ABSTRACT

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (NSCLC) provide recommended management for patients with NSCLC, including diagnosis, primary treatment, surveillance for relapse, and subsequent treatment. Patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer. This selection from the NCCN Guidelines for NSCLC focuses on targeted therapies for patients with metastatic NSCLC and actionable mutations.

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Non–Small Cell Lung Cancer, Version 3.2022

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

The complete NCCN Guidelines for Non–Small Cell Lung Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN 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 530. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Overview

Lung cancer is the leading cause of cancer death in the United States.1,2 In 2022, an estimated 236,740 new cases (117,910 in men and 118,830 in women) of lung and bronchial cancer will be diagnosed, and 130,180 deaths (68,820 in men and 61,360 in women) are estimated to occur because of the disease.1 During the COVID pandemic, the diagnosis and treatment of lung cancer have been hampered; however, this has not been reflected in the 2022 estimates for incidence and mortality because of the typical delays in collecting, calculating, and reporting the data.1 Only 21.7% of all patients with lung cancer are alive 5 years or more after diagnosis, which includes patients with both non–small cell lung cancer (NSCLC) and small cell lung cancer.3 From 2010 to 2016, the overall 5-year relative survival rate for NSCLC was 26.5% in the United States.4 Recommended management of NSCLC is described in the complete version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC, which includes the algorithm and the supporting discussion text. This selection from the NCCN Guidelines for NSCLC focuses on targeted therapies for patients with metastatic NSCLC and actionable mutations (to view the complete and most recent version of these Guidelines, visit NCCN.org).

Much progress has been made recently for lung cancer, such as screening; minimally invasive techniques for diagnosis and treatment; advances in radiation therapy (RT), including stereotactic ablative radiotherapy; new targeted therapies; and new immunotherapies.5–10 These new treatments are reflected in the improved survival rates for patients with NSCLC. From 2015 to 2016, 2-year relative survival for NSCLC was 42% compared with 34% from 2009 to 2010.11 From 1990 to 2019, the death rate from lung cancer dropped by 56% in men; from 2002 to 2019, the death rate dropped by 32% in women.1 Patients with metastatic lung cancer who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range from 15% to 50%, depending on the biomarker.10,12–25 Thus, death rates for lung cancer have been declining, although there are still more deaths from lung cancer than from breast, prostate, colorectal, and brain cancers combined together.1 Common symptoms of lung cancer include cough, hemoptysis, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease.25

These NCCN Guidelines for NSCLC were first published in 1996.27 Subsequently, the NCCN Guidelines have been updated at least once a year by the NCCN NSCLC Panel; there were 7 updates for the 2021 guidelines. The
“Summary of the Guidelines Updates” (available at NCCN.org) describes the most recent revisions to the algorithms, which have been incorporated into this updated Discussion text. For example, the NCCN NSCLC Panel now recommends molecular testing in eligible patients with metastatic NSCLC for novel epidermal growth factor (EGFR) mutations, including EGFR S768I, L861Q, and/or G719X, based on data showing the efficacy of certain EGFR tyrosine kinase inhibitors (TKIs) for patients with these mutations.

All the systemic therapy regimens have been categorized by preference—based on the biomedical literature and experience of the panel members—using the following categories: (1) preferred interventions; (2) other recommended interventions; and (3) interventions that are useful in certain circumstances. These preference categories emphasize the preferred regimens in clinical practice and do not replace the NCCN categories of evidence and consensus, such as category 1 or category 2A. The preference categories and the categories of evidence/consensus are 2 separate sets of recommendations.

Category 1 recommendations indicate uniform NCCN consensus (at least 85% of the NCCN Member Institutions on the panel) that the intervention is appropriate based on high-level evidence, such as randomized phase 3 trials. Category 2A recommendations indicate uniform NCCN consensus that the intervention is appropriate based on lower level evidence, such as phase 2 trials. It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2B recommendations indicate NCCN consensus (50%–85% of the NCCN Member Institutions) that the intervention is appropriate based on lower level evidence. Category 3 recommendations indicate major NCCN disagreement (at least 50% of the NCCN Member Institutions) that the intervention is appropriate based on any level of evidence. For a category 3 recommendation to remain in the guideline, at least 25% of the NCCN Member Institutions on the panel must vote that the intervention is appropriate. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

**Literature Search Criteria and Guidelines Update Methodology**

An electronic search of the PubMed database was performed to obtain key literature in NSCLC using the following...
search term: “non-small cell lung cancer.” The PubMed database was chosen because it is the most widely used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

Data from key PubMed articles selected by the NCCN NSCLC Panel for review during the NCCN Guidelines update meeting, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, recommendations are based on the panel’s review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available online (at NCCN.org).

**Metastatic NSCLC**

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-18, page 498).[^29] Biomarker testing for somatic, disease-associated variants/mutations is recommended before starting therapy, if feasible, in eligible patients with metastatic NSCLC, because targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific somatic genomic alterations. For the 2022 update (Version 1), the panel added a caveat that if molecular testing results are pending and patients require an urgent start to therapy, clinicians can consider holding immunotherapy for one cycle (ie, just use platinum-based chemotherapy regimens). In the NCCN Guidelines, many targeted agents are recommended for first-line therapy in patients with specific actionable mutations, such as afatinib, alec-tinib, brigatinib, capmatinib, ceritinib, crizotinib, dacomitinib (± trametinib), entrectinib, erlotinib, gefitinib, lorlatinib, osimertinib, pralsetinib, selpercatinib, and tepotinib.[^30] The number of available targeted agents is increasing. For example, newer agents are now recommended as second-line and beyond (subsequent) therapy options—such as amivantamab, mobocertinib, and sotorasib—in patients with specific actionable driver mutations.
Additional targeted therapies for patients with other somatic genomic alterations are also recommended, although there is less evidence for these agents and they have not been FDA approved for lung cancer; therefore, they are referred to as emerging biomarkers (see NSCL-I, page 505). The following targeted agents are recommended as monotherapy options for patients with metastatic NSCLC and emerging somatic genomic alterations:

1. capmatinib, crizotinib, or tepotinib for high-level MET amplification; and
2. ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki for ERBB2 (HER2) mutations (see NSCL-I, page 505).31–36 Certain targeted therapies, such as alectinib, brigatinib, ceritinib, lorlatinib, and osimertinib, are recommended as subsequent therapies (if not previously given) for patients with the indicated driver mutations whose disease becomes resistant to first-line targeted therapies; other targeted therapies are being investigated for resistance.

Biomarker testing for actionable oncogenic driver mutations is recommended in the NCCN Guidelines based on the improved outcomes associated with use of targeted therapy in eligible patients with metastatic NSCLC. It is important to note that (1) several different tests may be used to identify the same biomarker, including FDA-approved biomarker tests and validated laboratory tests done in CLIA-approved laboratories; and (2) biomarker testing is rapidly changing and improving. The NCCN NSCLC Panel also recommends upfront testing for PD-L1, which is an immune biomarker (category 1) before first-line therapy in patients with metastatic NSCLC to assess whether patients are candidates for immune checkpoint inhibitors (ICIs). In 2020, the NCCN Panel deleted tumor mutation burden as an emerging immune biomarker for patients with metastatic NSCLC based on clinical trial data and other issues.37

Molecular testing is recommended in all patients with metastatic nonsquamous NSCLC and NSCLC not otherwise specified (NOS). Compared with patients with nonsquamous NSCLC, those with squamous cell carcinoma have fewer actionable mutations (eg, ALK rearrangements, the common EGFR mutations) when considered as individual mutations. However, the cumulative incidence of targetable molecular alterations in squamous cell carcinoma across all alterations ranges from 2% to 10%; therefore, molecular testing should be considered in these patients, particularly if a diagnosis is based on a small sampling.38–41 The panel recommends that molecular testing be considered in all patients with
metastatic NSCLC squamous cell carcinoma and not just those with certain characteristics, such as never smoking status and mixed histology. Treatment recommendations and eligibility criteria for patients with nonsquamous NSCLC, NSCLC NOS, and squamous cell carcinoma are described in the full NCCN Guidelines (available at NCCN.org).

Single-agent targeted therapy is recommended for patients with actionable driver mutations (ie, ALK fusion, EGFR activating mutations, METex14 skipping, NTRK1/2/3 fusions, RET rearrangements, ROS1 rearrangements) or those with emerging driver mutations. Chemotherapy/immunotherapy regimens are recommended for patients without targetable somatic variants/mutations. Chemotherapy/immunotherapy regimens, such as pembrolizumab/carboplatin (or cisplatin)/pemetrexed, are recommended for patients with metastatic nonsquamous NSCLC and negative test results for actionable driver mutations (also known as wild-type), regardless of PD-L1 expression.

Testing for Molecular Biomarkers
Molecular testing is used to test for oncogenic genomic driver events for which targeted therapies are available; these somatic genomic alterations (also known as molecular biomarkers) include gene mutations and fusions. Testing for certain biomarkers is also recommended for eligible patients with resected early-stage and locally advanced NSCLC (to view the complete and most recent version of these Guidelines, visit NCCN.org). For the 2022 update (Version 1), the NCCN NSCLC Panel added content about molecular testing. For example, the panel added a definition for broad molecular profiling for NSCLC as molecular testing that identifies all of the classic actionable biomarkers described in the algorithm (eg, ALK, BRAF, EGFR, KRAS, METex14 skipping, NTRK1/2/3, RET, ROS1)—using either a single assay or a combination of a limited number of assays—and optimally also identifies the emerging biomarkers (eg, high-level MET amplification, ERBB2 mutations; see NSCL-18 and NSCL-I, pages 498 and 505). Tiered KRAS testing approaches, based on the low prevalence of co-occurring biomarkers, are acceptable. Broad genomic profiling may be used to assess for mechanisms of resistance in patients who have had disease progression on targeted therapy. In addition, broad molecular profiling may be used to distinguish separate primary lung cancers from intrapulmonary

<table>
<thead>
<tr>
<th>ALK REARRANGEMENT POSITIVE</th>
<th>SUBSEQUENT THERAPY</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
<td>Consider definitive local therapy (eg, SABR or surgery) for limited lesions†.</td>
</tr>
<tr>
<td></td>
<td>Continue alectinib or brigatinib or lorlatinib</td>
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<tr>
<td></td>
<td>Lorlatinib (ALK G1202R)</td>
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<tr>
<td></td>
<td>Consider definitive local therapy (eg, SRS) for limited lesions††</td>
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<tr>
<td></td>
<td>Continue alectinib or brigatinib or lorlatinib</td>
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<tr>
<td></td>
<td>Lorlatinib (ALK G1202R)</td>
</tr>
<tr>
<td>Systemic</td>
<td>NCCN Guidelines for CNS Cancers†</td>
</tr>
<tr>
<td></td>
<td>Consider definitive local therapy (eg, SABR or surgery)††</td>
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<tr>
<td></td>
<td>Continue alectinib or brigatinib or lorlatinib</td>
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<tr>
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<td>Lorlatinib (ALK G1202R) or Therapy for multiple lesions, below</td>
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<tr>
<td></td>
<td>Lorlatinib (if not previously given)</td>
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<tr>
<td>Symptomatic</td>
<td>Systemic therapy††</td>
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<td></td>
<td>Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)</td>
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</tbody>
</table>

†IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-G*).

‡Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-L*).

††Limited number is undefined but clinical trials have included 3 to 5 metastases.

†‡Therm Ablation Therapy (NSCL-D*).

†‡‡Thermal Ablation Therapy (NSCL-C*).
metastases. Broad genomic profiling may also help determine eligibility for certain molecularly driven clinical trials.

The various testing methods that may be used to assess for the different biomarkers are described in the algorithm. Broad molecular profiling systems may be used to simultaneously test for multiple biomarkers. Next generation sequencing (NGS) (also known as massively parallel sequencing) is a type of broad molecular profiling system that can detect panels of mutations and gene fusions if the NGS platforms have been designed and validated to detect these somatic genomic alterations.\textsuperscript{46–54} It is important to recognize that NGS requires quality control as much as any other diagnostic technique; because it is design dependent, the panel of genes and abnormalities detected with NGS will vary depending on the design of the NGS platform. For example, some NGS platforms can detect both mutations and gene fusions, as well as copy number variation, but they are not uniformly present in all NGS assays being conducted either commercially or in institutional laboratories.

Several systems are available to classify the pathogenicity of variants. One classification system uses (1) variants with strong clinical significance (tier I), (2) variants with potential clinical significance (tier II), (3) variants of unknown clinical significance (tier III), and (4) variants that are benign or likely benign (tier IV).\textsuperscript{18} Another classification system uses pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely not pathogenic (likely benign), and not pathogenic (benign); this schema is most commonly applied to germline alterations, with some adoption in somatic testing interpretation.\textsuperscript{56,57} Laboratories that adopt either approach (or others) typically do not report alterations that are classified as not pathogenic/tier IV.

Molecular testing methods, such as NGS or Sanger, can identify VUS alterations, while targeted assays generally do not. For the 2022 update (Version 1), the NCCN Guidelines now clarify that any variant that is classified as VUS should not be used to select targeted therapy even if the VUS occurs in a gene in which other variants are clinically actionable.

