Non–Small Cell Lung Cancer, Version 5.2017

Clinical Practice Guidelines in Oncology

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Overview

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non–Small Cell Lung Cancer (NSCLC) focuses on targeted therapies and immunotherapies for metastatic NSCLC, because new recommendations were added for the 2017 updates. For example, new recommendations were added for atezolizumab, ceritinib, osimertinib, and pembrolizumab for the 2017 updates.

Abstract

This selection from the NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC) focuses on targeted therapies and immunotherapies for metastatic NSCLC, because therapeutic recommendations are rapidly changing for metastatic disease. For example, new recommendations were added for atezolizumab, ceritinib, osimertinib, and pembrolizumab for the 2017 updates.

Please Note

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Disclosures for the Non–Small Cell Lung Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Non–Small Cell Lung Cancer Panel members can be found on page 535. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.
recommendations were added for atezolizumab, ceritinib, osimertinib, and pembrolizumab.

The complete version of the NCCN Guidelines for NSCLC, available at NCCN.org, addresses all aspects of management for NSCLC. Additional sections in the complete version of the NCCN Guidelines include “Principles of Pathologic Review,” “Principles of Surgical Therapy,” “Principles of Radiation Therapy,” “Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy,” “Systemic Therapy for Advanced or Metastatic Disease,” “Cancer Survivorship Care,” “Emerging Agents for Patients with Genetic Alterations,” and “Staging.”

The NCCN Guidelines for NSCLC were first published in 1996, and are updated at least once a year by the NCCN panel; there were 5 updates from January 2016 to January 2017. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. A brief introduction to NSCLC is provided in the following paragraphs.

Lung cancer is the leading cause of cancer death in the United States. In 2017, an estimated 222,500 new cases (116,990 in men and 105,510 in women) of lung and bronchial cancer will be diagnosed, and 155,870 deaths (84,590 in men and 71,280 in women) are estimated to occur because of the disease. Only 17.7% of all patients with lung cancer are alive ≥5 years after diagnosis. However, much progress has been made recently for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, and advances in radiation therapy (RT), including stereotactic ablative RT (SABR), targeted

Text cont. on page 515.
## Sensitizing EGFR Mutation Positive

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### CLINICAL PRESENTATION

Metastatic Disease

### HISTOLOGIC SUBTYPE

- Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate)
- Smoking cessation counseling
- Integrate palliative care (See NCCN Guidelines for Palliative Care, available at NCCN.org)

### TESTING

- Molecular testing
  - EGFR mutation testing (category 1)
  - ALK testing (category 1)
  - ROS1 testing
  - Testing should be conducted as part of broad molecular profiling
  - PD-L1 testing

### TESTING RESULTS

- Sensitizing EGFR mutation positive
  - See First-Line Therapy (NSCL-18)
  - ALK positive
    - See First-Line Therapy (NSCL-20)
  - ROS1 positive
    - See First-Line Therapy (NSCL-22)
  - PD-L1 positive and EGFR, ALK, ROS1 negative or unknown
    - See First-Line Therapy (NSCL-23)
  - EGFR, ALK, ROS1, PD-L1 are negative or unknown
    - See First-Line Therapy (NSCL-24)

- Sensitizing EGFR mutation positive
  - See First-Line Therapy (NSCL-18)
  - ALK positive
    - See First-Line Therapy (NSCL-20)
  - ROS1 positive
    - See First-Line Therapy (NSCL-22)
  - PD-L1 positive and EGFR, ALK, ROS1 negative or unknown
    - See First-Line Therapy (NSCL-23)
  - EGFR, ALK, ROS1, PD-L1 are negative or unknown
    - See First-Line Therapy (NSCL-25)

### Metastatic NSCLC

#### CLINICAL PRESENTATION

- The NCCN NSCLC Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H, available online, in these guidelines, at NCCN.org).

### Metastatic NSCLC

#### CLINICAL PRESENTATION

- If repeat biopsy is not feasible, plasma biopsy should be considered.

### Metastatic NSCLC

#### CLINICAL PRESENTATION

- For performance status 0-4.

### Metastatic NSCLC

#### CLINICAL PRESENTATION

- In patients with squamous cell carcinoma, the observed incidence of EGFR mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bhamra G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet. 2008; chapter 10: unit 10.11.

### Metastatic NSCLC

#### CLINICAL PRESENTATION


### Metastatic NSCLC

#### CLINICAL PRESENTATION


### Metastatic NSCLC

#### CLINICAL PRESENTATION

- PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.
NSCL-18

**SENSITIZING EGFR MUTATION POSITIVE**

**FIRST-LINE THERAPY**

- **EGFR mutation discovered prior to first-line chemotherapy**
  - Erlotinib\(^b\) (category 1) or Afatinib\(^b\) (category 1) or Gefitinib\(^b\) (category 1)

- **Progression**
  - See Subsequent Therapy (NSCL-19)

- **Complete planned chemotherapy, including maintenance therapy, or interrupt, followed by erlotinib or afatinib or gefitinib**

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\(^a\)See Principles of Pathologic Review (NSCL-A, available online, in these guidelines, at NCCN.org).

\(^b\)For performance status 0-4.
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NSCL-19

SENSITIZING EGFR MUTATION POSITIVE

Asymptomatic

Progression[mm] → T790M testing[mm]

Symptomatic

Brain[pp]

Isolated lesion

Systemic

Multiple lesions

SUBSEQUENT THERAPY

- Consider local therapy
- Osimertinib (if T790M+)
  (category 1)
  or
- Continue erlotinib or afatinib or gefitinib[pp]

- Consider local therapy
- Osimertinib (if T790M+)
  (category 1)
  or
- Continue erlotinib or afatinib or gefitinib
- See NCCN Guidelines for CNS Cancers, available at NCCN.org

Consider local therapy
- Continue erlotinib or afatinib or gefitinib
- See subsequent therapy for multiple lesions, noted below

Osimertinib (category 1)
(if not previously given)

T790M+

See subsequent therapy for multiple lesions, noted below

T790M-

See First-line therapy options[pp]
Adenocarcinoma (NSCL-24)
Squamous cell carcinoma (NSCL-25)
or
PD-L1 expression positive (≥50%)
See First-Line Therapy (NSCL-23)

 progression

PROGRESSION OF DISEASE

See Principles of Pathologic Review (NSCL-A, available online, in these guidelines, at NCCN.org).

[mm] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

[pp] If tissue biopsy is not feasible, plasma biopsy should be considered. Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation.

[pp] Consider pulse erlotinib for carcinomatosis meningitis.

[pp] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

[pp] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
ALK REARRANGEMENT POSITIVE

**FIRST-LINE THERAPY**

- **ALK rearrangement discovered prior to first-line chemotherapy**
  - **Crizotinib** (category 1) or **Ceritinib** (category 1)

- **ALK rearrangement discovered during first-line chemotherapy**
  - Complete planned chemotherapy, including maintenance therapy, or interrupt, followed by crizotinib or ceritinib

**Progression**

See Subsequent Therapy (NSCL-21)

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*a See Principles of Pathologic Review (NSCL-A, available online, in these guidelines, at NCCN.org).

*b For performance status 0-4.
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See Principles of Pathologic Review (NSCL-A, available online, in these guidelines, at NCCN.org).

For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

Patients who are intolerant to crizotinib may be switched to ceritinib or alectinib.

If not previously given.

