapy	86 assigned to trametinib (2 mg/d)	43 assigned to docetaxel (75 mg/m^2)

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

Study	PFS (95% CI%)	OS (95% CI%)	ORR (95% CI), %	Adverse Events, %		
				Grade ≥3	%	Serious
SELECT1 (2017)[108]						
N	510	510	510	505		505
Selumetinib plus docetaxel	3.9 mo	8.7 mo	20.1	· Overall · Diarrhea · Asthenia · Dyspnea · Anemia · Neutropenia	· 67 · 7 · 9 · 8 · 5 · 7	49
Docetaxel	2.8 mo	7.9 mo	13.7	· Overall · Diarrhea · Asthenia · Dyspnea · Anemia · Neutropenia	· 45 · 3 · 3 · 2 · 4 · 4	32
TE (95% CI)	HR=0.93 (0.77 to 1.12)	HR=1.05 (0.85 to 1.30)	OR=1.61 (1.00 to 2.62)			
Blumenschein et al (2015)[109]						
N	129	129	129	130		130
Trametinib	12 wk	8 mo	12	· Overall · Rash · Diarrhea · Asthenia	· 41 · 6 · 5 · 5	37

Study	PFS (95% CI%)	OS (95% CI%)	ORR (95% CI), %	Adverse Events, %		
				· Hypertension · Neutropenia · Decreased neutrophils	· 9 · 0 · 0	
Docetaxel	11 wk	Not reached	12	· Overall · Rash · Diarrhea · Asthenia · Hypertension · Neutropenia · Decreased neutrophils	· 37 · 0 · 2 · 0 · 0 · 14 · 7	21
HR (95% CI)	1.14 (0.75 to 1.75)	0.97 (0.52 to 1.83)				

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

Section Summary: *KRAS* Gene Variants

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

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

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

***HER2* Gene Variants**

Mok et al (2016) reported on the biomarker subgroup analyses from the FASTACT-2 study.[110,] FASTACT-2 is a multicenter, randomized, placebo-controlled, double-blind, phase 3 study of intercalated first-line erlotinib or placebo with gemcitabine and platinum, followed by maintenance therapy with erlotinib or placebo, for Asian patients with stage IIIB or IV NSCLC. In addition to analyzing for *EGFR*, *HER2* and *HER3* biomarkers were analyzed by immunohistochemistry. Only *EGFR* variants ($p<0.001$) were predictive of outcomes; *HER2 and HER3* biomarkers were not significant.

Shen et al (2015) retrospectively reviewed 111 patients from a Uygur population who received gefitinib 250 mg once daily and were evaluated for *HER2* expression.[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 praseltinib.[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

Study; Citation	Study Type	Sites, Countries	Dates	Participants	Treatment	Median FU, mo
LIBRETTO NCT03157128 Drilon et al 2020[92,]	Single-arm, open-label phase 1-2 trial	65 centers in 12 countries	2017-2018	Patients with advanced *RET* fusion–positive NSCLC • 105 who had previously received platinum-based chemotherapy • 39 previously untreated	Selpercatinib	12.1
ARROW NCT03037385 FDA (2020)[113,]	Multicohort, open-label phase 1-2 trial	53 centers in 11 countries	Data cutoff Nov 2019	Patients with metastatic *RET* fusion positive NSCLC • 87 previously treated with platinum-based chemotherapy • 27 previously untreated	Pralsetinib	10.5

Table 17. Results of Key Nonrandomized Trials of Kinase Inhibitors in *RET-Fusion Positive* NSCLC

Study	Response (95% CI), %	PFS (95% CI), mo	Adverse Events
LIBRETTO NCT03157128 Drilon et al 2020[92,]	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)
ARROW NCT03037385 FDA (2020)[113,]	Previously treated: 57% (46% to 68%)	12.7 months (95% CI: 9.1 to NE)	Serious adverse reactions occurred in 45% of patients.