**Targeted Therapies**

Specific targeted therapies are available for the treatment of eligible patients with metastatic NSCLC (see NSCL-J, page 506).\textsuperscript{58–60} Afatinib, alectinib, brigatinib, cabozantinib, capmatinib, ceritinib, crizotinib, dacomitinib, dacomitinib, entrectinib, erlotinib, gefitinib, larotrectinib, lorlatinib, osimertinib, pralsetinib, selpercatinib, tepotinib, and trametinib are oral TKIs. Erlotinib, gefitinib, afatinib, and...
dacomitinib inhibit EGFR mutations (such as exon 19 deletions, L858R, S768I, L861Q, G719X); osimertinib inhibits these EGFR mutations and T790M.61 Cetuximab is a monoclonal antibody that targets EGFR. Alectinib inhibits ALK and RET rearrangements.62 Brigatinib inhibits various ALK rearrangements and other targets.63 Ceritinib inhibits ALK and ROS1 rearrangements. Crizotinib inhibits ALK rearrangements, ROS1 rearrangements, and MET tyrosine kinases (ie, high-level MET amplification, METex14 skipping mutation). Lorlatinib inhibits ALK and ROS1 rearrangements.64–67 Dabrafenib inhibits BRAF p.V600E mutations; trametinib inhibits MEK; both agents inhibit different kinases in the RAS/RAF/MEK/ERK pathway.68–69 Entrectinib and larotrectinib inhibit TRK fusion proteins.70–72 Capmatinib and tepotinib inhibit several MET tyrosine kinases including METex14 skipping mutations and high-level MET amplification.31,34,73–74 Selpercatinib, pralsetinib, and cabozantinib inhibit RET rearrangements.75–77 Bevacizumab and ramucirumab are recombinant monoclonal antibodies that target the vascular endothelial growth factor (VEGF) or VEGF receptor, respectively. Flare phenomenon may occur in some patients who discontinue targeted therapies for ALK, EGFR, MET exon 14 skipping, RET, or ROS1 variants/mutations. If disease flare occurs, then the targeted therapies should be restarted.73–82

Targeted therapies are recommended for patients with metastatic NSCLC and specific oncogenic drivers, independent of PD-L1 levels. Patients with metastatic NSCLC and PD-L1 expression levels of 1% or more—but who also have a targetable driver oncogene molecular variant (ie, EGFR exon 19 deletions, EGFR L858R, ALK)—should receive first-line targeted therapy for that oncogene and not first-line ICIs, because targeted therapies yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, targeted therapy is better tolerated, and these patients are unlikely to respond to ICIs.40,83,84 Molecular testing results for the actionable oncogenic mutations should be known before starting systemic therapy with ICI regimens in eligible patients with advanced NSCLC, if clinically feasible. If it is not feasible to do molecular testing, then patients are treated as though they do not have driver oncogenes.40,83–86 For the 2022 update (Version 1), the panel add a caveat that if molecular testing results are pending and patients require an urgent start to therapy, clinicians should consider holding immunotherapy for one cycle (ie, just use platinum-based chemotherapy regimens). Monitoring is
recommended during initial therapy with response assessment with CT, with or without contrast, of known or high-risk sites of disease after 2 cycles and then every 2 to 4 cycles. Likewise, monitoring is also recommended during maintenance or subsequent therapy with CT, with or without contrast, every 6 to 12 weeks.

Oral TKIs That Inhibit ALK Rearrangements

About 5% of patients with NSCLC have ALK gene rearrangements. The NCCN NSCLC Panel recommends ALK rearrangement testing (category 1) in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents for patients with ALK rearrangements. ALK testing should be considered in patients with metastatic squamous cell carcinoma. The NCCN NSCLC Panel recommends 5 agents for patients with ALK-positive metastatic NSCLC—alecinitib, brigatinib, ceritinib, crizotinib, and lorlatinib—based on clinical trial data and FDA approvals, which are described in the following sections.

**Alectinib**

Alectinib is a second-generation oral TKI that inhibits ALK rearrangements.62

**First-Line Therapy**

**ALEX**, a phase 3 randomized trial, assessed first-line therapy with alectinib versus crizotinib in 303 patients with ALK-positive advanced NSCLC including those with asymptomatic central nervous system (CNS) disease.87 Disease progression or death occurred in fewer patients receiving alectinib (41% [62/152]; median follow-up of 18.6 months) when compared with crizotinib (68% [102/151]; median follow-up of 17.6 months). The hazard ratio (HR) was 0.47 (95% CI, 0.34–0.65; P<.001) for disease progression or death. Progression-free survival (PFS) was significantly increased with alectinib (68.4%; 95% CI, 61.0%–75.9%) versus crizotinib (48.7%; 95% CI, 40.4%–56.9%). The median PFS was not reached for alectinib (95% CI, 17.7–not reached) when compared with crizotinib at 11.1 months (95% CI, 9.1–13.1). Fewer patients receiving alectinib had CNS progression (12% [18/152]) versus crizotinib (45% [68/151]). Response rates were 83% (126/152) in the alectinib group versus 75% (114/151) in the crizotinib group (P=.09). Patients receiving alectinib had fewer grade 3 to 5 adverse events when compared with crizotinib (41% [63/152] vs 50% [75/151], respectively) even though patients receiving alectinib for a longer duration than crizotinib (median, 17.9 vs 10.7 months). Fewer deaths were reported with alectinib (3.3% [5/152]) versus crizotinib (4.6% [7/151]); 2

<table>
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<tr>
<th>Genetic Alteration (ie, Driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
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<tbody>
<tr>
<td>High-level MET amplification*</td>
<td>Crizotinib1-2, Capmatinib3, Tepotinib4</td>
</tr>
<tr>
<td>ERBB2 (HER2) mutations**</td>
<td>Ado-trastuzumab emtansine5, Fam-trastuzumab deruxtecan-nxki6</td>
</tr>
</tbody>
</table>

* The definition of high-level MET amplification is evolving and may differ according to the assay used for testing. For NGS-based results, a copy number greater than 10 is consistent with high-level MET amplification.

** For oncogenic or likely oncogenic HER2 mutations, refer to definitions at oncopkb.org.

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treatment-related deaths were reported in the crizotinib arm and none in the alectinib arm.

J-ALEX, a phase 3 randomized trial, assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with ALK-positive advanced NSCLC.88 Median PFS was not reached with alectinib (95% CI, 20.3 months – not reached) versus 10.2 months (95% CI, 8.2 – 12.0) with crizotinib (HR, 0.34; 99.7% CI, 0.17 – 0.71; stratified log-rank P, .0001). Grade 3 or 4 adverse events were less frequent with alectinib (26% [27/103]) when compared with crizotinib (52% [54/104]); adverse events did not lead to death in either group. Fewer patients stopped taking alectinib (9%) because of an adverse event when compared with crizotinib (20%).

The NCCN NSCLC Panel recommends alectinib as a first-line therapy option for patients with ALK-positive metastatic NSCLC based on clinical trial data and the FDA approval.87–89 Panel members voted that alectinib is a preferred first-line therapy option for patients with ALK-positive metastatic NSCLC based on these trials. Alectinib is a category 1 (preferred) option if an ALK rearrangement is discovered before giving first-line systemic therapy. Alectinib is a preferred option if an ALK rearrangement is discovered during first-line systemic therapy (eg, carboplatin/pemetrexed or paclitaxel). Brigatinib, ceritinib, crizotinib, and lorlatinib are also recommended as first-line therapy options in patients with ALK-positive NSCLC. The NCCN NSCLC Panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred first-line therapy options for patients with ALK-positive metastatic NSCLC. Ceritinib is an “other recommended” option, whereas crizotinib is useful in certain circumstances.

Subsequent Therapy
Phase 2 trials assessed alectinib in patients with ALK-positive metastatic NSCLC and disease progression on crizotinib; overall response rates were 48%–50%.90,91 In the larger trial (138 patients), patients on alectinib had a response rate of 50% (95% CI, 41%–59%), and median duration of response of 11.2 months (95% CI, 9.6–not reached).91 For CNS disease, the control rate was 83% (95% CI, 74%–91%) and the median duration of response was 10.3 months (95% CI, 7.6–11.2). 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 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 NCCN NSCLC Panel recommends alectinib as a subsequent therapy option for patients with ALK-positive metastatic NSCLC and disease progression after crizotinib based on these trials and FDA approval.99–101 Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib.

**Brigatinib**

Brigatinib is a second-generation oral TKI that inhibits ALK rearrangements.

**First-Line Therapy**

**ALTA-1L**, a phase 3 randomized trial, assessed brigatinib versus crizotinib as first-line therapy for patients with ALK-positive metastatic NSCLC.92 At the first interim analysis, PFS was increased in patients receiving brigatinib (67%; 95% CI, 56%–75%) versus those receiving crizotinib (43%; 95% CI, 32%–53%) (HR for disease progression or death, 0.49; 95% CI, 0.33–0.74; \( P < .001 \)). Intracranial response was also increased with brigatinib (78%; 95% CI, 52%–94%) versus crizotinib (29%; 95% CI, 11%–52%). At the second interim analysis (24.9 months of follow-up), brigatinib continued to show improved PFS when compared with crizotinib (HR, 0.43; 95% CI, 0.31–0.61; median, 29.4 vs 9.2 months).93

The NCCN NSCLC Panel recommends brigatinib as a first-line therapy option for patients with ALK-positive NSCLC based on clinical trial data and FDA approval.92 Brigatinib is a category 1 (preferred) option if an ALK rearrangement is discovered before giving first-line systemic therapy. Brigatinib is a preferred option if an ALK rearrangement is discovered during first-line systemic therapy (eg, carboplatin/[pemetrexed or paclitaxel]). Other first-line therapy options include alectinib, ceritinib, crizotinib, and lorlatinib for patients with ALK-positive NSCLC. The panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with ALK-positive metastatic NSCLC; ceritinib is an “other recommended” option and crizotinib is useful in certain circumstances.93

**Subsequent Therapy**

**ALTA**, a phase 2 study, assessed 2 different doses of brigatinib: 90 mg (arm A) or 180 mg (arm B) every day in patients with ALK-positive metastatic NSCLC and disease progression on, or were intolerant to, crizotinib.94,95 The overall response rates were 45% (97% CI, 34%–56%) and 54% (97% CI, 43%–65%) in arms A and B, respectively. Many patients had brain metastases (71% and 67%, respectively). The intracranial overall response rates were 42% (11/26) and 67% (12/18), respectively, in patients with measurable brain metastases. The median PFS was 9.2 months (95% CI, 7.4–15.6) and 12.9 months (95% CI, 11.1–not reached), respectively. Grade 3 or higher adverse events included hypertension (6% and 6%, respectively) and pneumonia (3% and 5%, respectively).

The NCCN NSCLC Panel recommends brigatinib as a subsequent therapy option for patients with ALK-positive NSCLC and disease progression after crizotinib based on clinical trial data and FDA approval.94,95 Patients receiving brigatinib should be carefully monitored for respiratory symptoms, especially during the first week of treatment. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib.

**Ceritinib**

Ceritinib is a second-generation oral TKI that inhibits ALK and ROS1 rearrangements.96

**First-Line Therapy**

**ASCEND-4**, a phase 3 randomized trial, assessed ceritinib versus platinum-based chemotherapy as first-line therapy for patients with ALK-positive metastatic NSCLC.97 The median PFS was 16.6 months (95% CI, 12.6–27.2) for ceritinib and 8.1 months (95% CI, 5.8–11.1) for chemotherapy (HR, 0.55; 95% CI, 0.42–0.73; \( P < .0001 \)). For ceritinib, common adverse events included diarrhea (85% [160/189] of patients), nausea (69% [130/189]), vomiting (66% [125/189]), and an increase in ALT (60% [114/189]). For chemotherapy, common adverse events included nausea (55% [97/175]), vomiting (36% [63/175]), and anemia (35% [62/175]).

The NCCN NSCLC Panel recommends ceritinib as a first-line therapy option for patients with ALK-positive metastatic NSCLC based on clinical trial data and FDA approval. Ceritinib is a category 1 (recommended) option if an ALK rearrangement is discovered before giving first-line systemic therapy. Ceritinib is an option if an ALK rearrangement is discovered during first-line systemic therapy (eg, carboplatin/[pemetrexed or paclitaxel]). Alectinib, brigatinib, crizotinib, and lorlatinib are also recommended as first-line therapy options in patients with ALK-positive NSCLC. The panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with ALK-positive metastatic NSCLC; ceritinib is an “other recommended” option and crizotinib is useful in certain circumstances.