NSCL-21
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**ROS1 REARRANGEMENT POSITIVE**

**FIRST-LINE THERAPY**

![Diagram showing the flow of therapy options for ROS1 rearrangement positive cases](image)

- ROS1 rearrangement positive
  - Crizotinib
  - Progression

**SUBSEQUENT THERAPY**

- See First-line therapy options
- Adenocarcinoma (NSCL-24)
- Squamous cell carcinoma (NSCL-25)
- or
- PD-L1 expression positive (≥50%)
- See First-Line Therapy (NSCL-23)

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*See Principles of Pathologic Review (NSCL-A, available online, in these guidelines, at NCCN.org).*
Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
ADENOCARCINOMA, LARGE CELL, NSCLC NOS

FIRST-LINE THERAPY

PS 0-2
- Systemic therapy
- Tumor response evaluation

PS 3-4
- Best supportive care

SUBSEQUENT THERAPY

PS 0-2
- Progression
  - Systemic immune checkpoint inhibitors (preferred)
    - Nivolumab (category 1)*
    - Pembrolizumab (category 1)*
    - Atezolizumab (category 1)*
    - Other systemic therapy:
      - Docetaxel or pemetrexed or gemcitabine or ramucirumab + docetaxel

PS 3-4
- Progression
  - Best supportive care

Response or stable disease

4–6 cycles (total)
Tumor response evaluation

NSCL-24

*If not previously given.

**See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F, available online, in these guidelines, at NCCN.org).

††If pembrolizumab not previously given.

‡‡Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

§§If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

¶¶If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.
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**NSCL-25**

If not previously given.

**SS** See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F, available online, in these guidelines, at NCCN.org).

**WW** Pembrolizumab not previously given.

**Ww** Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

**Zz** If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.
therapies, and immunotherapies. Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease. The WHO divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC and small cell lung cancer (SCLC) (see the NCCN Guidelines for SCLC, available at NCCN.org). NSCLC accounts for >80% of all lung cancer cases, and it includes 2 major types: nonsquamous, including adenocarcinoma, large-cell carcinoma, and other cell types; and squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common type of lung cancer seen in the United States and is also the most frequently occurring histology in nonsmokers.

Currently, most patients with NSCLC are diagnosed with advanced cancer, although increasing use of lung cancer screening may alter the most typical stage at diagnosis. Symptoms of metastatic cancer include weight loss, bone pain, headaches, anemia, and paraneoplastic syndromes. The preliminary diagnosis of metastatic disease is based on symptoms, signs, and laboratory tests; it is aided by imaging (eg, PET/CT scan, brain MRI). Patients with widespread metastatic disease (stage IV) are usually candidates for systemic therapy (consisting of chemotherapy, targeted therapy, or immunotherapy, depending on performance status [PS] and results from biomarker testing), clinical trials, and/or palliative treatment.

Predictive and Prognostic Biomarkers

Several biomarkers have emerged as predictive and prognostic markers for NSCLC. A predictive biomarker is indicative of therapeutic efficacy, because there is an interaction between the biomarker and therapy on patient outcome. A prognostic biomarker is indicative of patient survival independent of the treatment received, because the biomarker is an indicator of the innate tumor aggressiveness (see “KRAS Mutations,” page 518).

Predictive biomarkers include the ALK fusion oncogene (fusion between ALK and other genes [eg, echinoderm microtubule-associated protein-like 4]), ROS1 gene rearrangements, and sensitizing EGFR mutations (see “Principles of Pathologic Review” in the complete version of these guidelines, available at NCCN.org [NSCL-A]). Emerging biomarkers include HER2 (also known as ERBB2) and BRAF V600E mutations, RET gene rearrangements, and high-level MET amplifications or MET exon 14 skipping mutations (see “Emerging Targeted Agents for Patients with Genetic Alterations” in the complete version of these guidelines, at NCCN.org [NSCL-H]).

EGFR Mutations

In patients with NSCLC, the most commonly found EGFR mutations are deletions in exon 19 (exon 19del [with conserved deletion of the LREA sequence] in 45% of patients with EGFR mutations) and a mutation in exon 21 (L858R in 40%). Both mutations result in activation of the tyrosine kinase domain, and both are associated with sensitivity to the small molecule tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib, and afatinib (see “EGFR TKIs,” page 519). Thus, these mutations are referred to as sensitizing EGFR mutations. Previously, erlotinib was commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib was recently reapproved by the FDA based on a phase IV study and is now available in the United States. Afatinib is an oral TKI that inhibits the entire ErbB/HER family of receptors, including EGFR and HER2. The FDA has approved afatinib for first-line treatment of patients with metastatic nonsquamous NSCLC who have sensitizing EGFR mutations.

These sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients. Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X). Primary resistance to TKI therapy is associated with KRAS mutations and ALK or ROS1 gene rearrangements. Patients with exon 20 insertion mutations are also resistant to TKIs. EGFR T790M is a mutation associated with acquired resistance to EGFR TKI therapy and has been reported in approximately 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib. Most patients with sensitizing EGFR mutations become resistant to erlotinib, gefitinib, or afatinib after approximately 9 to 13 months of EGFR TKI therapy. However, studies suggest T790M may also occur in patients who have not previously received EGFR TKI therapy, although this is a rare event.
Osimertinib is recommended (category 1) as second-line and beyond (subsequent) therapy for patients with EGFR T790M whose disease has progressed on sensitizing EGFR TKI therapy, such as, erlotinib, gefitinib, afatinib (see “Osimertinib,” page 520).\(^{37,39}\) Acquired resistance may also be associated with histologic transformation from NSCLC to SCLC and with epithelial to mesenchymal transition (see “Principles of Pathologic Review” in the complete version of these guidelines, at NCCN.org).\(^{40-42}\)

DNA mutational analysis is the preferred method to assess for EGFR status.\(^{43-45}\) Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells.\(^{46}\) Direct sequencing of DNA corresponding to exons 18 to 21 (or just testing for exons 19 and 21) is a reasonable approach; however, more sensitive methods are available.\(^{21,44,47-49}\) Mutation screening assays using multiplex PCR (eg, Sequenom’s MassARRAY system, SNaPshot Multiplex System) can detect >50 point mutations, including EGFR.\(^{50}\) Next-generation sequencing (NGS) can also be used to detect EGFR mutations.\(^{51}\)

The predictive effects of the drug-sensitive EGFR mutations—exon 19del (LREA deletion) and L858R—are well defined. Patients with these mutations have a significantly better response to erlotinib, gefitinib, or afatinib.\(^{15}\) Retrospective studies have shown an objective response rate of approximately 80% with a median progression-free survival (PFS) of 13 months to single-agent EGFR TKI therapy in patients with a bronchioloalveolar variant of adenocarcinoma and a sensitizing EGFR mutation.\(^{52}\) A prospective study has shown that the objective response rate in North American patients with nonsquamous NSCLC and sensitizing EGFR mutations (53% exon 19del [LREA deletion], 26% L858R, and 21% other mutations) is 55%, with a median PFS of 9.2 months.\(^{53}\) EGFR mutation testing is not usually recommended in patients with pure squamous cell carcinoma (SCC) unless they never smoked, if only a small biopsy specimen (ie, not a surgical resection) was used to assess histology, or if the histology is mixed.\(^{54}\) Data suggest that EGFR mutations can occur in patients with adenocarcinoma or squamous cell carcinoma, which is harder to discriminate from SCC in small specimens.\(^{54}\)