Study	Response (95% CI), %	PFS (95% CI), mo	Adverse Events
	Previously untreated: 70% (50% to 86%)		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 alteration.[7,]

Capmatinib
In 2020, FDA approved the MET inhibitor capmatinib for treatment of adult patients with metastatic NSCLC whose tumors have a mutation an alteration 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 Alterations or MET Exon 14 skipping Alteration

Study; Trial	Study Type	Country	Dates	Participants	Treatment
GEOMETRY mono-1 NCT02414139 Wolf et al 2020[114,]	Multiple-cohort, phase 2 trial			364 patients with NSCLC • 97 patients had a *MET* exon 14 skipping alteration • 210 had MET amplification	Capmatinib

Table 19. Results of Key Nonrandomized Trials of Capmatinib in MET Alterations or MET Exon 14 skipping Alteration

Study	Response	PFS (95% CI), mo	Median Duration of Response	Adverse Events
GEOMETRY mono-1 NCT02414139 Wolf et al 2020[114,]	Patients with *MET* exon 14 skipping mutation alteration: • 41% (29 to 53) of 69 patients who had received 1 or 2 lines of therapy previously • 68% (48 to 84) of 28 patients who had not received treatment previously Patients with *MET* amplification: • 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) • 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 previously treated patients and in 40% (95% CI, 16 to 68) of those who had not received treatment previously.	Previously treated: 4.1 months (95% CI, 2.9 to 4.8) No previous treatment: 4.2 months (95% CI, 1.4 to 6.9)	9.7 months	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%)

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.[115,] 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.[116,] An updated analysis of 153 patients from this data set was consistent with the earlier analusis.[117,]

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.[118,] 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.[7,]

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).[119,] 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.[120,] 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.[121,] 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).[6,]

In exploratory analyses, retrospective observational studies have reported an association between higher tumor mutational burden (TMB) and longer PFS[122,]and OS[123,] in patients receiving immunotherapy.

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

Study; Trial	Dates	Participants	Interventions	
			Nivolumab plus ipilimumab	*Chemotherapy*
CHECKMATE 227 (NCT02477826) Hellmann et al (2018)[6,]NCT02477826	2015-2016	Adult patients with histologically confirmed squamous or nonsquamous stage IV or recurrent NSCLC who had received no previous systemic anticancer therapy as primary therapy for advanced or metastatic disease and high tumor mutational burden (>10 mutations per megabase)	N=139	N=160

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

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

Study	1-year PFS	Median PFS (95% CI)	ORR (95% CI), %	Adverse Events, %	
Hellmann et al (2018)[6,] NCT02477826				Grade ≥3	%
N	299	299	299	294	
Nivolumab plus ipilimumab	42.6%	7.2 months (5.5 to 13.2)	45.3 (36.9 to 54.0)	• Any event • Any serious event • Any event leading to discontinuation	• 37 • 21 • 16

Study	1-year PFS	Median PFS (95% CI)	ORR (95% CI), %	Adverse Events, %	
Chemotherapy	5.5 %	5.5 months (4.4 to 5.8)	26.9 (20.2 to 34.4)	• Any event • Any serious event • Any event leading to discontinuation	• 36 • 11 • 6
TE (95% CI)		HR= 0.58; 97.5% CI, 0.41 to 0.81; P<0.001	Difference 18.4 (7.6– 28.8)		

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

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 treatment-related morbidity. 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. 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 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.[124,] 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.[125,] 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).[126,] 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.[127,] Table 17 summarizes the recommendations and associated quality and strength of evidence.

Table 17. Recommendations on Systemic Therapy for Stage IV NSCLC

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

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

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.[125,] 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* recommendations.[126,] *ROS1* testing is recommended for all patients with lung adenocarcinoma irrespective of clinical characteristics (strong recommendation). *BRAF*, *RET*, *HER2*, *KRAS*, and *MET* testing are not recommended as routine stand-alone tests but may be considered as part of a larger testing panel or if *EGFR*, *ALK*, and *ROS1* are negative (expert consensus opinion).