**Subsequent Therapy**

**ASCEND-5**, a phase 3 randomized trial, assessed ceritinib versus chemotherapy (with pemetrexed or docetaxel) in patients with advanced ALK-
positive NSCLC who had previously received at least 2 or more treatments (including chemotherapy and crizotinib) and had disease progression. Patients receiving ceritinib had a significant improvement in median PFS when compared with chemotherapy (5.4 months [95% CI, 4.1–6.9] vs 16 months [95% CI, 1.4–2.8]) for chemotherapy; HR, 0.49; 95% CI, 0.36–0.67; P< .0001). Serious adverse events were reported in 43% (49/115) of patients receiving ceritinib versus 32% (36/113) of those receiving chemotherapy. ASCEND-2, a phase 2 study, assessed ceritinib in patients who had previously received at least 2 or more treatments, with disease progression on crizotinib, and with brain metastases. The overall response rate was 38%; the duration of response was 9.7 months (95% CI, 7.1–11.1). The intracranial overall response rate was 45.0% (95% CI, 23.1%–68.5%).

The NCCN NSCLC Panel recommends ceritinib as a subsequent therapy option for patients with ALK-positive metastatic NSCLC and disease progression after crizotinib based on clinical trial data and the FDA approval. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib.

**Crizotinib**

Crizotinib is a first-generation oral TKI that inhibits ALK rearrangements, ROS1 rearrangements, and some MET tyrosine kinases (high-level MET amplification or METex14 skipping mutation).

**First-Line Therapy**

Randomized phase 3 trials have compared crizotinib with first-line chemotherapy (PROFILE 1014) and with subsequent chemotherapy (PROFILE 1007) for patients with ALK-positive metastatic NSCLC. First-line therapy with crizotinib improved PFS, response rate (74% vs 45%; P< .001), lung cancer symptoms, and quality of life when compared with chemotherapy (pemetrexed with either cisplatin or carboplatin). Crizotinib yields high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements, including those with brain metastases. Patients whose disease responds to crizotinib may have rapid improvement in symptoms; median time to progression on crizotinib is about 7 months to 1 year. Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function). However, some patients have had pneumonitis; crizotinib should be discontinued in these patients. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib unless an adverse side effect requiring discontinuation has occurred (eg, pneumonitis).

The NCCN NSCLC Panel recommends crizotinib as a first-line treatment option for patients with ALK rearrangement-positive metastatic NSCLC based on clinical trial data and the FDA approval. Crizotinib is a category 1 (useful in certain circumstances) option if an ALK rearrangement is discovered before giving first-line systemic therapy. Crizotinib is an option if an ALK rearrangement is discovered during first-line systemic therapy (eg, carboplatin/pemetrexed or paclitaxel). Alectinib, brigatinib, ceritinib, and lorlatinib are also recommended as first-line therapy options in patients with ALK-positive NSCLC. The NCCN NSCLC Panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with ALK-positive metastatic NSCLC, whereas ceritinib is an “other recommended” option. Patients who do not tolerate crizotinib may be switched to alectinib, brigatinib, ceritinib, or lorlatinib.

**Subsequent Therapy**

Subsequent therapy with crizotinib improved PFS (7.7 vs 3.0 months; P< .001) and response rate (65% vs 20%; P< .001) when compared with either docetaxel or pemetrexed in patients with ALK-positive NSCLC and disease progression after first-line chemotherapy who had not previously received ALK inhibitors. Therefore, crizotinib may also be continued for patients with ALK rearrangements and disease progression on crizotinib, depending on the type of progression. The NCCN NSCLC Panel does not recommend continuing crizotinib for patients with brain metastases and disease progression after first-line therapy with crizotinib; the other ALK inhibitors are recommended options in this setting because they have better CNS response rates (ie, alectinib, brigatinib, ceritinib, or lorlatinib).

**Lorlatinib**

Lorlatinib is a third-generation oral TKI that targets ALK and ROS1 tyrosine kinases and has good CNS penetration; it inhibits a broad range of ALK resistance mutations that develop after treatment with first- and second-generation ALK inhibitors.

**First-Line Therapy**

CROWN, a phase 3 randomized trial, assessed lorlatinib versus crizotinib as first-line therapy for patients with ALK-positive metastatic NSCLC. At 12 months, 78% (95% CI, 70%–84%) of patients were alive without disease progression in the lorlatinib group versus 39% (95% CI, 30%–48%) in the crizotinib group (HR for disease progression or death, 0.28; 95% CI, 0.19 to 0.41; P< .001). The objective response rate was 76% (95% CI, 68%–83%) for patients receiving lorlatinib and 58% (95% CI, 49%–66%) for crizotinib. For patients with measurable brain metastases, 82% (95% CI, 57%–96%) of those receiving lorlatinib had an intracranial response and 23% (95% CI,
5%–54%) of those receiving crizotinib responded. Of patients who received lorlatinib, 71% had a complete intracranial response. Hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects were the most common adverse events with lorlatinib. More grade 3 or 4 adverse events (mainly altered lipid levels) occurred with lorlatinib than crizotinib (72% vs 56%, respectively). Discontinuation of treatment because of adverse events was similar in both groups (7% for lorlatinib and 9% for crizotinib).

The NCCN NSCLC Panel recommends lorlatinib as a first-line therapy option for patients with ALK-positive metastatic NSCLC based on clinical trial data and FDA approval. Panel members voted that lorlatinib is a preferred first-line therapy option for patients with ALK-positive metastatic NSCLC based on trial data. Lorlatinib is a category 1 (preferred) option if an ALK rearrangement is discovered before giving first-line systemic therapy. Lorlatinib is a preferred option if an ALK rearrangement is discovered during first-line systemic therapy (eg, carboplatin/pemetrexed or paclitaxel). Alectinib, brigatinib, ceritinib, and crizotinib are also recommended as first-line therapy options in patients with ALK-positive metastatic NSCLC. The panel has preference stratified the first-line therapy regimens and decided that alectinib, brigatinib, and lorlatinib are all preferred options for patients with ALK-positive metastatic NSCLC; ceritinib is an “other recommended” option and crizotinib is useful in certain circumstances.

Subsequent Therapy

Data show that lorlatinib is effective in select patients with disease progression after treatment with ALK inhibitors, including those with CNS metastases. A phase 2 trial assessed lorlatinib in patients with ALK-positive or ROS1-positive metastatic NSCLC and disease progression after ALK inhibitor therapy; many patients had asymptomatic CNS metastases. In patients who had received at least one previous ALK inhibitor, objective responses were achieved in 47% of patients (93/198; 95% CI, 39.9%–54.2%); there were 4 complete responses and 89 partial responses. In those with measurable baseline CNS lesions, an objective intracranial response was observed in 63% of patients (51/81; 95% CI, 51.5%–73.4%). Lorlatinib was effective in patients who had received up to 3 previous ALK inhibitors. Grade 3 to 4 adverse events included hypercholesterolemia and hypertriglyceridemia (43/275 [16%] for both). Serious treatment-related adverse events occurred in 7% of patients (19/275) including cognitive effects in 1% (2/275); the cognitive effects resulted in permanent discontinuation of lorlatinib. No treatment-related deaths were reported. Data from this phase 2 trial also show that lorlatinib is effective as subsequent therapy in patients with the resistance mutation ALK G1202R, which is often detected after progression on second-generation ALK TKIs such as, brigatinib, alectinib, or ceritinib. The objective response rate with lorlatinib was 62% when using plasma ctDNA (and 69% when using tissue) for patients with ALK resistance mutations and disease progression on second-generation ALK TKIs compared with 32% (plasma) and 27% (tissue) in patients without ALK mutations.

The NCCN NSCLC Panel recommends lorlatinib as a subsequent therapy option for select patients with ALK-positive metastatic NSCLC and disease progression after treatment with ALK inhibitors based on clinical trial data and FDA approval. For the 2022 update (Version 1), the panel clarified that lorlatinib is recommended as a subsequent therapy option for select patients with ALK G1202R-positive metastatic NSCLC after progression on alectinib, brigatinib, or ceritinib (depending on the type of progression) based on clinical trial data (see NSCLC-27, page 502). At progression, the panel recommends considering plasma and/or tissue-based testing using broad molecular profiling for genomic resistance mechanisms. Lorlatinib is recommended as a subsequent therapy option for select patients with ALK-positive metastatic NSCLC after progression on crizotinib. If not previously given, lorlatinib is also recommended as a subsequent therapy option for ALK-positive metastatic NSCLC after progression on crizotinib followed by progression on either alectinib, brigatinib, or ceritinib.

Oral Agents That Inhibit BRAF Mutations

BRAF (v-Raf murine sarcoma viral oncogene homolog B) is a serine/threonine kinase that is part of the MAP/ERK signaling pathway. The BRAF V600E mutation occurs in 1%–2% of patients with lung adenocarcinoma; it is the most common of the BRAF point mutations when considered across all tumor types. Although other BRAF mutations occur in patients with NSCLC at a rate approximately equal to p.V600E (unlike many other tumor types), specific targeted therapy is not available for these other mutations. Patients with BRAF V600E mutations are typically current or former smokers. The NCCN NSCLC Panel recommends BRAF mutation testing in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents for patients with BRAF mutations. BRAF mutation testing should be considered in patients with metastatic squamous cell carcinoma.

Dabrafenib and Trametinib

Dabrafenib and trametinib inhibit kinases in the RAS/RAF/MEK/ERK pathway. Dabrafenib inhibits BRAF harboring p.V600E mutations; trametinib inhibits MEK 1/2, which is downstream of BRAF signaling.
First-Line Therapy

A phase 2 trial assessed first-line combination therapy with dabrafenib/trametinib for 36 patients with metastatic NSCLC and **BRAF** p.V600E mutations.\(^\text{13,118}\) The overall response rate was 64% (23/36; 95% CI, 46%–79%); there were 2 complete responses. The median PFS was 10.9 months (95% CI, 7.0–16.6). Many patients (69% [25/36]) had one or more grade 3 or 4 adverse events. Serious adverse events included increased alanine aminotransferase (ALT; 14% [5/36]), increased aspartate transaminase (AST; 8% [3/36]), pyrexia (11% [4/36]), and decreased ejection fraction (8% [3/36]). An updated analysis reported that patients receiving dabrafenib/trametinib had a median overall survival of 17.3 months (95% CI, 12.3–40.2).\(^\text{12}\) After 5 years, the overall survival rate was 22%.

The NCCN NSCLC Panel recommends combination therapy with dabrafenib/trametinib as a preferred first-line therapy option for patients with metastatic NSCLC and **BRAF** p.V600E mutations based on these trials and the FDA approval.\(^\text{13,118,121}\) Single-agent therapy with dabrafenib or vemurafenib is also an option for patients with **BRAF** p.V600E mutations who do not tolerate combination therapy with dabrafenib/trametinib.\(^\text{69,119,122}\) Other systemic therapy regimens are also recommended (useful in certain circumstances) for patients with **BRAF** p.V600E mutations; the same initial systemic regimens used for patients with metastatic NSCLC may be used (eg, carboplatin/[pemetrexed or paclitaxel]). The panel has preference stratified the first-line therapy options for patients with **BRAF** p.V600E mutation-positive metastatic NSCLC and decided that: (1) dabrafenib/trametinib is the preferred option; and (2) dabrafenib, vemurafenib, or other systemic therapy regimens (eg, carboplatin/[pemetrexed or paclitaxel]) are useful in certain circumstances.

Subsequent Therapy

A phase 2 study assessed the dabrafenib/trametinib regimen as subsequent therapy in 57 patients with advanced NSCLC and **BRAF** p.V600E mutations and disease progression on chemotherapy.\(^\text{13,68,120}\) The overall response rate was 68% (23/36; 95% CI, 55%–80%) PFS was 9.7 months (6.9–19.6). Serious adverse events occurred in 56% (32/57) of patients, including pyrexia, anemia, confusional state, hemoptysis, hypercalcemia, and cutaneous squamous cell carcinoma. Grade 3 to 4 adverse events included neutropenia in 9% of patients (5/57), hyponatremia in 7% (4/57), and anemia in 5% (3/57). Four patients died during the study, but these deaths were not felt to be related to treatment (deaths were due to retroperitoneal hemorrhage, subarachnoid hemorrhage, respiratory distress, or severe disease progression). An updated analysis reported that the median overall survival was 18.2 months (95% CI, 14.3–28.6).\(^\text{13}\) After 5 years, the overall survival rate was 19%.

The NCCN NSCLC Panel recommends dabrafenib/trametinib as a subsequent therapy option if patients with **BRAF** p.V600E mutations have disease progression after first-line systemic therapy regimens (eg, carboplatin/[pemetrexed or paclitaxel]) and have not received **BRAF** p.V600E inhibitors as first-line therapy.\(^\text{68,120}\) Single-agent therapy with dabrafenib or vemurafenib is also an option for patients with **BRAF** p.V600E mutations who do not tolerate combination therapy with dabrafenib/trametinib.\(^\text{69,119,122}\) Clinicians should be aware of common adverse events that may occur with dabrafenib/trametinib including pyrexia, vomiting, and nausea along with less frequent and unique adverse events, such as cutaneous, ocular, and hemorrhagic events.\(^\text{123}\)

Agents That Inhibit EGFR Mutations

**Oral TKIs That Inhibit EGFR Exon 19 Deletions and Exon 21 (L858R) Mutations**

The NCCN NSCLC Panel recommends **EGFR** mutation testing (category 1) in all patients with metastatic non-squamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents for patients with **EGFR** mutations.\(^\text{51,124}\) **EGFR** mutation testing should be considered in patients with metastatic squamous cell carcinoma. The NCCN NSCLC Panel recommends afatinib, dacomitinib, erlotinib (± bevacizumab or ramucirumab), gefitinib, and osimertinib for patients with metastatic NSCLC and **EGFR** exon 19 deletions or exon 21 (L858R) mutations based on clinical trial data and FDA approvals, which are described in the following sections.