Data show that erlotinib, gefitinib, or afatinib (instead of standard first-line chemotherapy) should be used as first-line systemic therapy in patients with sensitizing EGFR mutations documented before first-line therapy.\(^{20,35,55-58}\) PFS is improved with use of EGFR TKI in patients with sensitizing EGFR mutations when compared with standard chemotherapy, although overall survival (OS) is not statistically different.\(^{20,35,36}\) Patients receiving erlotinib have fewer treatment-related severe side effects when compared with those receiving chemotherapy.\(^{35,59}\) A phase IV trial showed that gefitinib is safe and effective in patients with sensitizing EGFR mutations.\(^{16,35}\) In a phase III randomized trial, patients receiving afatinib had decreased cough, decreased dyspnea, and improved health-related quality of life compared with those receiving cisplatin/pemetrexed.\(^{55}\) Based on these data and the FDA approvals, erlotinib and gefitinib are recommended (category 1) as first-line systemic therapy in patients with sensitizing EGFR mutations.\(^{20}\) However, afatinib was potentially associated with 4 treatment-related deaths, whereas there were none in the chemotherapy group.\(^{20}\) A combined analysis (LUX 3 and LUX 6) reported a survival advantage in patients with exon 19del who received afatinib compared with chemotherapy.\(^{60}\)

### ALK Gene Rearrangements

An estimated 2% to 7% of patients with NSCLC have ALK gene rearrangements, approximately 10,000 of whom live in the United States.\(^{61}\) Patients with ALK rearrangements are resistant to EGFR TKIs but have similar clinical characteristics to patients with EGFR mutations (ie, adenocarcinoma histology, never smokers, light smokers) except that they are more likely to be men and may be younger.\(^{62}\) In these selected populations, estimates show that approximately 30% of patients will have ALK rearrangements.\(^{62,63}\) ALK rearrangements are not routinely found in patients with SCC. Although rare, patients with ALK gene rearrangements can have mixed squamous cell histology.\(^{64}\) It can be challenging to accurately determine histology in small biopsy specimens; thus, patients may have mixed squamous cell histology (or squamous components) instead of pure squamous cell. The NCCN panel recommends testing for ALK rearrangements if small biopsy specimens were used to assess histology, mixed histology was reported, or patients never smoked. A molecular diagnostic test
Crizotinib—an inhibitor of ALK, ROS1, and some MET tyrosine kinases (high-level MET amplification or MET exon 14 skipping mutation)—is FDA-approved for patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements (ie, ALK-positive disease) or ROS1 rearrangements.\textsuperscript{78–85} Crizotinib yields very high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements, including those with brain metastases.\textsuperscript{61,81,86–88} Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).\textsuperscript{87,89,90} However, a few patients have had life-threatening pneumonitis; crizotinib should be discontinued in these patients.\textsuperscript{81} Patients whose disease responds to crizotinib may have rapid improvement in symptoms (eg, cough, dyspnea, pain); median time to progression on crizotinib is approximately 7 months to 1 year.\textsuperscript{89,92}

Randomized phase III trials have compared crizotinib with standard second-line (ie, subsequent) chemotherapy (PROFILE 1007) and with standard first-line therapy (PROFILE 1014).\textsuperscript{7,41,91} First-line therapy with crizotinib improved PFS, response rate (74% vs 45%; P<.001), lung cancer symptoms, and quality of life compared with chemotherapy (pemetrexed with either cisplatin or carboplatin).\textsuperscript{81} Based on this trial, crizotinib is recommended (category 1) for first-line therapy in patients with ALK-positive NSCLC (see NSCL-20, page 509). Subsequent therapy with crizotinib improved PFS (7.7 vs 3.0 months; P<.001) and response rate (65% vs 20%; P<.001) compared with single-agent therapy (either docetaxel or pemetrexed) in patients with ALK-positive NSCLC whose disease had progressed after first-line chemotherapy.\textsuperscript{82} Based on this trial, crizotinib is recommended as subsequent therapy in patients with ALK-positive disease. The term subsequent therapy was recently substituted for second-line or beyond systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents.

For patients whose disease progresses on crizotinib, second-generation ALK inhibitors include ceritinib and alectinib; others are in development.\textsuperscript{94–104} Ceritinib is an orally active TKI of ALK, which also inhibits the insulin-like growth factor 1 (IGF-1) receptor but not MET. An expanded phase I trial showed that ceritinib was very active in 122 patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements.\textsuperscript{98} The overall response rate to ceritinib was 56% in patients who had previously received crizotinib; the median PFS was 7 months. Based on this study, ceritinib was FDA-approved for patients with ALK-positive metastatic NSCLC that progresses on or who are intolerant of crizotinib.\textsuperscript{105} The NCCN panel recommends ceritinib for patients with ALK-positive metastatic NSCLC that has progressed on crizotinib or who are intolerant to crizotinib based on the data from Shaw et al\textsuperscript{98} and FDA approval.\textsuperscript{105} For the 2017 update (Version 5), the panel also recommends (category 1) ceritinib as first-line treatment for ALK-positive metastatic NSCLC based on a recent phase III trial (see “Ceritinib,” page 521).

Alectinib is another oral TKI of ALK, which also inhibits RET but not MET or ROS1. Two phase II trials in patients with ALK rearrangements showed that alectinib was very active in those who had progressed on crizotinib,\textsuperscript{95,106} In the larger trial (138 patients) by Ou et al,\textsuperscript{95} patients on alectinib had a response rate of 50% (95% CI, 41%–59%), and median response duration of 11.2 months (95% CI, 9.6 months–not reached). For central nervous system (CNS) disease, the control rate was 83% (95% CI, 74%–91%) and the median response duration was 10.3 months (95% CI, 7.6–11.2 months). Of 84 patients with baseline CNS metastases, 23 (27%) had a complete CNS response to alectinib. Of 23 patients with baseline CNS metastases and no previous brain RT, 10 (43%) had a complete CNS response to alectinib. Most adverse events (AEs) were only grade 1 to 2 (constipation, fatigue, and peripheral edema); 4 patients (3%) had grade 3 dyspnea. One death due to intestinal perforation may have been related to alectinib. The other phase II trial in 87 patients with ALK-positive NSCLC that progressed on crizotinib reported that 48% of patients had an objective response to alectinib.\textsuperscript{106} Of 16 patients with baseline
CNS metastases, 4 (25%) achieved a complete response in the CNS; 11 had previously received RT.106 One treatment-related death occurred due to hemorrhage. Based on these studies, alectinib was FDA-approved for patients with ALK-positive metastatic NSCLC that progresses on or who are intolerant to crizotinib.107 The NCCN panel recommends alectinib (category 2A) for patients with ALK-positive metastatic NSCLC that has progressed on crizotinib or who are intolerant to crizotinib based on these 2 trials and FDA approval.95,106,107

ALK or ROS1 rearrangements and sensitizing EGFR mutations are generally mutually exclusive.68,108,109 Thus, erlotinib, gefitinib, and afatinib are not recommended as subsequent therapy in patients with ALK or ROS1 rearrangements who experience relapse on crizotinib.62,110 Likewise, crizotinib, ceritinib, and alectinib are not recommended for patients with sensitizing EGFR mutations whose disease relapses on erlotinib, gefitinib, or afatinib. For patients who experience disease progression on crizotinib, subsequent treatment for ALK-positive NSCLC includes ceritinib or alectinib (see “Ceritinib” and “Alectinib,” pages 521 and 522, and NSCL-21, page 510).87,95,111,112 Continuing crizotinib may also be appropriate for patients whose disease progresses on crizotinib.113