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[5,]:

- *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), dacomitinnib (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[5,]:

- *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[5,]:

- *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 *BRAF*V600E 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[5,]:

- *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), entrictinib (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."[5,] 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.[5,]

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.[5,]

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.[5,]

Immunotherapy and Tumor Mutational Burden
In the NCCN guideline (v.8.2020), nibolumab/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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01306045	Pilot Trial of Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	469	Dec 2021
NCT03225664[a]	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	102	Sep 2020
NCT02622581[a]	Clinical Research Platform into Molecular Testing, Treatment and Outcome of Non-Small Cell Lung Carcinoma Patients (CRISP)	7500	Dec 2025
NCT02117167[a]	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	999	Feb 2021
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Jun 2022
NCT02576431[a]	A Phase II Basket Study of the Oral TRK Inhibitor LOXO-101 in Subjects With NTRK Fusion-positive Tumors	203	May 2025
NCT02568267[a]	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	300	Dec 2024
NCT01639508	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	68	Jul 2021
NCT03469960	A Randomized Phase 3 Trial Comparing Continuation Nivolumab-Ipilimumab Doublet Immunotherapy Until Progression Versus Observation in Treatment-naive Patients With PDL1-positive Stage IV Non-Small Cell Lung Cancer (NSCLC) After Nivolumab-Ipilimumab Induction Treatment	1360	May 2023
NCT03037385[a]	A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors	647	Feb 2024
Unpublished			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01248247[a]	BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer	334	Jun 2020

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

CODING

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

CPT/HCPCS

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
81210	BRAF (B-RAF Proto-Oncogene, Serine/Threonine Kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
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)
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)
81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81479	Unlisted molecular pathology procedure
88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
88364	In situ hybridization (e.g., FISH), per specimen; each additional single probe stain procedure
88365	In situ hybridization (e.g., FISH), per specimen; initial single probe stain procedure

88366	In situ hybridization (e.g., FISH), per specimen; each multiplex probe stain procedure
0022U	Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider

ICD-10 Diagnoses

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

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

REVISIONS

09-28-2014	Policy added to the bcbsks.com web site on 08-29-2014. Effective on 09-28-2014, 30 days after posting.
02-08-2015	Title of policy changed from "Epidermal Growth Factor Receptor Mutation Analysis for Patients with Non-Small Cell Lung Cancer"
	Updated Description section.
	In Policy section: ▪ Added "D. Analysis of somatic mutations of the KRAS gene is considered experimental / investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC." ▪ Added "E. Testing for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2, for targeted therapy in patients with NSCLC, is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ The following CPT codes were added: 81275, 81404, 81405, 81406, 81479, 88342, 88365.
	Updated References section.
05-14-2015	Updated Description section.
	In Policy section: ▪ Added Item D, "Analysis of somatic rearrangement mutations of the ALK gene may be considered medically necessary to predict treatment response to crizotinib in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)." ▪ Added Item E, " Analysis of somatic rearrangement mutations of the ALK gene is considered experimental / investigational in all other clinical situations."

	▪ In Item G, added "Analysis" and removed "Testing", to read " Analysis for genetic alterations in the genes ROS, RET, MET, BRAF, and HER2, for targeted therapy in patients with NSCLC, is considered experimental / investigational." ▪ In Policy Guidelines, Item 2, added "The 2015", "as a category 1 recommendation that", and "and ALK rearrangement testing be performed in the workup of NSCLC in patients with histologic subtypes adenocardcinoma, large-cell carcinoma, and NSCLC not otherwise specified," and removed "a) for patients with advanced lung cancer, nonsquamous cell type, or b) when biopsy specimens are small and histology is mixed," to read, "2. The 2015 guidelines from the National Comprehensive Cancer Network recommend as a category 1 recommendation that EGFR mutation testing and ALK rearrangement testing be performed in the workup of NSCLC in patients with histologic subtypes adenocarcinoma, large-cell carcinoma, and NSCLC not otherwise specified." ▪ In Policy Guidelines, Item 3, added "The", "and ALK rearrangement" and "and ALK", and removed "Current", to read, "The 2014 guidelines issued jointly by the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend: a) EGFR mutation and ALK rearrangement testing in patients with lung adenocarcinoma regardless of clinical characteristics (e.g., smoking history); b) In the setting of fully excised lung cancer specimens, EGFR and ALK mutation testing is not recommended in lung cancers when an adenocarcinoma component is lacking (such as pure squamous cell lacking any immunohistochemical evidence of adenocarcinomatous differentiation); and c) In the setting of more limited lung cancer specimens (e.g., biopsies, cytology) where an adenocarcinoma component cannot be completely excluded, EGFR and ALK testing may be performed in cases showing squamous cell histology. Clinical criteria (e.g., young age, lack of smoking history) may be useful to select a subset of these samples for testing."
	Updated Rationale section.
	Updated References section.
01-01-2016	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Revised nomenclature to CPT code: 81275. ▪ Revised bullets under CPT/HCPCS coding.
	Updated References section.
	Added Appendix section.
11-22-2016	Updated Description section.
	In Policy section: ▪ In Item A, added "an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g.,", "[Tarceva®], gefitinib [Iressa®],", and "[Gilotrif®])" to read, "Except as noted below, analysis of 2 types of somatic mutation within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)." ▪ Added new Item B, "Analysis for the T790M mutation in the gene for the EGFR is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy." ▪ In Policy Guidelines, revised guideline dates for Items 2 and 3 and added "Genetic Counseling."
	Updated Rationale section.