**Afatinib**

Afatinib is a second-generation oral TKI that irreversibly inhibits the ErbB/HER family of receptors including EGFR and ERBB2.\(^\text{125,126}\) LUX-Lung 3, a phase 3 randomized trial, reported that first-line therapy with afatinib improved PFS when compared with cisplatin/pemetrexed in patients with metastatic adenocarcinoma who had **EGFR** mutations (11.1 vs 6.9 months, \(P=.001\)).\(^\text{127}\) The NCCN NSCLC Panel recommends afatinib as a first-line therapy option in patients with metastatic NSCLC and **EGFR** exon 19 deletions or L858R mutations based on the clinical trial and FDA approval.\(^\text{125,127–130}\) Afatinib is a category 1 (other recommended) option if an **EGFR** exon 19 deletion or L858R mutation is discovered before giving first-line systemic therapy. Afatinib is an option if an **EGFR** exon 19 deletion or L858R mutation is discovered during first-line systemic therapy (eg, carboplatin/[pemetrexed or paclitaxel]).

The NCCN NSCLC Panel has preference stratified the systemic therapy regimens for patients with metastatic
NSCLC and EGFR exon 19 deletions or L858R mutations and decided that afatinib is an “other recommended” option; osimertinib is the preferred option in this setting. Afatinib may also be continued in patients with disease progression if they do not have multiple systemic symptomatic lesions.131 However, afatinib is not recommended as subsequent therapy in patients with metastatic squamous cell NSCLC but without EGFR mutations based on a phase 3 randomized trial showing low response rates (11%); it is less efficacious and safe compared with other available options.132 Afatinib is also recommended for eligible patients with metastatic NSCLC and EGFR S768I, L861Q, and/or G719X mutations.133

A phase 2B trial assessed afatinib compared with gefitinib for first-line therapy in patients with metastatic adenocarcinoma and common EGFR mutations.134 The median PFS was 11.0 months (95% CI, 10.6–12.9) with afatinib versus 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. Updated results indicate that overall survival was not significantly different between afatinib and gefitinib (27.9 vs 24.5 months; HR, 0.86; 95% CI, 0.66–1.12; P = .2580).135 Patients receiving afatinib had more serious treatment-related side effects when compared with those receiving gefitinib (11% [17/160] for afatinib vs 4% [7/159] for gefitinib). One patient receiving gefitinib died of treatment-related hepatic and renal failure; other deaths were not considered to be related to treatment (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%). The NCCN Guidelines do not state that afatinib is more efficacious than gefitinib (see the NCCN Guidelines with Evidence Blocks for NSCLC, available at NCCN.org).136 Afatinib is rated as slightly less safe than erlotinib or gefitinib (ie, a rating of 3 for afatinib vs 4 for erlotinib and gefitinib).

Erlotinib and Gefitinib

Erlotinib and gefitinib are first-generation oral TKIs that inhibit EGFR exon 19 deletions and L858R (both are common mutations) as well as EGFR S768I, L861Q, and/or G719X (less common mutations). EGFR TKIs are recommended in patients with metastatic NSCLC and EGFR mutations, because quality of life is improved when compared with chemotherapy. Erlotinib and gefitinib are orally active TKIs that are very well tolerated by most patients.137,138

Clinical Trial Data

IPASS, a phase 3 randomized trial, assessed first-line therapy with gefitinib alone versus carboplatin/paclitaxel in Asian patients with EGFR-positive metastatic NSCLC.124 Patients with EGFR mutations who received gefitinib had longer PFS (24.9% vs 6.7%), increased response rate (71.2% vs 47.3%), and improved quality of life with fewer side effects (eg, neutropenia) compared with carboplatin/paclitaxel.124 Updated results from the IPASS trial showed that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of EGFR mutation status.139 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 EGFR mutations.

EURTAC, a phase 3 randomized trial, assessed first-line therapy with erlotinib versus chemotherapy in European patients with metastatic NSCLC and EGFR mutations.61 PFS was longer and response rate was increased for those receiving erlotinib compared with chemotherapy.63 For erlotinib, the median PFS was 9.7 months (95% CI, 8.4–12.3) compared with 5.2 months (95% CI, 4.5–5.8) for chemotherapy (HR, 0.37; 95% CI, 0.25–0.54; P < .0001). Fewer patients receiving erlotinib had severe adverse events or died when compared with those receiving chemotherapy. The FDA has approved the use of erlotinib as first-line therapy in patients with the common EGFR mutations.140 Previously, erlotinib was often used in the United States in patients with the common EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib was reapproved by the FDA based on a phase 4 study and is available in the United States.141,142

CALGB 30406, a phase 3 randomized trial, compared first-line erlotinib monotherapy versus erlotinib plus carboplatin plus paclitaxel in patients (mainly Caucasian) with advanced NSCLC and EGFR mutations.143 Erlotinib monotherapy was associated with fewer side effects in patients with EGFR mutations compared with erlotinib/chemotherapy. Thus, it is appropriate to interrupt or complete planned chemotherapy and switch to EGFR TKI therapy in patients found to have EGFR mutations during first-line chemotherapy.30 The NCCN Guidelines do not recommend adding EGFR TKIs to current chemotherapy based on this CALGB study.143 EGFR TKIs may be continued in patients with disease progression if they do not have multiple systemic symptomatic lesions.

WJOG 5108L, a phase 3 randomized trial, 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.136 The median PFS was 8.3 months for gefitinib versus 10.0 months for erlotinib 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 ALT/AST levels (gefitinib, 6.1%/13.0% vs erlotinib, 2.2%/3.3%).
An analysis of 5 clinical trials in patients (n=223), mainly from the Western hemisphere, with NSCLC (stage IIIIB or IV) found that those with EGFR mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.144 The TORCH trial suggested that EGFR mutation testing should be done in patients with advanced nonsquamous NSCLC.145 Survival was longer 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 EGFR mutations who received erlotinib.146,147

RELAY, a phase 3 randomized trial, compared first-line therapy with erlotinib/ramucirumab versus erlotinib alone in patients with advanced NSCLC and EGFR mutations.148 PFS was 19.4 months (95% CI, 15.4–21.6) with erlotinib/ramucirumab versus 12.4 months (95% CI, 11.0–13.5) with erlotinib (HR, 0.59; 95% CI, 0.46–0.76; P<.0001). The overall response rate was similar (erlotinib/ramucirumab, 76% vs erlotinib alone, 75%). Serious adverse events (grade 3–4) occurred in 72% (159/221) of patients receiving erlotinib/ramucirumab (including hypertension) versus 54% (121/225) in those receiving erlotinib alone (including increased ALT). One treatment-related death occurred in a patient receiving erlotinib/ramucirumab.

NEJ026, a phase 3 randomized trial, compared first-line erlotinib plus bevacizumab versus erlotinib alone in 228 patients with EGFR-positive advanced nonsquamous NSCLC.149,150 At interim analysis, PFS was 16.9 months (95% CI, 14.2–21.0) for erlotinib/bevacizumab versus 13.3 months (95% CI, 11.1–15.3) for erlotinib alone (HR, 0.605; 95% CI, 0.417–0.877; P=.016).150 Grade 3 or worse events occurred in 88% (98/112) of patients receiving erlotinib/bevacizumab versus 46% (53/114) of erlotinib alone. Grade 4 adverse events occurred in 8% (9/112) of patients receiving erlotinib/bevacizumab (including neutropenia, hepatic dysfunction) versus 4% (5/114) of patients receiving erlotinib alone (hepatic dysfunction); no treatment-related deaths were reported.150 Updated data showed median overall survival was 50.7 months (95% CI, 37.3–not estimable) in those receiving erlotinib/bevacizumab versus 46.2 months (38.2–not estimable) in those receiving erlotinib alone (HR, 1.007; 95% CI, 0.681–1.490; P=.97).149

NCCN Recommendations
The NCCN NSCLC Panel recommends erlotinib and gefitinib as first-line therapy options in patients with metastatic nonsquamous NSCLC and EGFR exon 19 deletions or L858R mutations (regardless of their PS) based on these trials and FDA approvals.124,151–153 Erlotinib and gefitinib are category 1 (other recommended) options if an EGFR exon 19 deletions or L858R mutation is discovered before giving first-line systemic therapy. Erlotinib and gefitinib are options if an EGFR exon 19 deletions or L858R mutation is discovered during first-line systemic therapy (eg, carboplatin/[pemetrexed or paclitaxel]).

The NCCN NSCLC Panel recommends erlotinib/ramucirumab as a first-line therapy option for patients with metastatic NSCLC and EGFR exon 19 deletions or L858R mutations (other recommended intervention) based on clinical data.148 The panel also recommends erlotinib/bevacizumab as a first-line therapy option for eligible patients with metastatic nonsquamous NSCLC who have common EGFR mutations and no contraindications to bevacizumab (other recommended) based on clinical data.149,150 The panel recommends that bevacizumab biosimilars may be used in any of the regimens containing bevacizumab that are used for eligible patients with metastatic NSCLC.154–156 Erlotinib (± bevacizumab or ramucirumab) or gefitinib may also be continued in patients with disease progression if they do not have multiple systemic symptomatic lesions.131 However, erlotinib is not recommended as subsequent therapy in patients with metastatic squamous cell NSCLC but without EGFR mutations based on a phase 3 randomized trial showing low response rates (3%); it is less efficacious and safe compared with other available options.132

The NCCN NSCLC Panel has preference stratified the systemic therapy regimens and decided that erlotinib (± bevacizumab or ramucirumab) and gefitinib are “other recommended” first-line options for patients with metastatic NSCLC and EGFR exon 19 deletions or L858R mutations; osimertinib is the preferred option in this setting. Erlotinib and gefitinib are also recommended for eligible patients with metastatic NSCLC and EGFR S768I, L861Q, and/or G719X mutations (see “Oral TKIs That Inhibit EGFR S768I, L861Q, and G719X Alterations,” page 514).

Dacomitinib
Dacomitinib is a second-generation oral TKI that irreversibly inhibits ErbB/HER receptors including EGFR, HER1, HER2, and HER4.

Clinical Trial Data
ARCHER 1050, a phase 3 randomized trial, compared dacomitinib versus gefitinib as first-line therapy for patients with EGFR-positive metastatic NSCLC.159,160 Patients with brain metastases were not eligible for enrollment. PFS was increased in patients receiving dacomitinib (14.7 months; 95% CI, 11.1–16.6) compared with those receiving gefitinib (9.2 months; 95% CI, 9.1–11.0). Serious adverse events related to treatment were reported in 21 (9%) patients given dacomitinib and in 10 (4%) patients given gefitinib. Treatment-related
deaths included 2 patients in the dacomitinib group (one related to untreated diarrhea and one to untreated cholelithiasis/liver disease) and one patient in the gefitinib group (related to sigmoid colon diverticulitis/rupture complicated by pneumonia). An updated analysis reported that the median overall survival was 34.1 months (95% CI, 29.5–39.8) in patients receiving dacomitinib compared with 27.0 months (95% CI, 24.4–31.6) in those receiving gefitinib (HR, 0.748; 95% CI, 0.591–0.947; 2-sided P=.0155). NCCN Recommendations

The NCCN NSCLC Panel recommends dacomitinib as a first-line treatment option for patients with metastatic NSCLC and EGFR exon 19 deletions or L858R mutations based on clinical trial data and the FDA approval. Dacomitinib is a category 1 (other recommended) option if an EGFR exon 19 deletion or L858R mutation is discovered before giving first-line systemic therapy. Dacomitinib is also an option if an EGFR exon 19 deletion or L858R mutation is discovered during first-line systemic therapy (eg, carboplatin/ [pemetrexed or paclitaxel]). The panel has preference stratified the systemic therapy regimens and decided that dacomitinib is an “other recommended” option; osimertinib is the preferred option in this setting. Dacomitinib is also recommended for eligible patients with metastatic NSCLC and EGFR S768I, L861Q, and/or G719X mutations.

Osimertinib

Osimertinib is a third-generation oral TKI that inhibits the common and uncommon EGFR mutations and T790M. Common EGFR mutations include exon 19 deletions and L858R; less common mutations include S768I, L861Q, and/or G719X. Patients with these mutations are sensitive to the small-molecule oral EGFR TKIs, such as osimertinib, erlotinib, gefitinib, afatinib, and dacomitinib. EGFR T790M is a mutation associated with acquired resistance to first-line therapy with EGFR TKIs and has been reported in about 60% of patients with disease progression after initial response to first-line EGFR TKIs (eg, erlotinib, gefitinib). Most patients with EGFR mutations and metastatic NSCLC typically have disease progression after about 9.7 to 13 months of therapy with erlotinib, gefitinib, or afatinib. Data show that patients receiving osimertinib as first-line therapy have PFS of about 19 months. Flare phenomenon may occur in some patients who discontinue EGFR TKIs. If disease flare occurs, then the EGFR TKIs should be restarted.