ROS1 Rearrangements
Although ROS1 is a distinct receptor tyrosine kinase, it is very similar to ALK and members of the insulin receptor family (see “Principles of Pathologic Review” in the complete version of these guidelines, at NCCN.org).114,115 It is estimated that ROS1 gene rearrangements occur in approximately 1% to 2% of patients with NSCLC; they occur more frequently in younger women with adenocarcinoma who are never smokers and in those who are negative for EGFR mutations, KRAS mutations, and ALK gene rearrangements (also known as triple-negative).115-117 Crizotinib is very effective for patients with ROS1 rearrangements, with response rates of approximately 70%, including complete responses.115 In 50 patients, crizotinib yielded a response rate of 66% (95% CI, 51%-79%); the median duration of response was 18 months.118 The FDA has approved crizotinib for patients with ROS1 rearrangements.118

For the 2017 update (Version 1), the NCCN panel moved the recommendation for ROS1 testing into the main algorithm (and deleted the footnote recommending ROS1 testing), added a new algorithm for ROS1, and added a new section on ROS1 to the molecular diagnostic studies section based on data showing the efficacy of crizotinib for patients with ROS1 rearrangements and on the FDA approval (see NSCL-22, page 511 and “Principles of Pathologic Review” in the complete version of these guidelines, at NCCN.org).80,115,116 Similar to testing for ALK rearrangements, testing for ROS1 is also performed using FISH.85,116,119-121 NGS can also be used to assess whether ROS1 rearrangements are present, if the platform has been appropriately designed and validated to detect ROS1 rearrangements.115 Because a companion diagnostic test has not been approved for ROS1, clinicians should use an appropriately validated test to detect ROS1.118 Alectinib and ceritinib are not effective in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib.115 Studies are ongoing regarding new agents for patients with ROS1 rearrangements whose disease becomes resistant to crizotinib.122-125

KRAS Mutations
Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have KRAS mutations; KRAS is the most common mutation.52,126-128 KRAS mutation prevalence is associated with cigarette smoking.130 Patients with KRAS mutations appear to have a shorter survival than those with wild-type KRAS; therefore, KRAS mutations are prognostic biomarkers.129,131,132 KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR TKIs; however, it does not appear to affect chemotherapeutic efficacy.52,128,133 KRAS mutations do not generally overlap with EGFR mutations, ALK rearrangements, or ROS1 rearrangements.68,134,135 Therefore, KRAS testing may identify patients who may not benefit from further molecular testing.133,136 Targeted therapy is not currently available for patients with KRAS mutations, although immune checkpoint inhibitors appear to be effective; MEK inhibitors are in clinical trials.97,127,137,138

Targeted Therapies
Specific targeted therapies are available for the treatment of advanced NSCLC.139-141 Erlotinib, gefitinib, and afatinib are small molecule inhibitors of EGFR; osimertinib targets T790M. Crizotinib is a small
molecule inhibitor that targets ALK, ROS1, and MET (ie, high-level MET amplification, MET exon 14 skipping mutation). Ceritinib is a small molecule inhibitor that targets ALK and IGF-1 receptor. Alectinib is a small molecule inhibitor that targets ALK and RET. Erlotinib, gefitinib, afatinib, crizotinib, ceritinib, alectinib, and osimertinib are oral TKIs. Other targeted therapies are being developed (see “Emerging Targeted Agents for Patients With Genetic Alterations” in the complete version of these guidelines, at NCCN.org).

**EGFR TKIs**

**Erlotinib and Gefitinib:** In 2004, erlotinib was approved by the FDA for the treatment of patients with locally advanced or metastatic NSCLC after progression on at least one prior chemotherapy regimen. The FDA has also approved the use of erlotinib as first-line therapy in patients with sensitizing EGFR mutations. Erlotinib and gefitinib are recommended (category 1) in the NSCLC algorithm as first-line therapy in patients with advanced, recurrent, or metastatic nonsquamous NSCLC who have known active sensitizing EGFR mutations regardless of their PS (see NSCL-18, page 507). These recommendations are based on a phase III randomized trial (IPASS) in which patients with sensitizing EGFR mutations who received gefitinib had increased PFS (24.9% vs 6.7%), response rate (71.2% vs 47.3%), and quality of life, with fewer side effects (eg, neutropenia) compared with those receiving chemotherapy (carboplatin/paclitaxel). Updated results from the IPASS study showed that OS was similar in patients receiving gefitinib or chemotherapy regardless of sensitizing EGFR mutation status. However, these results probably occurred because patients who had been assigned to first-line chemotherapy were able to receive TKIs as subsequent therapy if they were found to have sensitizing EGFR mutations. A phase III randomized trial (EURTAC) in European patients with metastatic NSCLC and sensitizing EGFR mutations showed increased PFS and response rate for those receiving erlotinib compared with chemotherapy. For erlotinib, the median PFS was 9.7 months compared with 5.2 months for chemotherapy (hazard ratio [HR], 0.37; 95% CI, 0.25–0.54; P<.0001). Fewer patients receiving erlotinib had severe AEs or died compared with those receiving chemotherapy.

TKIs are recommended in patients with metastatic NSCLC and sensitizing EGFR mutations, because quality of life is improved when compared with chemotherapy. Previously, erlotinib was commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib was reapproved by the FDA based on a phase IV study and is now available in the United States. Erlotinib and gefitinib are orally active TKIs that are very well tolerated by most patients. An analysis of 5 clinical trials in patients, mainly from the Western hemisphere (n=223), with advanced NSCLC (stage IIIB or IV) found that those with sensitizing EGFR mutations who received TKIs had a 67% response rate and an OS of approximately 24 months. The TORCH trial suggested that EGFR mutation testing should be performed in patients with advanced nonsquamous NSCLC. Survival was increased in patients with wild-type EGFR who received first-line chemotherapy compared with those who received erlotinib first followed by subsequent chemotherapy (11.6 vs 8.7 months). The OPTIMAL trial reported that PFS was increased in patients with sensitizing EGFR mutations who received erlotinib. ASCO recommends that patients be tested for EGFR mutations. However, the ESMO Guidelines specify that only patients with nonsquamous NSCLC (eg, adenocarcinoma) be assessed for EGFR mutations. Patients with pure SCC are unlikely to have sensitizing EGFR mutations; however, those with adenocarcinoma may have mutations.

An updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC. The data showed that erlotinib alone was associated with fewer side effects in patients with sensitizing EGFR mutations when compared with erlotinib/chemotherapy. Thus, it is appropriate to interrupt or complete planned chemotherapy and switch to erlotinib, gefitinib, or afatinib therapy in patients found to have sensitizing EGFR mutations during chemotherapy (see NSCL-18, page 507). The NCCN Guidelines do not recommend adding erlotinib, gefitinib, or afatinib to current chemotherapy based on this CALGB study. Erlotinib, gefitinib, or afatinib may be continued in patients who have progressed if patients do not have multiple systemic symptomatic lesions (see “Continuation of...
Erlotinib, Gefitinib, or Afatinib After Progression,” page 525).

A phase III trial (WJOG 5108L) assessed gefitinib versus erlotinib for patients with advanced lung cancer who had been previously treated with chemotherapy; most patients (72%) were positive for EGFR mutations. The median PFS for gefitinib versus erlotinib was 8.3 and 10.0 months, respectively, in patients positive for EGFR mutations (HR, 1.093; 95% CI, 0.879–1.358; \( P=.424 \)). The main grade 3 or 4 toxicities included rash (gefitinib: 2.2% vs erlotinib: 18.1%) and increases in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels (gefitinib: 6.1%/13.0% vs erlotinib: 2.2%/3.3%).