	In Coding section: ▪ Added CPT code: 81276. ▪ Updated coding bullets.
	Updated References section.
10-01-2017	In Policy section: ▪ Removed Genetic Counseling information from Policy Guidelines.
	In Coding section: ▪ Added CPT code: 0022U.
03-14-2018	Updated Description section.
	In Policy section: ▪ In Item A, removed "mutation", "point mutation", and "with advanced lung adenocradcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)" and added "variants", "single-nucleotide variant", and "with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified" to read, "Except as noted below, analysis of 2 types of somatic variants within the EGFR gene – small deletions in exon 19 and a single-nucleotide variant in exon 21 (L85I4) – may be considered medically necessary to predict treatment resonse to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item B, removed "mutation" and added "variants" to read, "Analysis of the T790M variants in the EGFR gene is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy." ▪ In Item C, removed "mutation" and added "variants" to read, "Analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—is considered experimental / investigational for patients with advanced squamous cell NSCLC." ▪ In Item D, removed "mutations" and added "variants" to read, "Analysis of other *EGFR* variants within exons 18 to 24, or other applications related to NSCLC, is considered experimental / investigational." ▪ In Item E, removed "mutations" and "with advanced lung adenocarcinoma or in whom an adenocarcinoma component cannot be excluded (see Policy Guidelines)" and added "variants", "ALK inhibitor therapy (e.g.," "[Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™])", and "with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified" to read, "Analysis of somatic rearrangement variants of the *ALK* gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [Zykadia™], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item F, removed "mutations" and "clinical" and added "variants" to read, "Analysis of somatic rearrangement variants of the *ALK* gene is considered experimental / investigational in all other situations." ▪ Added new Item G, "Analysis of the *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 metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ Added new Item H, "Analysis of somatic rearrangement variants of the *ROS1* gene may be considered medically necessary to predict treatment response to ALK inhibitor

	therapy (crizotinib [Xalkori®]) in patients with metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In previous Item G (now Item I), removed "mutations" and added "variants" to read, "Analysis of somatic variants of the *KRAS* gene is considered experimental / investigational as a technique to predict treatment non-response to anti-EGFR therapy with tyrosine-kinase inhibitors and for the use of the anti-EGFR monoclonal antibody cetuximab in NSCLC." ▪ In Previous Item H (now Item J), removed "ROS" and "BRAF" to read, "Analysis for genetic alterations in the genes RET, MET, and HER2 for targeted therapy in patients with NSCLC is considered experimental / investigational." ▪ Added new Item K, "Programmed death receptor 1 (PD-1) or its ligand (PD-L1) expression analysis may be considered medically necessary as a technique to predict treatment response to drug therapy." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Updated nomenclature for CPT codes: 88342, 88365. ▪ Updated coding bullets. ▪ Removed ICD-9 codes.
	Updated References section.
09-12-2018	In Policy section: ▪ In Item A, removed "metastatic" and added "stage III or IV" to read, "Except as noted below, analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a single-nucleotide variant in exon 21 (L858R)—may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor (TKI) therapy (e.g., erlotinib [Tarceva®], gefitinib [Iressa®], or afatinib [Gilotrif®]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item E, removed "metastatic" and added "stage III or IV" to read, "Analysis of somatic rearrangement variants of the ALK gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (e.g., crizotinib [Xalkori®], ceritinib [ZykadiaTM], alectinib [Alecensa®], or brigatinib [Alunbrig™]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item G, removed "metastatic" and added "stage III or IV" to read, "Analysis of the BRAF V600E variant may be considered medically necessary to predict treatment response to BRAF or MEK inhibitor therapy (e.g., dabrafenib [Tafinlar®] and trametinib [Mekinist®]), in patients with stage III or IV metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ In Item H, removed "metastatic" and added "stage III or IV" to read, "Analysis of somatic rearrangement variants of the ROS1 gene may be considered medically necessary to predict treatment response to ALK inhibitor therapy (crizotinib [Xalkori®]) in patients with stage III or IV metastatic disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified."
	Updated References section.
02-01-2019	Policy posted 01-04-2019 with an effective date of 02-01-2019.
	Updated Description section.
	In Policy section: ▪ In Item A, removed "Except as noted below," "2 types of," "small deletions in exon 19 and a single nucleotide variant in exon 21 (L858R)" and added "in exons 18 through