Clinical Trial Data for First-Line Therapy

FLAURA, a phase 3 randomized trial, assessed first-line therapy with osimertinib compared with either erlotinib or gefitinib in patients with metastatic NSCLC and EGFR mutations regardless of T790M status. PFS was longer with osimertinib (18.9 months; 95% CI, 15.2–21.4) compared with either erlotinib or gefitinib (10.2 months; 95% CI, 9.6–11.1; HR, 0.46; 95% CI, 0.37–0.57; P<.001). The median duration of response was longer with osimertinib compared with erlotinib or gefitinib (median response, 17.2 vs 8.5 months). Only 6% (17/279) of patients receiving osimertinib had CNS progression events when compared with 15% (42/277) of those receiving erlotinib or gefitinib. Grade 3 or higher adverse events were reported in 34% (94/279) of patients receiving osimertinib and 45% (124/277) of patients receiving erlotinib or gefitinib. An updated analysis showed that median overall survival was 38.6 months with osimertinib (95% CI, 34.5–41.8) compared with 31.8 months (95% CI, 26.6–36.0) for either erlotinib or gefitinib (HR, 0.8; 95% CI, 0.64–1.0; P=.046).

NCCN Recommendations for First-Line Therapy

The NCCN NSCLC Panel recommends osimertinib as a preferred first-line therapy option for patients with metastatic NSCLC and EGFR exon 19 deletions or L858R mutations based on clinical data and FDA approval. Osimertinib is a category 1 (preferred) recommended option if an EGFR exon 19 deletion or L858R mutation is discovered before giving first-line systemic therapy. Osimertinib is a preferred option if an EGFR mutation is discovered during first-line systemic therapy (eg, carboplatin/ [pemetrexed or paclitaxel]). For patients receiving first-line ICIs with or without chemotherapy, oncologists should be aware of the long half-life of the ICIs and potential adverse effects when using osimertinib in combination with or following ICIs. For the 2022 update (Version 1), the panel added a caveat that if molecular testing results are pending in patients who require an urgent start to first-line therapy, then consider holding immunotherapy regimens and only using chemotherapy regimens for the first cycle.

Osimertinib is also recommended as an adjuvant therapy option for eligible patients with completely resected stage IB to IIIA NSCLC and EGFR exon 19 deletions or L858R mutations who have previously received adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy. In addition, osimertinib is recommended for eligible patients with metastatic NSCLC and EGFR S768I, L861Q, and/or G719X mutations.

Clinical Trial Data for Subsequent Therapy

AURA3, a phase 3 randomized trial, assessed osimertinib versus platinum-pemetrexed chemotherapy in patients with EGFR T790M-positive metastatic NSCLC and disease progression on first-line erlotinib, gefitinib, or afatinib. PFS was longer with osimertinib compared with...
chemotherapy (10.1 vs 4.4 months; HR, 0.30; 95% CI, 0.23–0.41; P<.001). PFS was also longer in patients with CNS metastases who received osimertinib versus chemotherapy (8.5 vs 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). In addition, the objective response rate was increased 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 was about 93% with osimertinib (95% CI, 90%–96%) and about 74% with chemotherapy (95% CI, 66%–81%). Patients receiving osimertinib had fewer grade 3 or higher adverse events compared with those receiving chemotherapy (23% vs 47% [63/279 vs 64/136]). There were 4 fatal events with osimertinib (respiratory failure [2 patients], pneumonitis, and ischemic stroke) and one with chemotherapy (hypovolemic shock).

**NCCN Recommendations for Subsequent Therapy**

The NCCN NSCLC Panel recommends broad molecular profiling for *T790M* and other genomic resistance mutations for eligible patients with *EGFR* mutation-positive NSCLC and disease progression on certain EGFR TKIs based on the efficacy of osimertinib; for the 2022 update (Version 1), the panel revised the *T790M* testing recommendation to category 1 from 2A based on clinical trial data.170 The panel recommends osimertinib (category 1) as a subsequent therapy option for patients with metastatic *EGFR T790M*–positive NSCLC and disease progression on certain EGFR TKIs (including erlotinib, afatinib, dacomitinib, osimertinib); but not including osimertinib) based on clinical trial data and FDA approval.170 For patients with *EGFR* mutations who have disease progression during or after first-line therapy with osimertinib, recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: (1) considering local therapy (eg, stereotactic ablative radiotherapy or surgery); (2) continuing osimertinib; or (3) a first-line systemic therapy regimen for metastatic NSCLC (such as carboplatin/paclitaxel). There are no data to support using erlotinib (with or without ramucirumab or bevacizumab), gefitinib, afatinib, or dacomitinib based on data showing an improvement.162,170-180,182

Updated data from the BLOOM study suggest that osimertinib is beneficial for patients with *EGFR* mutations (regardless of *T790M* status) who have progressive leptomeningeal disease.183 In the BLOOM study (n=32), 23 patients receiving osimertinib (160 mg once daily) had brain imaging assessment; 10 had radiologic improvement and 13 had stable disease. At a 12-week neurologic assessment, 88% (7/8) of symptomatic patients had improved and one had stable disease. Of 15 asymptomatic patients, 87% (13/15) remained asymptomatic.183 The NCCN NSCLC Panel recommends that osimertinib (regardless of *T790M* status) can be considered for patients with *EGFR* mutations who have progressive CNS disease or leptomeningeal disease.

**Oral TKIs That Inhibit EGFR S768I, L861Q, and G719X Alterations**

*EGFR L861Q, G719X,* and *S768I* are less common *EGFR* mutations (10%) that are also sensitive to first-, second-, and third-generation EGFR TKIs (such as erlotinib, gefitinib, afatinib, dacomitinib, osimertinib).133,176-184,185 For the 2022 update (Version 1), the NCCN NSCLC Panel recommends testing for *EGFR S768I, L861Q,* and *G719X* mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of EGFR TKIs as first-line therapy options for patients with these mutations (see NSCLC-23, page 499).133,176-184 *EGFR S768I, L861Q,* and *G719X* mutation testing should be considered in patients with metastatic squamous cell carcinoma.

**Clinical Trial Data**

KC5G-LU15-09, a phase 2 trial, assessed first-line therapy with osimertinib in 37 patients with metastatic NSCLC and less common *EGFR* mutations, including *S768I, L861Q,* and *G719X*.176 The median PFS was 8.2 months (95% CI, 5.9–10.5 months). The objective response rate was 50% (18/36; 95% CI, 33%–67%). Manageable adverse events included rash, pruritis, decreased appetite, diarrhea, and dyspnea.176

A posthoc analysis of several LUX-Lung trials (LUX-Lung 2, 3, and 6) assessed afatinib in a few patients with *EGFR L861Q, G719X,* and *S768I* mutation-positive metastatic NSCLC.133 Median overall survival was 19.4 months (95% CI, 16.4–26.9). Of patients with *EGFR G719X* mutations, 77.8% (95% CI, 52.4%–93.6%) had an objective response to afatinib. Of those with *EGFR S768I* mutations, 100% (95% CI, 63.1%–100%) responded to afatinib. Of those with *EGFR L861Q,* 56% (95% CI, 29.9%–80.2%) responded to afatinib.

**NCCN Recommendations**

For the 2022 update (Version 1), the NCCN NSCLC Panel recommends testing for *EGFR S768I, L861Q,* and *G719X*...
mutations in eligible patients with metastatic NSCLC based on data showing the efficacy of EGFR TKIs as first-line therapy options for patients with these mutations (see NSCL-23, page 499). The panel recommends afatinib or osimertinib as first-line therapy options (preferred) for patients with metastatic NSCLC who have these less common EGFR mutations based on clinical trial data. The panel has preference stratified the systemic therapy regimens and decided that afatinib or osimertinib are preferred recommended options for patients with metastatic NSCLC and EGFR L861Q, G719X, and S768I mutations; other recommended options include erlotinib, gefitinib, or dacomitinib.

**Agents That Inhibit EGFR Exon 20 Insertion Mutations**

EGFR exon 20 mutations are a heterogenous group; most variants do not respond to first-, second- or third-generation EGFR TKIs. However, some EGFR exon 20 alterations, such as p.A763_Y764insFQEA, are sensitive to EGFR TKIs; p.A763_Y764insLQEA may be sensitive to first and third-generation EGFR TKIs. First-line platinum-based chemotherapy is typically recommended for most patients with EGFR exon 20 insertion-positive metastatic NSCLC (eg, carboplatin/pemetrexed or paclitaxel). The response rates (0%-25%) to immunotherapy regimens vary, depending on the specific EGFR 20 insertion mutation. Response rates to classic subsequent therapy regimens, such as docetaxel, are low (14%) in patients with metastatic NSCLC and disease progression after first-line therapy.

The NCCN NSCLC Panel recommends testing for EGFR exon 20 insertion mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents as subsequent therapy options for patients with EGFR exon 20 insertion-positive metastatic NSCLC. EGFR exon 20 insertion mutation testing should be considered in patients with metastatic squamous cell carcinoma.

**Amivantamab**

Amivantamab-vmjw is a bispecific human antibody to EGFR and MET receptors that bypasses resistance to the TKIs and has immune-cell directing activity.

**Subsequent Therapy**

CHRYSLIS, a phase 1 study, assessed subsequent therapy with amivantamab-vmjw in 81 patients with EGFR exon 20 insertion-positive metastatic NSCLC who had received one or more previous lines of therapy. The reported overall response rate was 40% (95% CI, 29%-51%) with 3 complete responses. The median PFS was 8.3 months (95% CI, 6.5–10.9). Common treatment-related adverse events included cutaneous reactions, infusion-related reactions, and paronychia. The most common grade 3 to 4 adverse events included hypokalemia (5% [6/114]) as well as pulmonary embolism, neutropenia, diarrhea, and rash (4% for each [4/114]).

The NCCN NSCLC Panel recommends amivantamab as a subsequent therapy option for patients with EGFR exon 20 insertion mutation-positive metastatic NSCLC and disease progression on or after initial systemic therapy options based on clinical trial data and FDA approval. If patients have disease progression on amivantamab, then the panel recommends either mobocertinib or subsequent systemic therapy options (eg, albumin-bound paclitaxel).

**Mobocertinib**

Mobocertinib is an oral TKI that selectively inhibits diverse EGFR and ERBB2 (HER2) exon 20 insertion mutations.

**Subsequent Therapy**

Phase 1/2 trials (n=114) assessed subsequent therapy with mobocertinib for patients with EGFR exon 20 insertion mutation-positive metastatic NSCLC who had received first-line platinum-based chemotherapy. The objective response rate was 28% (95% CI, 20%–37%). Median overall survival was 24 months (95% CI, 14.6–28.8). Patients with brain metastases had a lower overall response rate (18%; 95% CI, 7%–33%) to mobocertinib compared with those without brain metastases (34%; 95% CI, 23%–46%). Diarrhea and rash were the most common treatment-related adverse events. Grade 3 or 4 treatment-related adverse events were reported in 47% of patients (54/114); diarrhea was the most common grade 3 or 4 adverse event (21% [24/114]). One death (cardiac failure) was reported to be related to treatment with mobocertinib.

The NCCN NSCLC Panel recommends mobocertinib as a subsequent therapy option for patients with EGFR exon 20 insertion mutation-positive metastatic NSCLC and disease progression on or after initial systemic therapy options based on clinical trial data and FDA approval. If patients have disease progression on mobocertinib, then the panel recommends either amivantamab or subsequent systemic therapy options (eg, albumin-bound paclitaxel).

**Monoclonal Antibody That Inhibits EGFR**

**Cetuximab**

Cetuximab is a monoclonal antibody that targets EGFR. Data suggest that an afatinib/cetuximab regimen may be useful for patients who have progressed after receiving erlotinib, afatinib, or gefitinib and after chemotherapy.
Patients with T790M-positive and T790M-negative tumors had a similar response rate to an afatinib/cetuximab regimen (32% vs 25%; P=.341). The NCCN NSCLC Panel recommends considering afatinib/cetuximab as an option for certain patients with multiple symptomatic systemic lesions after receiving afatinib, dacomitinib, erlotinib (± bevacizumab or ramucirumab), gefitinib, or osimertinib and after chemotherapy based on these data.

FLEX, a large phase 3 randomized trial, assessed cisplatin/vinorelbine with (or without) cetuximab for patients with advanced NSCLC; most patients had stage IV disease.196 Adding cetuximab slightly increased overall survival (11.3 vs 10.1 months; HR for death, 0.87; 95% CI, 0.762–0.996; P=.044). Patients receiving cetuximab had increased grade 4 events versus control (62% vs 52%, P<.01); cetuximab was also associated with grade 2 acne-like rash.