**Afatinib:** A randomized phase III trial reported that first-line therapy with afatinib improved PFS compared with cisplatin/pemetrexed in patients with metastatic adenocarcinoma who have sensitizing EGFR mutations (11.1 vs 6.9 months; \( P=.001 \)).\(^{32} \) The FDA approved afatinib for the first-line treatment of patients with metastatic NSCLC who have sensitizing EGFR mutations.\(^{9,157} \) Based on this phase III randomized trial and the FDA approval, the NCCN panel recommends afatinib for first-line therapy (category 1) in patients with metastatic nonsquamous NSCLC who have sensitizing EGFR mutations (see NSCL-18, page 507).\(^{17,20,112} \) Afatinib may also be continued in patients whose disease has progressed if they do not have multiple systemic symptomatic lesions (see “Continuation of Erlotinib, Gefitinib, or Afatinib After Progression,” page 525).\(^{15} \) However, afatinib is not recommended as subsequent therapy based on a phase III randomized trial (see “Second-Line and Beyond (Subsequent) Systemic Therapy,” page 526).\(^{138} \)

A phase IIB trial assessed afatinib compared with gefitinib for first-line therapy in patients with metastatic adenocarcinoma and sensitizing EGFR mutations.\(^{159} \) The PFS was essentially the same in patients receiving afatinib compared with those receiving gefitinib (median PFS: 11.0 months [95% CI, 10.6–12.9] with afatinib vs 10.9 months [95% CI, 9.1–11.5] with gefitinib; HR, 0.73; 95% CI, 0.57–0.95; \( P=.017 \)). These slight PFS differences are not clinically relevant and the NCCN Guidelines do not state that one EGFR TKI is more efficacious than another (see the NCCN Guidelines for NSCLC With Evidence Blocks, available at NCCN.org).\(^{356} \) OS data are not yet available. Patients receiving afatinib had more serious treatment-related side effects compared with those receiving gefitinib (11% [17/160] for afatinib vs 4% [7/159] for gefitinib). One patient receiving gefitinib died from treatment-related hepatic and renal failure; other deaths were not considered to be treatment-related (9% vs 6% [15/160 vs 10/159]). More patients receiving afatinib had diarrhea (13% vs 1%), whereas more patients receiving gefitinib had elevations in liver enzyme levels (0% vs 9%).

For the 2017 update (Version 1), the NCCN panel revised the afatinib evidence block for efficacy to highly effective (ie, the highest rating of 5), so the value is now the same as that for erlotinib and gefitinib (see the NCCN Guidelines for NSCLC With Evidence Blocks, available at NCCN.org). However, afatinib is rated as slightly less safe than erlotinib or gefitinib (ie, a rating of 3 for afatinib versus 4 for erlotinib and gefitinib).

**Osimertinib:** As previously mentioned, most patients with sensitizing EGFR mutations and metastatic NSCLC typically experience disease progression after approximately 9 to 13 months of erlotinib, gefitinib, or afatinib therapy.\(^{29,35–37} \) EGFR T790M is a mutation associated with acquired resistance to EGFR TKI therapy and has been reported in approximately 60% of patients with disease progression after initial response to sensitizing EGFR TKI therapy.\(^{27–34} \) Osimertinib (AZD9291) is an oral TKI that inhibits both EGFR-sensitizing mutations and T790M.

A phase III randomized trial assessed osimertinib versus platinum-pemetrexed chemotherapy in patients with EGFR T790M-positive metastatic NSCLC. Data show that osimertinib increased PFS compared with chemotherapy (10.1 vs 4.4 months; HR, 0.30; 95% CI, 0.23–0.41; \( P<.001 \)).\(^{37} \) PFS was also increased in patients with CNS metastases who received osimertinib (8.5 vs 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). In addition, the objective response rate was improved with osimertinib (71%; 95% CI, 65%–76%) compared with chemotherapy (31%; 95% CI, 24%–40%) (odds ratio for objective response, 5.39; 95% CI, 3.47–8.48; \( P<.001 \)). The disease control rate is approximately 93% with osimertinib (95% CI, 90%–96%) and approximately 74% with chemotherapy (95% CI, 66%–81%). Patients receiving osimertinib had fewer grade \( \geq 3 \) AEs compared with those receiving chemotherapy (23% vs 47% [63/279 vs 64/136]); however, there were 4 fatal events with osimertinib (respiratory failure [2],
pneumonitis, ischemic stroke) and 1 with chemotherapy (hypovolemic shock).

Data from a multicenter, single-arm phase II clinical trial indicate that osimertinib is associated with a response rate of approximately 61% (78/127; 95% CI, 52–70), PFS of 9.6 months (95% CI, 8.3–not reached), and disease control rate of approximately 95% (121/127; 95% CI, 90–98) in patients with EGFR T790M whose disease has progressed on sensitizing EGFR TKI therapy; 13% (33/253) of patients had drug-related grade ≥3 AEs with 1 fatal event from pneumonia possibly related to treatment. In patients without EGFR T790M, the response rate was 21% (13/61; 95% CI, 12–34) and the PFS was 2.8 months (95% CI, 2.1–4.3). The FDA has approved osimertinib for patients with metastatic EGFR T790M–positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy. Based on the data and FDA approval, the NCCN panel recommends osimertinib (category 1) as subsequent therapy for patients with metastatic EGFR T790M–positive NSCLC whose disease has progressed on erlotinib, gefitinib, or afatinib therapy (see “Second-Line and Beyond (Subsequent) Systemic Therapy,” page 526). For the 2017 update (Version 4), the NCCN panel revised the recommendation to category 1 (from category 2A) for osimertinib in patients with EGFR T790M–positive metastatic NSCLC based on the phase 3 randomized trial. T790M can be assessed using an FDA-approved test or other validated laboratory test done in a CLIA-approved laboratory. Data suggest that plasma genotyping (also known as liquid biopsy or plasma biopsy) may be considered instead of tissue biopsy to detect whether patients have T790M; however, if the plasma biopsy is negative, then tissue biopsy is recommended if feasible.. For the 2017 update (Version 4), the NCCN panel now also recommends osimertinib (category 1) for patients with T790M who have experienced progression with symptomatic brain metastases based on data showing an improvement..

ALK/ROS1 Inhibitors

Crizotinib: Crizotinib is approved by the FDA for patients with locally advanced or metastatic NSCLC who are positive for the ALK gene rearrangement. The approval is based on a phase II trial that showed dramatic response rates (>80%) to crizotinib in patients whose disease had previously progressed. Patients receiving crizotinib reported clinically significant improvements in pain, dyspnea, and cough. A phase III trial compared first-line crizotinib versus chemotherapy in patients with ALK rearrangements; patients receiving crizotinib had improved PFS, quality of life, and response rates compared with those receiving chemotherapy. The NCCN panel recommends first-line therapy with crizotinib (category 1) based on the results of this phase III trial and the FDA approval; the panel also feels that crizotinib is appropriate for patients with PS 0 to 4. Crizotinib may also be continued for patients with ALK rearrangements whose disease has progressed if patients do not have multiple systemic symptomatic lesions.

Crizotinib is also very effective for patients with ROS1 rearrangements with response rates of approximately 70%, including complete responses (see “ROS1 Rearrangements,” page 518). For the 2017 update (Version 1), the NCCN Panel moved the recommendation for ROS1 testing into the main algorithm (and deleted the footnote recommending ROS1 testing), added a new algorithm for ROS1, and added a new section on ROS1 to the molecular diagnostic studies section based on data showing the efficacy of crizotinib for patients with ROS1 rearrangements and on the FDA approval (see “Principles of Pathologic Review” in the complete version of these guidelines, at NCCN, org). Alectinib and ceritinib are not effective in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib.