	21 (e.g., G719X, L858R, T790M, S6781, L861Q)" and "osimertinib [Tagrisso]" to read, "Analysis of somatic variants in exons 18 through 21 (e.g., G719X, L858R, T790M, S6781, L861Q) within the EGFR gene may be considered medically necessary to predict treatment response to an EGFR tyrosine kinase inhibitor therapy (e.g., erlotinib [Tarceva], gefitinib [Iressa}, afatinib [Gilotrif], or osimertinib [Tagrisso]) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified." ▪ Removed Item B, "Analysis of the T790M variants in the EGFR gene is considered medically necessary as a technique to predict treatment response to osimertinib (Tagrisso™) in patients who have progressed on or after EGFR-TKI therapy." ▪ Removed Item C, "Analysis of 2 types of somatic variants within the EGFR gene—small deletions in exon 19 and a point mutation in exon 21 (L858R)—is considered experimental / investigational for patients with advanced squamous cell NSCLC." ▪ In previous Item D, now Item B, removed "18" and added "22" to read, "Analysis of other EGFR variants within exons 22 to 24, or other applications related to NSCLC, is considered experimental / investigational." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	Updated References section.
	Removed Appendix section.
03-29-21	Policy Title change from *"Molecular Analysis for Targeted Therapy of Non-Small-Cell Lung Cancer"* to *"Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer"*
	Updated Description section
	In the Policy section: • Added F. Analysis of BRAF V600E variant is considered **experimental /investigationa**l in all other situations H. Analysis of somatic rearrangement variants of the ROS1 gene is considered **experimental / investigational** in all other situations. J. Analysis of genetic alterations in the *HER2* gene for targeted therapy in patients with NSCLC is considered **experimental / investigational.** K. Analysis of NTRK gene fusions may be considered **medically necessary** to predict treatment response to entrectinib (Rozlytrek) or larotrectinib (Vitrakvi) in patients with stage III or IV disease with histologic subtypes adenocarcinoma, large cell carcinoma, and non-small-cell lung cancer not otherwise specified. L. Analysis of NTRK gene fusions is considered **experimental / investigational** in all other situations. M. 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. N. Analysis of genetic alterations in the RET gene is considered **experimental / investigational** in all other situations. O. 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. P. Analysis of genetic alterations of the MET gene is considered **experimental / investigational** in all other situations Q. 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. R. PD-L1 testing is considered **experimental /investigational** in all other situations

	S. Analysis of tumor mutational burden for targeted therapy in patients with NSCLC is considered **experimental / investigational.** • Deleted Analysis for genetic alterations in the genes *RET*, *MET*, and *HER2* for targeted therapy in patients with NSCLC is considered **experimental / investigational**. Programmed death receptor 1 (PD-1) or its ligand (PD-L1) expression analysis may be considered **medically necessary** as a technique to predict treatment response to drug therapy.
	Updated Reference section
	In Coding section • Added CPT codes: 81191, 81192, 81193, 81194, 81210, 88364, 88366 • Removed CPT code 81406
	Updated Rationale section

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