The NCCN NSCLC Panel does not recommend the cetuximab plus cisplatin plus vinorelbine regimen based on the clinical data.196 The benefits of this cetuximab-based regimen are very slight; it is a difficult regimen to administer, and patients have poorer tolerance for this regimen when compared with other regimens; for example, almost 40% of patients have grade 4 neutropenia.197 Patients may also have comorbid conditions that prevent them from receiving cisplatin such as poor kidney function. Cisplatin/vinorelbine with (or without) cetuximab is generally not used in the United States because of concerns about toxicity.196–198 Although the FLEX trial results were reported to be statistically significant, panel members feel they were not clinically significant.197 The panel does not recommend the cisplatin/vinorelbine and carboplatin/vinorelbine regimens for patients with metastatic NSCLC with all histologies.

**Oral Agent That Inhibits KRAS Mutations**

KRAS is a G-protein with GTPase activity that is part of the MAP/ERK pathway; point mutations in KRAS most commonly occur at codon 12. Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have KRAS mutations; KRAS is the most common mutation in this population.52,151,199–201 KRAS mutation prevalence is associated with cigarette smoking, unlike many of the other actionable mutations (eg, EGFR mutations, ALK rearrangements).202 In patients with KRAS mutation-positive metastatic NSCLC, data suggest the response rate is about 26% to single-agent ICls.60,203 First-line platinum-based chemotherapy (± immunotherapy) is a recommended option for patients with KRAS mutations (eg, carboplatin/[pemetrexed or paclitaxel]). The NCCN NSCLC Panel recommends testing for KRAS mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of sotorasib as a subsequent therapy option for patients with KRAS G12C mutation-positive metastatic NSCLC. KRAS mutation testing should be considered in patients with metastatic squamous cell carcinoma.

**Sotorasib**

Sotorasib is an oral RAS GTPase inhibitor that inhibits KRAS p.G12C mutations in patients with metastatic NSCLC who have previously treated with combination chemotherapy regimens (± immunotherapy). A phase 2 study assessed sotorasib as subsequent therapy in 126 patients who had previously received platinum-based chemotherapy (± immunotherapy).204 The median overall survival was 12.5 months (95% CI, 10.0–could not be evaluated). The response rate was 37.1% (95% CI, 28.6%–46.2%). Grade 3 adverse events occurred in 19.8% of patients (25/126); one grade 4 event occurred.

The NCCN NSCLC Panel recommends sotorasib as a subsequent therapy option for select patients with metastatic NSCLC and KRAS p.G12C mutations who have disease progression after treatment with platinum-based chemotherapy (± immunotherapy) based on clinical trial data and FDA approval (see NSCL-25, page 501).204 However, responsiveness to sotorasib has not been assessed for mutations other than KRAS G12C.

**Oral TKIs That Inhibit METex14 Skipping Mutations**

Oncogenic driver genomic alterations in MET include METex14 skipping mutations, MET gene copy number (GCN) gain or amplification, and MET protein overexpression. METex14 skipping mutations occur in 3%–4% of patients with adenocarcinoma NSCLC and 1%–2% of patients with other NSCLC histologies.205,206 High-level MET amplification is discussed in another section (see “Agents That Inhibit ERBB2 (HER2) Mutations and High-Level MET Amplifications,” page 522). The NCCN panel recommends testing for METex14 skipping mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data.34,73,207 METex14 skipping mutation testing should be considered in patients with metastatic squamous cell carcinoma.

**Capmatinib**

Capmatinib is an oral TKI that selectively inhibits MET genomic alterations. Capmatinib has been assessed in phase 1 and 2 studies of patients with advanced NSCLC.34,74,208,209 GEOMETRY, a phase 2 study, assessed capmatinib in different cohorts of patients with MET genomic alterations, including those with METex14 skipping mutations; patients had stage IIIIB or IV NSCLC and were wild-type for EGFR and ALK genomic alterations.34,74 Updated results from GEOMETRY show that first-line therapy with capmatinib yielded an overall response rate of 68% (95% CI, 48%–84%) in 28 patients with METex14 skipping mutations; the median PFS was
9.13 months (5.52–13.9 months) for first-line therapy.\textsuperscript{34} Subsequent therapy with capmatinib yielded an overall response rate of 41% (95% CI, 29%–53%) in 69 patients with METex14 skipping mutations; the median PFS was 5.42 months (95% CI, 4.17–6.97 months) for subsequent therapy.\textsuperscript{34} Updated results from GEOMETRY suggest that capmatinib is effective for patients with brain metastases.\textsuperscript{34,208} Of patients with brain metastases, 54% (7/13) responded to capmatinib; 4 patients had a complete response in the brain. However, 43% (3/7) of patients who responded had previously received RT.\textsuperscript{34} Common adverse events for patients with METex14 skipping mutations across all cohorts included peripheral edema (65%), nausea (46%), and vomiting (26%), but most of these events were grades 1 to 2.\textsuperscript{34} Grade 3 to 4 adverse events occurred in 75% of patients. One treatment-related death occurred. There were fewer adverse GI events when capmatinib was administered without fasting.

The NCCN NSCLC Panel recommends capmatinib as either a first-line therapy or subsequent therapy option (preferred) for patients with metastatic NSCLC who are positive for METex14 skipping mutations based on clinical trial data and the FDA approval.\textsuperscript{34,73,208} Capmatinib may be used as a subsequent therapy option if it, tepotinib, or crizotinib were not previously given as first-line therapy. The panel preference stratified the recommended regimens for patients with METex14 skipping mutation-positive metastatic NSCLC and decided that capmatinib and tepotinib are preferred first-line therapy or subsequent therapy options. The panel preference stratified the overall response rate is about 42% (10/24). Preliminary data suggest the overall response rate is about 42% (10/24).

The NCCN NSCLC Panel recommends tepotinib as either a first-line or subsequent therapy option (preferred) for eligible patients with METex14 skipping mutations based on clinical trial data. Tepotinib is an oral TKI that selectively inhibits MET ex14 skipping mutations and high-level MET amplification. VISION, a phase 2 study, assessed tepotinib in patients with METex14 skipping mutations; patients mainly had stage IV NSCLC and were wild-type (negative) for EGFR and ALK genomic alteration. The response rate to tepotinib was 46% (95% CI, 36%–57%); PFS was 8.5 months (95% CI, 6.7–11) in the combined biopsy group (tissue biopsy plus plasma circulating tumor DNA). Grade 3 or higher adverse events occurred in 28% of patients receiving tepotinib, such as peripheral edema (7%); 11% of patients had to permanently discontinue tepotinib because of peripheral edema, pleural effusion, or dyspnea. One treatment-related death occurred. Another cohort of the VISION trial assessed tepotinib in 24 patients with advanced NSCLC and MET amplification but without METex14 skipping mutations.\textsuperscript{31} Systemic therapy regimens were also recommended as useful in certain circumstances for first-line therapy (eg, carboplatin/pemetrexed or paclitaxel). These platinum doublets may be used as subsequent therapy options for patients with disease progression on capmatinib, tepotinib, or crizotinib.

### Tepotinib

Tepotinib is an oral TKI that selectively inhibits METex14 skipping mutations and high-level MET amplification. VISION, a phase 2 study, assessed tepotinib in patients with METex14 skipping mutations; patients mainly had stage IV NSCLC and were wild-type (negative) for EGFR and ALK genomic alteration. The response rate to tepotinib was 46% (95% CI, 36%–57%); PFS was 8.5 months (95% CI, 6.7–11) in the combined biopsy group (tissue biopsy plus plasma circulating tumor DNA). Grade 3 or higher adverse events occurred in 28% of patients receiving tepotinib, such as peripheral edema (7%); 11% of patients had to permanently discontinue tepotinib because of peripheral edema, pleural effusion, or dyspnea. One treatment-related death occurred. Another cohort of the VISION trial assessed tepotinib in 24 patients with advanced NSCLC and MET amplification but without METex14 skipping mutations. Preliminary data suggest the overall response rate is about 42% (10/24).

The NCCN NSCLC Panel recommends tepotinib as either a first-line or subsequent therapy option (preferred) for eligible patients with metastatic NSCLC who are positive for METex14 skipping mutations based on clinical trial data and FDA approval. Tepotinib may be used as a subsequent therapy option for METex14 skipping mutation-positive metastatic NSCLC if tepotinib, capmatinib, or crizotinib were not previously given as first-line therapy. The NCCN NSCLC Panel preference stratified the recommended regimens for patients with METex14 skipping mutation-positive metastatic NSCLC and decided that tepotinib and capmatinib are preferred first-line therapy or subsequent therapy options based on clinical trial data. For the 2022 update (Version 1), the panel added tepotinib for patients with advanced NSCLC and high-level MET amplification based on preliminary data; capmatinib and crizotinib are also recommended options in this setting. As previously
mentioned, high-level MET amplification is an emerging biomarker in the NCCN Guidelines.

**Oral Agents That Inhibit NTRK1/2/3 Gene Fusions**

NTRK1/2/3 gene fusions encode TRK fusion proteins that act as oncogenic drivers for various solid tumors, including lung, salivary gland, thyroid, and sarcoma. The NCCN panel recommends testing for NTRK1/2/3 gene fusions in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data. NTRK1/2/3 gene fusions testing should be considered in patients with metastatic squamous cell carcinoma.

**Entrectinib**

Entrectinib inhibits TRK fusion proteins across a range of solid tumors in young and older patients with unresectable or metastatic disease; thus, entrectinib is an age- and tumor-agnostic therapy. Entrectinib has been assessed in several phase 1 and 2 trials in patients with NTRK gene fusion-positive metastatic NSCLC (phase 2 STARTRK-2 trial, phase 1 STARTRK-1 trial, and phase 1 ALKA-372-001 trial). Pooled data from these 3 trials in 10 patients with NTRK gene fusion-positive NSCLC showed that entrectinib yielded an overall response rate of 70% (95% CI, 35%–93%); 7/10: 7/7 adenocarcinoma NSCLC, 0/3 squamous cell carcinoma, unclassified, or undifferentiated NSCLC; there was one complete response. Most patients (70%) with NTRK gene fusion-positive NSCLC had received one or more lines of previous therapy. In 6 patients with CNS disease, entrectinib yielded an intracranial response rate of 67% (4/6; 2 complete responses and 2 partial responses). Grade 3 adverse events with entrectinib across a range of solid tumors included anemia and increased weight. Grade 4 adverse events occurred in 3 patients (ie, increased AST, increased ALT, blood uric acid, hyperuricemia). Nervous system disorders were the most common serious treatment-related adverse event (4% [3/68] and 3% [10/355]). No treatment-related deaths were reported.

The NCCN NSCLC Panel recommends entrectinib as either a first-line or subsequent therapy option for patients with NTRK1/2/3 gene fusion-positive metastatic NSCLC based on these data and the FDA approval. Larotrectinib may be used as a subsequent therapy option for patients with NTRK1/2/3 gene fusion-positive metastatic NSCLC if larotrectinib or entrectinib were not previously given as first-line therapy. The panel has preference stratified the systemic therapy options for patients with NTRK1/2/3 gene fusion-positive metastatic NSCLC and decided that larotrectinib and entrectinib are preferred first-line therapy options. Other systemic therapy regimens (eg, carboplatin/[pemetrexed or paclitaxel]) are also recommended as either first-line or subsequent therapy options and categorized as useful in certain circumstances.

**Larotrectinib**

Larotrectinib is an oral TKI that inhibits TRK fusion proteins across a diverse range of solid tumors in younger and older patients with unresectable or metastatic disease; thus, larotrectinib is referred to as an age- and tumor-agnostic therapy. A study in 55 patients with NTRK gene fusion-positive disease across a range of solid tumors showed that larotrectinib yielded an overall response rate of 75% (95% CI, 61%–85%). An updated analysis showed that 90% of patients were still alive after 1 year, 18% of patients had a complete response, 69% of patients were still responding, and 58% of patients did not have disease progression. An additional 35 patients with NTRK gene fusion-positive disease had an overall response rate of 74%. Fewer than 3% of patients had adverse events of grade 3 to 4. A combined analysis of pediatric and adult patients reported an overall response rate of 79% (95% CI, 72%–85%).

The NCCN NSCLC Panel recommends larotrectinib as either a first-line or subsequent therapy option for patients with NTRK1/2/3 gene fusion-positive metastatic NSCLC based on these data and the FDA approval. Larotrectinib may be used as a subsequent therapy option for patients with NTRK1/2/3 gene fusion-positive metastatic NSCLC if larotrectinib or entrectinib were not previously given as first-line therapy. The panel has preference stratified the systemic therapy options for patients with NTRK1/2/3 gene fusion-positive metastatic NSCLC and decided that larotrectinib and entrectinib are preferred first-line therapy options. Other systemic therapy regimens (eg, carboplatin/[pemetrexed or paclitaxel]) are also recommended as either first-line or subsequent therapy options and categorized as useful in certain circumstances.

**Oral TKIs That Inhibit RET Rearrangements**

RET is a tyrosine kinase receptor that affects cell proliferation and differentiation. Rearrangements may occur in NSCLC between the RET gene and other domains, especially kinesin family 5B (KIF5B) and coiled coil domain containing-6 (CCDC6), which lead to overexpression of the RET protein. RET rearrangements occur in about 1%–2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology. The NCCN panel recommends testing for RET rearrangements in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data and FDA approvals of several agents. RET rearrangement testing should be considered in patients with metastatic squamous cell carcinoma.