Ceritinib: Ceritinib is approved by the FDA for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. The approval is based on an expanded phase I study (ASCEND-1) showing overall response rates of 56% to ceritinib in patients (92/163) who had previously received crizotinib; the median duration of response was 8.3 months (range, 6.8–9.7 months). Common grade 3/4 AEs included increased alanine aminotransferase (73 [30%] patients) and increased aspartate aminotransferase (25 [10%]). Some patients with CNS lesions experienced response to ceritinib. Based on the study and the FDA approval, the NCCN panel recommends ceritinib as subsequent therapy for patients with ALK-positive NSCLC that progressed after crizotinib; patients who do not
Immunotherapeutic Agents

Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-1 ligand (PD-L1), which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.\textsuperscript{171–173} The NCCN panel recommends immune checkpoint inhibitors as preferred agents for subsequent therapy based on improved OS rates, longer duration of response, and fewer AEs when compared with cytotoxic chemotherapy.\textsuperscript{171,174–176} Immune checkpoint inhibitors are associated with a delay in benefit compared with targeted therapy or cytotoxic chemotherapy. Pseudoprogession has been reported; therefore, traditional RECIST criteria may not be applicable.\textsuperscript{177} Current or former smoking status correlated with the response rate to immune checkpoint inhibitors.\textsuperscript{171,178–180} Data suggest that mismatch repair deficiency is associated with response to immune checkpoint inhibitors.\textsuperscript{181} Immune-related AEs, such as pneumonitis, may occur with immune checkpoint inhibitors.\textsuperscript{173,178,182–189} Intravenous high-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated AEs. Immune checkpoint inhibitors should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated AEs when indicated (see prescribing information).

Nivolumab: The NCCN panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic nonsquamous NSCLC that has progressed on or after first-line chemotherapy based on data from a phase III randomized trial (CheckMate-057) and FDA approval (see NSCL-24, page 513).\textsuperscript{171,190} Nivolumab inhibits PD-1 receptors.\textsuperscript{175} The category 1 recommendation for nivolumab is based on the published data from CheckMate-057 and FDA approval of nivolumab for patients with metastatic nonsquamous NSCLC. For patients receiving nivolumab, median OS was 12.2 months compared with 9.4 months for docetaxel (HR, 0.73; 95% CI, 0.59–0.89; \textit{P}<.002). The median duration of response was 17.2 months with nivolumab compared with 5.6 months for docetaxel. At 18 months, the OS rate was 39% (95% CI, 34%–45%) with nivolumab compared with 23% (95% CI, 19%–28%) with docetaxel. Fewer grade 3 to 5 AEs were reported for nivolumab (10%) compared with docetaxel (54%) in the CheckMate-057 trial.
Although many patients with metastatic non–squamous NSCLC benefit from nivolumab, those whose tumors have PD-L1 staining of 1% to ≥10% have an OS of 17 to 19 months compared with 8 to 9 months for docetaxel. For patients who did not have PD-L1 expression, there was no difference in OS for nivolumab versus docetaxel; however, nivolumab was associated with a longer duration of response and fewer side effects. To help clinicians determine which patients with nonsquamous NSCLC may benefit most from treatment with nivolumab, the FDA approved a complementary diagnostic biomarker test to assess for PD-L1 protein expression. Testing for PD-L1 is not required for prescribing nivolumab but may provide useful information.

The NCCN panel also recommends (category 1) nivolumab as subsequent therapy for patients with metastatic squamous cell NSCLC that has progressed on or after first-line chemotherapy based on data from a phase III randomized trial (CheckMate-017), FDA approval, and results of a phase II trial (see NSCL-25, page 514). In the CheckMate-017 trial, the median OS was 9.2 months with nivolumab compared with 6.0 months for docetaxel. Patients had a response rate of 20% with nivolumab compared with 9% for docetaxel (\(P = .008\)). PD-L1 expression was not associated with response to nivolumab in patients with squamous cell NSCLC. There were fewer grade 3/4 AEs with nivolumab (7%) compared with docetaxel (55%). No patients died in the nivolumab arm versus 3 deaths in the docetaxel arm.

**Pembrolizumab:** For the 2017 updates (Versions 1 and 2), the NCCN panel recommends pembrolizumab (category 1) as first-line therapy for patients with PD-L1 expression levels of ≥50% and with negative or unknown tests results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements based on a phase III randomized trial (Keynote-024) comparing pembrolizumab versus platinum-based chemotherapy; the FDA approved pembrolizumab for first-line therapy based on this trial (see NSCL-23, page 512). At 6 months, the OS rate was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (HR for death, 0.60; 95% CI, 0.41–0.89; \(P = .005\)). Responses were higher in the pembrolizumab group than in the chemotherapy group (44.8% vs 27.8%). There were fewer severe treatment-related AEs (grades 3–5) in patients receiving pembrolizumab compared with those receiving chemotherapy (26.6% vs 53.3%).

For the 2017 update (Version 1), the NCCN panel recommends (category 2A) IHC testing for PD-L1 expression before first-line treatment in patients with metastatic NSCLC with negative or unknown tests results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements. Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether patients are candidates for pembrolizumab. PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses. Unique anti–PD-L1 IHC assays are being developed for each one of the different immune checkpoint inhibitors currently in clinical trials. The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.

Ideally, PD-L1 expression levels are assessed in patients with negative or unknown test results for EGFR mutations, ALK rearrangements, or ROS1 rearrangements. Every effort needs to be made to establish the genetic alteration status. However, if the risk of biopsy is high and genetic alteration testing is not feasible and therefore technically unknown, then it is appropriate to test for PD-L1 expression levels. There are blood assays to evaluate for EGFR mutations and ALK rearrangements, although they are less sensitive than tissue assays.

The NCCN panel also recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression based on the randomized phase II/III trial (KEYNOTE-010), the phase I KEYNOTE-001 trial, and FDA approval (see NSCL-24, page 513 and NSCL-25, page 514). Pembrolizumab inhibits the PD-1 receptor.

A randomized phase II/III trial (KEYNOTE-010) assessed pembrolizumab in patients with previously treated advanced nonsquamous and squamous NSCLC who were PD-L1 positive (≥1%); most patients were current or former smokers. There were 3 arms in this trial: pembrolizumab at 2 mg/kg, pembrolizumab at 10 mg/kg, and docetaxel at 75 mg/m² every 3 weeks. The median OS was 10.4 months for the lower dose of pembrolizumab, 12.7 months for the higher dose, and 8.5 months for...
Data show that patients with nonsquamous NSCLC based on a recent phase III trial, and recent FDA approval (see NSCL-24, page 513 and NSCL-25, page 514). Testing for PD-L1 expression levels is not required for prescribing atezolizumab but may provide useful information. Atezolizumab inhibits PD-L1.

A phase III randomized trial (OAK) assessed atezolizumab versus docetaxel alone in patients with metastatic NSCLC that had progressed during or after systemic therapy. Most patients were current or former smokers and had received platinum-based chemotherapy; few patients (10%) had EGFR mutations, and ALK rearrangements were not reported. Data show that patients with nonsquamous NSCLC who received atezolizumab had improved OS compared with those receiving docetaxel (15.6 vs 11.2 months; HR, 0.73 [0.6–0.89]; \( P = .0015 \)). OS was only slightly improved in patients with squamous cell NSCLC receiving atezolizumab versus docetaxel (8.9 vs 7.7 months; HR, 0.73 [0.54–0.98]; \( P = .038 \)); however, there were fewer patients in the squamous NSCLC group compared with the nonsquamous group (222 vs 628). There were fewer treatment-related severe AEs (grades 3/4) for atezolizumab versus docetaxel (15% vs 43% \[90/609 vs 247/578\]). For the 2017 update (Version 4), the NCCN panel revised the atezolizumab evidence block for efficacy to a rating of 4 (very effective) from the previous rating of 3 (moderately effective) (see the NCCN Guidelines for NSCLC With Evidence Blocks, available at NCCN.org).

### Treatment of Recurrences and Distant Metastases

For patients with recurrent and metastatic disease, the NCCN Guidelines recommend that histologic subtype should be determined before therapy so that the best treatment can be selected (see NSCL-17, page 506). In addition, testing for genetic alterations (ie, driver events) is recommended in patients with NSCLC, because targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific genetic alterations. The number of available targeted agents is increasing. Several targeted agents, such as erlotinib, gefitinib, afatinib, and crizotinib, have category 1 recommendations for first-line therapy based on larger trials.

EGFR mutation testing (category 1) is recommended in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or NSCLC not otherwise specified (NOS), because erlotinib, gefitinib, and afatinib (category 1 for all) are recom-
mended for patients who are positive for sensitizing EGFR mutations (see NSCL-17, page 506 and NSCL-18, page 507). Testing for ALK rearrangements (category 1) is also recommended in patients with nonsquamous NSCLC, because crizotinib is recommended (category 1) for patients who are positive for ALK rearrangements. Crizotinib is also recommended for patients who are positive for ROS1 rearrangements and MET amplification. For the 2017 update (Version 1), the NCCN panel added a recommendation for testing for ROS1 rearrangements (category 2A). Testing for ROS1 has typically been performed using FISH; however, a validated NGS platform that can detect this gene fusion may also be used. The NCCN panel recommends that EGFR mutation testing be performed as part of broad molecular profiling (eg, multiplex mutation screening assays or NGS). Testing for ALK gene rearrangements can be performed with FISH or with NGS if the platform is validated and can identify gene fusions. For the 2017 update (Version 1), the NCCN panel also added a recommendation for upfront PD-L1 expression testing before first-line therapy in patients with metastatic NSCLC to assess whether patients are candidates for immune checkpoint inhibitors (see “Pembrolizumab,” page 523).

As previously mentioned, recommendations from an international panel suggest that general histologic categories be avoided (eg, NSCLC), because more effective treatment can be selected when the histology is known. Patients with pure squamous cell carcinoma do not seem to have ALK rearrangements, ROS1 rearrangements, or sensitizing EGFR mutations; therefore, routine testing is not recommended in these patients. However, testing for ALK rearrangements, ROS1 rearrangements, or EGFR mutations can be considered in patients with squamous cell carcinomas who never smoked and whose histology was determined using small biopsy specimens or mixed histology specimens. Treatment recommendations and eligibility criteria for patients with squamous cell carcinoma are also described in the complete version of the NCCN Guidelines.

**Continuation of Erlotinib, Gefitinib, or Afatinib After Progression**

Previously, erlotinib was commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib was reapproved by the FDA based on a phase IV study and is now available in the United States. Patients may continue to derive benefit from erlotinib, gefitinib, or afatinib after disease progression; discontinuation of these TKIs leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan). This strategy mirrors the experience in other oncogene-addicted cancers, particularly HER2-amplified breast cancer. In women with HER2-amplified breast cancer who have had disease progression on trastuzumab, improved radiographic response rate, time to progression, and OS are observed when conventional chemotherapy is added to trastuzumab.

After development of acquired resistance in patients with lung adenocarcinoma and sensitizing EGFR mutations, erlotinib, gefitinib, or afatinib may be continued, but osimertinib is also an option for select patients; local therapy should be considered (eg, stereotactic radiosurgery to brain metastases or other sites, SABR for thoracic disease). The NCCN panel recommends continuing erlotinib, gefitinib, or afatinib and considering local therapy in patients with asymptomatic progression; however, treatment varies for patients with symptomatic progression (see NSCL-19, page 508). For the 2017 updates (Versions 1 and 4), the NCCN panel revised the recommendations for patients with sensitizing EGFR mutations whose disease has progressed on erlotinib, gefitinib, or afatinib. Osimertinib is now recommended (category 1) for patients with symptomatic brain metastases. Another option is to continue use of erlotinib, gefitinib, or afatinib for these patients; however, additional therapy may be added or substituted (eg, local therapy, systemic therapy). First-line systemic therapy options are recommended for patients with multiple symptomatic lesions who are negative for T790M; osimertinib is recommended (category 1) for patients positive for T790M.

Accumulating data suggest how cancers become resistant to EGFR inhibitors. The most common
known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, or afatinib. Therefore, if patients are T790M-positive, osimertinib is recommended (category 1) and erlotinib, gefitinib, or afatinib are discontinued. Amplification of the MET oncogene is another validated resistance mechanism. To overcome resistance, EGFR must still be inhibited. In the case of MET amplification, new inhibitors must be added to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely et al show that when cancers start to progress, which were once sensitive to EGFR inhibitors, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer. Thus, continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.

Second-Line and Beyond (Subsequent) Systemic Therapy

The phrase subsequent therapy was substituted for the terms second-line, third-line, and beyond systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents. Subsequent systemic therapy regimens for patients who have disease progression during or after first-line therapy are described in the NSCLC algorithm and depend on the specific genetic alteration, the histologic subtype, and whether the patient has symptoms (see the complete version of these guidelines available at NCCN.org). For the 2017 update (Version 1), the NCCN panel now recommends response assessment of known sites of disease with CT (with contrast) every 6 to 12 weeks in patients receiving subsequent therapy. Note that traditional RECIST 1.1 criteria are used to assess response for most types of systemic therapy, but different response criteria may be useful for assessing response in patients receiving immunotherapy.

The NCCN panel recommends immune checkpoint inhibitors as preferred agents for subsequent therapy in patients with metastatic NSCLC based on improved survival rates, longer duration of response, and fewer AEs compared with cytotoxic chemotherapy (see “Nivolumab,” “Pembrolizumab,” and “Atezolizumab,” pages 522, 523, and 524, respectively). Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.

The NCCN panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on a phase III randomized trial (CheckMate-057) and FDA approval. The NCCN panel recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC and PD-L1 expression based on a phase II/III randomized trial (KEYNOTE-010) trial, KEYNOTE-001 trial, and FDA approval. The NCCN panel also recommends atezolizumab (category 1) as subsequent therapy for patients with metastatic nonsquamous or squamous NSCLC based on a phase III randomized trial (OAK), data from a phase II trial (POPLAR), and FDA approval.

The NCCN panel recommends osimertinib (category 1) as subsequent therapy for patients with metastatic EGFR T790M–positive NSCLC that has progressed on erlotinib, gefitinib, or afatinib therapy based on data and FDA approval (see “Osimertinib,” page 520). Osimertinib (AZD9291) is an oral TKI that inhibits both EGFR-sensitizing mutations and T790M. Data from a phase III trial report that osimertinib is associated with a response rate of approximately 71% and disease control rate of approximately 93% (95% CI, 90%–96%) in patients whose disease has progressed on sensitizing EGFR TKI therapy; 23% of patients had drug-related grade ≥3 AEs with 4 fatal events. The FDA has approved osimertinib for patients with metastatic EGFR T790M–positive NSCLC, as detected by an FDA-approved test, that has progressed on or after EGFR TKI therapy. Most patients with sensitizing EGFR mutations and metastatic NSCLC typically experience disease progression after approximately 9 to 13 months of erlotinib or gefitinib therapy.