**Cabozantinib**

Cabozantinib is an oral TKIs that inhibits RET rearrangements but also inhibits other kinases. A phase 2 study.
assessed cabozantinib in 26 patients.\textsuperscript{77,78,220} The overall response rate was 28% (95% CI, 12%–49%). Many patients (19 [73%]) needed dose reductions because of adverse events. The most common grade 3 adverse events included lipase elevation (4 patients [15%]), increased ALT (2 [8%]), decreased platelet count (2 [8%]), and hypophosphatemia (2 [8%]). The NCCN NSCLC Panel recommends cabozantinib as a first-line or subsequent therapy option (useful in certain circumstances) for \textit{RET} rearrangement-positive metastatic NSCLC based on clinical trial data.\textsuperscript{77,78} Cabozantinib may be used as a subsequent therapy option if pralsetinib, selpercatinib, or cabozantinib were not previously given as first-line therapy for \textit{RET} rearrangement-positive metastatic NSCLC. For the 2022 update (Version 1), the panel deleted vandetanib because there are better therapy options.\textsuperscript{221,222}

\textbf{Pralsetinib}

Pralsetinib is an oral TKI that selectively inhibits \textit{RET} rearrangements. ARROW, a phase 1/2 study, assessed pralsetinib in patients with metastatic NSCLC and \textit{RET} rearrangements.\textsuperscript{79} First-line therapy with pralsetinib yielded an overall response rate of 70% (19/27; 95% CI, 50%–86%); 3 patients (11%) had a complete response. Second-line therapy with pralsetinib yielded an overall response rate of 61% (53/87; 95% CI, 50%–71%); 5 patients (6%) had a complete response. Nine patients had measurable brain metastases, and 56% of them responded to pralsetinib; 3 patients had an intracranial complete response. Grade 3 or more adverse events with pralsetinib include anemia (10%), neutropenia (18%), and hypertension (11%). Common adverse events with pralsetinib included increased AST levels (31%), increased ALT levels (21%), anemia (22%), hypertension (20%), constipation (21%), and neutropenia (19%). Only 4% of patients (5/132) had to stop taking pralsetinib because of side effects. No treatment-related deaths were reported. The NCCN NSCLC Panel recommends pralsetinib as a first-line or subsequent therapy option (preferred) for patients with metastatic NSCLC who are positive for \textit{RET} rearrangements based on clinical trial data.\textsuperscript{75,76} The panel decided that cabozantinib is useful in certain circumstances.\textsuperscript{77,78,220} Selpercatinib, pralsetinib, or cabozantinib may be used as subsequent therapy options if they were not previously given as first-line therapy for \textit{RET} rearrangement-positive metastatic NSCLC. Systemic therapy regimens (other recommended regimens) are also recommended as first-line therapy options for patients with metastatic NSCLC who are positive for \textit{RET} rearrangements; these systemic regimens include platinum doublets, (eg, carboplatin plus [pemetrexed or paclitaxel]). These platinum doublets may be used as subsequent therapy options for patients with disease progression on pralsetinib, selpercatinib, or cabozantinib.

\textbf{Selpercatinib}

Selpercatinib is an oral TKI that selectively inhibits \textit{RET} rearrangements. Libretto-001, a phase 1/2 study, assessed selpercatinib in patients with NSCLC and \textit{RET} rearrangements.\textsuperscript{66,219} Updated results from Libretto-001 show that first-line therapy with selpercatinib yielded an overall response rate of 85% (33/39; 95% CI, 70%–94%).\textsuperscript{76} Second-line therapy with selpercatinib yielded an overall response rate of 64% (67/105; 95% CI, 54%–73%); the median PFS was 18.4 months (95% CI, 16.4–24.8). Of patients with brain metastases, 91% (10/11) responded to selpercatinib. Common grade 3 or more adverse events with selpercatinib included hypertension (14%), increased liver enzyme levels (12%), hyponatremia (6%), and lymphopenia (6%). Only 2% of patients (12/531) had to stop taking selpercatinib because of side effects. The NCCN NSCLC Panel recommends selpercatinib as a first-line or subsequent therapy option (preferred) for patients with metastatic NSCLC who are positive for \textit{RET} rearrangements based on clinical trial data and FDA approval.\textsuperscript{208,219} Selpercatinib may be used as a subsequent therapy option for patients with \textit{RET} rearrangement-positive metastatic NSCLC if selpercatinib, pralsetinib, or cabozantinib were not previously given.

\textbf{Preference Stratification}

The NCCN NSCLC Panel preference stratified the recommended regimens for \textit{RET} rearrangement-positive metastatic NSCLC and decided that selpercatinib and pralsetinib are preferred first-line or subsequent therapy options based on clinical trial data.\textsuperscript{75,76} The panel decided that cabozantinib is useful in certain circumstances.\textsuperscript{77,78,220} Selpercatinib, pralsetinib, or cabozantinib may be used as subsequent therapy options if they were not previously given as first-line therapy for \textit{RET} rearrangement-positive metastatic NSCLC. Systemic therapy regimens (other recommended regimens) are also recommended as first-line therapy options for patients with metastatic NSCLC who are positive for \textit{RET} rearrangements; these systemic regimens include platinum doublets, (eg, carboplatin plus [pemetrexed or paclitaxel]). These platinum doublets may be used as subsequent therapy options for patients with disease progression on pralsetinib, selpercatinib, or cabozantinib.

\textbf{Oral TKIs That Inhibit ROS1 Rearrangements}

Although ROS proto-oncogene 1 (\textit{ROS1}) is a distinct receptor tyrosine kinase, it is very similar to ALK and members of the insulin receptor family.\textsuperscript{223,224} It is estimated that \textit{ROS1} rearrangements occur in about 1%–2% of patients with NSCLC.\textsuperscript{224–227} The NCCN panel recommends testing for \textit{ROS1} rearrangements in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data and FDA approvals of several agents.\textsuperscript{66,71,72,212,213,228} \textit{ROS1} rearrangement testing should be considered in patients with metastatic squamous cell carcinoma. The panel recommends four agents for patients with \textit{ROS1}-positive metastatic NSCLC—ceritinib, crizotinib, entrectinib, and lorlatinib—based on clinical trial data and FDA approvals, which are described in the following sections.
Ceritinib
Ceritinib is an oral second-generation TKI that inhibits ALK and ROS1 rearrangements.\textsuperscript{96} A phase 2 trial assessed ceritinib as first-line therapy in patients (n = 28 evaluable) with NSCLC and ROS1 rearrangements.\textsuperscript{96} One complete response and 19 partial responses (overall response rate, 62% [95% CI, 45%–77%]) were reported in patients receiving ceritinib. PFS was 19.3 months (95% CI, 1–37) for ceritinib-naive patients and 9.3 months (95% CI, 0–22) for all patients. The median overall survival was 24 months (95% CI, 5–43).

The NCCN NSCLC Panel recommends ceritinib as a first-line therapy option for patients with ROS1-positive metastatic NSCLC based on clinical trial data.\textsuperscript{96} Ceritinib is an option if an ROS1 rearrangement is discovered before giving, or during, first-line systemic therapy (eg, carboplatin/ [pemetrexed or paclitaxel]). The panel has preference stratified the first-line therapy options for patients with ROS1-positive metastatic NSCLC. The panel decided that crizotinib and entrectinib are preferred first-line therapy options for patients with ROS1-positive metastatic NSCLC because they are better tolerated, have been assessed in more patients, and are approved by the FDA for ROS1-positive NSCLC. Ceritinib is an “other recommended” option for patients with ROS1-positive metastatic NSCLC. Lorlatinib is recommended as a subsequent therapy option in patients with ROS1-positive metastatic NSCLC whose disease becomes resistant to ceritinib, crizotinib, or entrectinib.\textsuperscript{67} However, entrectinib is recommended as a subsequent therapy option for patients with CNS progression after crizotinib or ceritinib.

Crizotinib
Crizotinib is a first-generation oral TKI that inhibits ALK rearrangements, ROS1 rearrangements, and some MET tyrosine kinases (high-level MET amplification or METex14 skipping mutation).\textsuperscript{109–107} Crizotinib is very effective for patients with ROS1 rearrangements with response rates of about 70%–80% including complete responses.\textsuperscript{102,224–229,231} A phase 2 trial assessed crizotinib in 127 East Asian patients with ROS1-positive advanced NSCLC who had received 3 or fewer lines of therapy. The overall response rate was 72% (95% CI, 63%–79%) with 17 complete responses; the median duration of response was 19.7 months (95% CI, 14.1–not reached). The median PFS was 15.9 months (95% CI, 12.9–24.0).\textsuperscript{230}

PROFILE 1001, a phase 2 study, assessed crizotinib in 50 patients with advanced NSCLC who were positive for ROS1 rearrangements.\textsuperscript{224} Crizotinib yielded an objective response rate of 72% (95% CI, 58%–83%) with crizotinib including 6 confirmed complete responses in 53 patients with ROS1-positive advanced NSCLC.\textsuperscript{20} The median overall survival was 51.4 months (95% CI, 29.3–not reached). No grade 4 or higher treatment-related adverse events were reported.

The EUCROSS study reported crizotinib yielded an overall response rate of 70% (21/30; 95% CI, 51%–85%) in 30 patients with ROS1-positive advanced NSCLC.\textsuperscript{229} Adverse events related to treatment occurred in 97% (33/34) of patients. A retrospective European study in patients (n = 30 evaluable) with stage IV NSCLC and ROS1 rearrangements also assessed crizotinib.\textsuperscript{103} There were 5 complete responses (overall response rate, 80%; disease control rate, 86.7%). The median PFS was 9.1 months. Many patients (n = 26) received pemetrexed (either alone or in combination with platinum and either before or after crizotinib) and had a response rate of 57.7% and a median PFS of 7.2 months.

The NCCN NSCLC Panel recommends crizotinib as a first-line treatment option for patients with ROS1-positive metastatic NSCLC based on clinical trial data and FDA approval.\textsuperscript{20,224,228,230} Crizotinib is a preferred option if a ROS1 rearrangement is discovered before giving, or during, first-line systemic therapy (eg, carboplatin/ [pemetrexed or paclitaxel]). The panel decided that crizotinib and entrectinib are the preferred agents for first-line therapy in patients with ROS1-positive metastatic NSCLC, compared with ceritinib, because they are better tolerated, have been assessed in more patients, and are approved by the FDA for ROS1-positive NSCLC. Lorlatinib is recommended as a subsequent therapy option in patients with ROS1-positive metastatic NSCLC whose disease becomes resistant to crizotinib, ceritinib, or entrectinib. However, entrectinib is recommended as subsequent therapy for patients with CNS progression after crizotinib or ceritinib.\textsuperscript{67}

Entrectinib
Entrectinib is an oral TKI that inhibits several tyrosine kinases including ROS1 and TRK.\textsuperscript{228,232} Entrectinib has been assessed in several phase 1 and 2 trials in patients with ROS1-positive metastatic NSCLC (ie, phase 2 STARTRK-2 trial, phase 1 STARTRK-1 trial, phase 1 ALKA-372-001 trial).\textsuperscript{212,213} Pooled data from these 3 trials in 53 patients with ROS1-positive metastatic NSCLC receiving first-line entrectinib showed an overall response rate of 77% (41/53; 95% CI, 64%–88%; 3 complete responses).\textsuperscript{212,230} The intracranial overall response rate was 55% (95% CI, 32%–77%; 4 complete responses, 7 partial responses).\textsuperscript{212,213} In the larger ROS1 population (n = 134), grade 3 to 4 adverse events were seen in 34% of patients. Fifteen patients had serious adverse events such as nervous system disorders (4 patients [3%]) and cardiac disorders (3 patients [2%]). No treatment-related deaths were reported. Although entrectinib has better CNS penetration than crizotinib, it is more toxic.\textsuperscript{233}
The NCCN NSCLC Panel recommends entrectinib as a first-line therapy option for patients with ROS1-positive metastatic NSCLC (preferred) based on these data and FDA approval (see NSCL-29, page 503).

For the 2022 update (Version 1), the panel clarified that entrectinib is recommended as a subsequent therapy option for patients with ROS1-positive metastatic NSCLC and disease progression with brain metastases on crizotinib or ceritinib (see NSCL-30, page 504). Subsequent therapy with lorlatinib is also recommended for select patients with ROS1-positive metastatic NSCLC and disease progression after treatment with crizotinib, ceritinib, or entrectinib. The panel has preference stratified the recommended regimens for patients with ROS1-positive metastatic NSCLC and decided that entrectinib and crizotinib are preferred first-line therapy options; ceritinib is stratified as an “other recommended” option.