EGFR T790M is associated with acquired resistance to TKI therapy and has been reported in approximately 60% of patients with disease progression after initial response to sensitizing EGFR TKI therapy. T790M can be assessed using an FDA-approved test or other validated laboratory test performed in a CLIA-approved laboratory.

For patients with sensitizing EGFR mutations who progress during or after first-line targeted therapy, recommended therapy depends on whether the progression is asymptomatic or symptomatic and...
includes continuing erlotinib, afatinib, or gefitinib with (or without) local therapy; osimertinib; or a first-line systemic therapy regimen for either nonsquamous or squamous cell NSCLC (such as cisplatin/pemetrexed or cisplatin/gemcitabine, respectively). For the 2017 update (Version 4), the NCCN panel now also recommends osimertinib (category 1) for patients with T790M who have brain metastases.\textsuperscript{17,164–166} Data suggest that an afatinib/cetuximab regimen may be useful for patients whose disease has progressed after receiving EGFR TKI therapy and chemotherapy.\textsuperscript{238} Patients with T790M-positive and T790M-negative tumors had a similar response rate to an afatinib/cetuximab regimen (32% vs 25%; \(P=0.341\)). The NCCN panel recommends (category 2A) considering an afatinib/cetuximab regimen for patients whose disease has progressed after receiving EGFR TKIs and chemotherapy based on these data.

Among patients with sensitizing EGFR mutations, no improvement in OS has been noted in the phase III trials assessing pembrolizumab, nivolumab, or atezolizumab compared with docetaxel, but there were not enough patients with these mutations to determine whether there were statistically significant differences (see next paragraph).\textsuperscript{171,176,201,239} Immuno-therapy was not worse than chemotherapy and was better tolerated. In the phase III trials for pembrolizumab, nivolumab, or atezolizumab versus docetaxel as subsequent therapy for patients with metastatic NSCLC, subset analyses were performed in patients with EGFR mutations to determine the best subsequent therapy.\textsuperscript{171,176,201} The HRs for OS do not favor docetaxel over nivolumab (HR, 1.18; CI, 0.69–2.0), pembrolizumab (HR, 0.88; CI, 0.45–1.7), or atezolizumab (HR, 1.24; CI, 0.7–2.2); the CIs for the HRs are wide probably because there were so few patients with EGFR mutations. The HRs for PFS do favor docetaxel for patients with EGFR mutations compared with either pembrolizumab (HR, 1.79; CI, 0.94–3.42) or nivolumab (HR, 1.46; CI, 0.90–2.37). But again, the CIs are wide. The evidence is weak for recommending docetaxel, pembrolizumab, nivolumab, or atezolizumab as subsequent therapy for patients with EGFR mutations. Data suggest that patients with EGFR mutations or ALK rearrangements have a low response rate to PD-1 or PD-L1 inhibitors when compared with patients without these genetic alterations (response rate, 3.6% vs 23%, respectively).\textsuperscript{239}

For patients with ALK rearrangements whose disease progresses during or after first-line targeted therapy, recommended therapy also depends on whether the progression is asymptomatic or symptomatic and includes continuing crizotinib with (or without) local therapy; ceritinib; alectinib; or a first-line systemic therapy regimen for either nonsquamous or squamous cell NSCLC. After further progression on subsequent targeted therapy, first-line combination chemotherapy options for nonsquamous NSCLC or squamous cell carcinoma are recommended for patients with PS of 0 to 1, such as cisplatin/pemetrexed or cisplatin/gemcitabine (both are category 1), respectively.\textsuperscript{139,240} Other chemotherapy options are also recommended for patients with PS 2, such as docetaxel (see “Systemic Therapy for Advanced or Metastatic Disease” in the complete version of these guidelines, at NCCN.org).

Most patients with NSCLC do not have ALK rearrangements, ROS1 rearrangements, or sensitizing EGFR mutations. For patients with all histologic subtypes and PS of 0 to 2 but without these genetic alterations who have disease progression during or after first-line therapy, recommended subsequent systemic therapy options include nivolumab (category 1), pembrolizumab (category 1), atezolizumab (category 1), docetaxel with (or without) ramucirumab, or gemcitabine if not already given; pemetrexed is recommended for patients with nonsquamous NSCLC. For the 2017 update (Version 4), the NCCN panel revised the recommendation for atezolizumab to category 1 (from category 2A) as subsequent therapy. The NCCN panel recommends immune checkpoint inhibitors—nivolumab, pembrolizumab, and atezolizumab—as preferred options for subsequent therapy for all histologic subtypes based on improved survival rates, longer duration of response, and fewer AEs compared with cytotoxic chemotherapy (see “Nivolumab,” “Pembrolizumab,” and “Atezolizumab,” pages 522, 523, and 524).\textsuperscript{171,175,201}

For the 2017 update (Version 2.2017), the NCCN panel deleted the recommendation for erlotinib as subsequent therapy (and as switch maintenance therapy) for patients with nonsquamous NSCLC and PS 0 to 2 but without EGFR mutations based on results from a phase III randomized trial (IUNO) and revised indication by the FDA. The data showed that OS and PFS were not improved in patients receiving erlotinib compared with
Pemetrexed is recommended for subsequent therapy for patients with squamous cell NSCLC.\textsuperscript{175} In addition, only 7% of patients receiving nivolumab had grade ≥3 AEs. Erlotinib and afatinib are not recommended as second-line therapy for squamous cell carcinoma based on a phase III randomized trial showing low response rates and because they are less efficacious and safe compared with other available options.\textsuperscript{158}

If patients with either ALK fusions or sensitizing EGFR mutations progress with symptomatic systemic multiple lesions after therapy with crizotinib, erlotinib, gefitinib, or afatinib and/or after ceritinib, alectinib, or osimertinib, then first-line doublet chemotherapy options are recommended for either nonsquamous NSCLC or squamous cell carcinoma.\textsuperscript{250} Erlotinib, gefitinib, or afatinib may be continued in patients with sensitizing EGFR mutations whose disease has progressed after first-line therapy.\textsuperscript{15,218-220} Osimertinib is recommended for patients with T790M whose disease becomes resistant to erlotinib, afatinib, or gefitinib.\textsuperscript{39} Afatinib/cetuximab may be considered for patients with sensitizing EGFR mutations whose disease has progressed after EGFR TKI therapy and chemotherapy.\textsuperscript{238} Ceritinib or alectinib is recommended in patients with ALK-positive NSCLC whose disease has progressed after first-line therapy with crizotinib or who are intolerant to crizotinib.\textsuperscript{95,98} Nivolumab, pembrolizumab, atezolizumab, docetaxel with or without ramucirumab (category 2B for both), gemcitabine (category 2B), or pemetrexed (nonsquamous only) (category 2B) are recommended for subsequent therapy after second disease progression in patients with advanced NSCLC and PS 0 to 2 if these agents have not already been given.\textsuperscript{222,246,251,252}

References


Gainor JF, Shaw AT, Sc点缀 U. et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway inhibitors.


## Individual Disclosures for the Non–Small Cell Lung Cancer Panel

<table>
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The NCCN Guidelines Staff have no conflicts to disclose.

The following individuals have disclosed that they have an Employment/Governing Board, Patent, Equity, or Royalty conflict:

Robert C. Doebelie, MD, PhD: Abbott Molecular
Billy W. Loo Jr, MD, PhD: Stanford University, and TibraRay, Inc.