**Lorlatinib**

Lorlatinib is a third-generation oral TKI that targets ALK and ROS1 tyrosine kinases and has good CNS penetration. A phase 1 to 2 trial assessed lorlatinib in patients with ROS1-positive metastatic NSCLC. Many patients (58% [40/69]) had previously received crizotinib; some patients were TKI naïve (30% [21/69]). Objective responses were achieved in 35% (14/40) of patients who had previously received crizotinib and 62% (13/21) of TKI-naïve patients. An intracranial response was observed in 50% (12/24) of patients who had previously received crizotinib and 64% (7/11) of TKI-naïve patients. Serious treatment-related adverse events occurred in 7% (5/69) of patients; no treatment-related deaths were reported.

The NCCN NSCLC Panel recommends lorlatinib as a subsequent therapy option for select patients with ROS1-positive metastatic NSCLC and disease progression after treatment with crizotinib, ceritinib, or entrectinib, depending on the type of progression. However, entrectinib is recommended as subsequent therapy for patients with CNS progression after crizotinib or ceritinib alone. Grade 4 adverse events occurred in 8% (9/112) of patients receiving erlotinib/bevacizumab (including neutropenia, hepatic dysfunction) versus 4% (5/114) of patients receiving erlotinib alone (hepatic dysfunction). No treatment-related deaths were reported.

**Agents That Inhibit VEGF or VEGF Receptors**

**Bevacizumab**

Bevacizumab is a recombinant monoclonal antibody that targets VEGE NEJ026, a phase 3 randomized trial, compared first-line bevacizumab plus erlotinib versus erlotinib alone in 228 patients with EGFR-positive advanced nonsquamous NSCLC. At interim analysis, PFS was 16.9 months (95% CI, 14.2–21.0) for erlotinib/bevacizumab versus 13.3 months (95% CI, 11.1–15.3) for erlotinib alone (HR, 0.605; 95% CI, 0.417–0.877; P=.016). Grade 3 or worse events occurred in 88% (98/112) of patients receiving erlotinib/bevacizumab versus 46% (53/114) of erlotinib alone. Grade 4 adverse events occurred in 8% (9/112) of patients receiving erlotinib/bevacizumab (including neutropenia, hepatic dysfunction) versus 4% (5/114) of patients receiving erlotinib alone (hepatic dysfunction). No treatment-related deaths were reported. Updated data show median overall survival was 50.7 months (95% CI, 37.3–not estimable) in those receiving erlotinib/bevacizumab versus 46.2 months (95% CI, 38.2–not estimable) in those receiving erlotinib alone (HR, 1.007; 95% CI, 0.681–1.490; P=.97).

**Ramucirumab**

Ramucirumab is a recombinant monoclonal antibody that targets VEGF receptors.

**First-Line Therapy for Ramucirumab**

RELAY, a phase 3 randomized trial, compared first-line therapy with ramucirumab/erlotinib versus erlotinib alone in patients with advanced NSCLC and the common EGFR mutations. PFS was 19.4 months (95% CI, 15.4–21.6) with ramucirumab/erlotinib versus 12.4 months (95% CI, 11.0–13.5) with erlotinib alone (HR, 0.59; 95% CI, 0.46–0.76; P<.0001). Serious adverse events (grade 3–4) occurred in 72% (159/221) of patients receiving erlotinib/ramucirumab (including hypertension) versus 54% (121/225) in those receiving erlotinib alone (including increased ALT). One treatment-related death occurred in a patient receiving erlotinib/ramucirumab. The NCCN NSCLC Panel recommends erlotinib/ramucirumab as a first-line therapy option for patients with metastatic NSCLC and EGFR exon 19 deletions or L858R mutations (other recommended intervention) based on clinical data. The panel recommends osimertinib as a preferred first-line therapy option for patients with EGFR positive metastatic NSCLC.

**Subsequent Therapy for Ramucirumab**

REVEL, a phase 3 randomized trial, assessed ramucirumab/docetaxel versus docetaxel alone in patients with metastatic NSCLC and disease progression. The median overall survival was 10.5 months for ramucirumab/docetaxel versus 9.1 months for docetaxel alone (HR, 0.86; 95% CI, 0.75–0.98; P=.023). More than 70% of patients had grade 3 or higher adverse events in both groups (79% for ramucirumab/docetaxel vs 71% for docetaxel alone). Adverse events of special concern with ramucirumab/
docetaxel therapy include risk for severe hemorrhage, grade 3 to 4 gastrointestinal bleeding, gastrointestinal perforation or fistula, impaired wound healing, and poorly controlled hypertension. There were 16 deaths from grade 3 or worse pulmonary hemorrhage and other adverse events in the REVEL trial: 8 deaths in the ramucirumab/docetaxel arm and 8 deaths in the docetaxel alone arm. The NCCN NSCLC Panel recommends ramucirumab/docetaxel as a subsequent therapy option for patients with metastatic NSCLC, regardless of histology, based on clinical data and the FDA approval.234,235

**Agents That Inhibit ERBB2 (HER2) Mutations and High-Level MET Amplifications**

ERBB2 (HER2) mutations and high-level MET amplifications are designated as emerging biomarkers in the NCCN Guidelines, because there is less evidence for using targeted agents for these biomarkers and the recommended agents have not been FDA approved for these mutations in patients with NSCLC, although they are approved for other cancers. For the 2022 update (Version 1), the panel feels that optimal biomarker testing should include testing for ERBB2 (HER2) mutations and high-level MET amplifications in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on clinical trial data. Testing for these biomarkers can be considered in patients with squamous cell carcinoma.

ERBB2 (HER2) Mutations

The NCCN NSCLC Panel does not recommend single-agent therapy with trastuzumab or afatinib for patients with ERBB2 mutations, because response rates are lower and treatment is less effective with these agents.236,237

Ado-Trastuzumab Emtansine

A phase 2 basket trial assessed ado-trastuzumab emtansine in patients with metastatic NSCLC and ERBB2 (HER2) mutations.23,238 The partial response rate was 44% (95% CI, 22%–69%). The median PFS was 5 months (95% CI, 3–9). Minor toxicities (grade 1–2) included infusion reactions, thrombocytopenia, and transaminitis; no treatment-related deaths were reported. Patients (n=18) were mostly women (72%), nonsmokers, and all had adenocarcinomas. The NCCN NSCLC Panel recommends ado-trastuzumab emtansine as a treatment option for patients with metastatic NSCLC and ERBB2 (HER2) mutations based on this study (see NSCL-I, page 505).

Fam-Trastuzumab Deruxtecan-nxki

DESTINY-Lung01, a phase 2 study, assessed fam-trastuzumab deruxtecan-nxki in 91 patients with metastatic nonsquamous NSCLC and ERBB2 mutations.32,35-36 Updated results show that the overall response rate with fam-trastuzumab deruxtecan-nxki was 55% (95% CI, 44%–65%); most patients had received prior treatment.32 Median overall survival was 17.8 months (95% CI, 13.8–22.1).32 Grade 3 or higher adverse events occurred in 46% of patients including neutropenia (19%). Two patients died of drug-related interstitial lung disease. The NCCN NSCLC Panel recommends fam-trastuzumab deruxtecan-nxki as a treatment option for patients with metastatic NSCLC and ERBB2 mutations based on clinical trial data (see NSCL-I, page 505).32,35,36

**High-Level MET Amplification**

The definition of high-level MET amplification is evolving and may differ depending on which assay is used. When using NGS, a copy number greater than 10 is consistent with high-level MET amplification.34

**Capmatinib**

Capmatinib is an oral TKI that selectively inhibits MET genomic alterations. GEOMETRY assessed capmatinib in patients with metastatic NSCLC and high-level MET amplification.34 For first-line capmatinib, response rates were 40% (95% CI, 16%–68%); for second-line capmatinib, response rates were 29% (95% CI, 19%–41%). Adverse events for patients with high-level MET amplification across all cohorts included peripheral edema (49%), vomiting (30%), and nausea (48%); most of these events were grade 1 or 2. Grade 3 to 4 adverse events occurred in 68% of patients. The NCCN NSCLC Panel recommends capmatinib for patients with advanced NSCLC and high-level MET amplification based on clinical trial data; crizotinib and tepotinib are also recommended options in this setting (see NSCL-I, page 505).31,34,210,211,239

**Crizotinib**

Crizotinib is an oral TKI that inhibits some MET tyrosine kinases (high-level MET amplification or METex14 skipping mutation), ALK rearrangements, and ROS1 rearrangements. A subanalysis of PROFILE 1001 assessed crizotinib in patients with advanced NSCLC and different levels of MET amplification; 40% (6/15) of patients responded to crizotinib who had MET amplification with a gene copy number of 6 or more by NGS.39 Two of these patients who responded had concurrent MET exon 14 skipping mutations. The overall response rate to crizotinib was 29% in patients with a gene copy number of 10 or more. Patients who had concurrent KRAS, BRAF, or EGFR mutations did not respond to crizotinib. Most patients had adenocarcinoma and had received at least one line of therapy. The median overall survival was 11.4 months (95% CI, 7.2–19.3) in the group with higher MET amplification. There was one treatment-related death.
A patient with stage IV moderately differentiated adenocarcinoma had a partial response on first-line therapy with carboplatin plus gemcitabine plus bevacizumab; she received maintenance therapy with bevacizumab. Her tumor was found to have high-level MET amplification (MET/CEPT ratio >5.0) and was negative for ALK rearrangements. The patient had a rapid and durable response to single-agent therapy with crizotinib (54.8% reduction in aggregate tumor measurement). She had mild grade 1 side effects including asymptomatic sinus bradycardia and transient visual disturbances.

The NCCN NSCLC Panel recommends crizotinib for patients with advanced NSCLC and high-level MET amplification based on clinical trial data; capmatinib and tepotinib are also recommended options in this setting (see NSCL-I, page 505).31,34,210,211

**Tepotinib**

Tepotinib is an oral TKI that selectively inhibits METex14 skipping mutations and high-level MET amplification; it is approved by the FDA for patients with metastatic NSCLC who have METex14 skipping mutations. Another cohort of the VISION trial assessed tepotinib in 24 patients with advanced NSCLC and MET amplification but without METex14 skipping mutations.31 Preliminary data suggest the overall response rate is about 42% (10/24). For the 2022 update (Version 1), the NCCN NSCLC Panel now recommends tepotinib for patients with advanced NSCLC and high-level MET amplification based on preliminary data; capmatinib and crizotinib are also recommended options in this setting (see NSCL-I, page 505).31,34,210,211

**Summary**

The NCCN Guidelines for NSCLC are updated at least once a year by the NCCN NSCLC Panel; 2021 guidelines had 7 updates. The “Summary of the Guidelines Updates” describes the most recent revisions to the algorithms, which have been incorporated into this updated discussion text (to view the complete and most recent version of these Guidelines, visit NCCN.org). This selection from the NCCN Guidelines for NSCLC focuses on targeted therapies for patients with metastatic NSCLC and actionable mutations. A brief summary of some of the recent updates for 2022 (Version 1 and maintained in Version 3) for molecular testing is as follows. The NCCN NSCLC Panel now recommends molecular testing in eligible patients with metastatic NSCLC for less common EGFR mutations—EGFR S768I, L861Q, and G719X—based on data showing the efficacy of certain EGFR TKIs for patients with these mutations. The panel recommends afatinib or osimertinib as preferred first-line therapy options for patients with metastatic NSCLC and EGFR S768I, L861Q, and/or G719X mutations.176,240 Other recommended options in this setting include erlotinib, gefitinib, or dacomitinib. New algorithm pages with treatment recommendations were added for these less common EGFR mutations.

For the 2022 update (Version 1), the NCCN Panel added new content about biomarker testing in eligible patients with NSCLC. For example, broad molecular profiling is defined as molecular testing that identifies all of the established actionable driver mutations described in the algorithm (eg, ALK, BRAF, EGFR, KRAS p.G12C, METex14 skipping, NTRK1/2/3, RET, ROS1)—using either a single assay or a combination of a limited number of assays—and optimally also identifies emerging actionable molecular biomarkers, including high-level MET amplification and ERBB2 (HER2) mutations. Tiered testing approaches, based on the low prevalence of co-occurring biomarkers, are acceptable. Broad genomic profiling may also be used to assess for mechanisms of resistance in patients with disease progression on targeted therapy. In addition, broad molecular profiling may be used to distinguish separate primary lung cancers from intrapulmonary metastases. The panel added a caveat that if molecular testing results are pending and patients require an urgent start to therapy, clinicians should consider holding immunotherapy for one cycle. Variants can be classified based on their pathogenicity. One classification system uses (1) variants with strong clinical significance (tier I), (2) variants with potential clinical significance (tier II), (3) variants of unknown clinical significance (tier III), and (4) variants that are benign or likely benign (tier IV).55 The NCCN Guidelines now clarify that any variant that is classified as VUS should not be used to select targeted therapy even if the VUS occurs in a gene in which other variants are clinically actionable.

For the 2022 update (Version 1), the NCCN panel added single-agent therapy with dabrafenib as an option for certain patients with BRAF.p.V600E mutation-positive metastatic NSCLC. If combination therapy with dabrafenib/trametinib is not tolerated, single-agent therapy with dabrafenib or vemurafenib are options. The panel added more detailed recommendations for subsequent therapy options for patients with ROSI-positive metastatic NSCLC and disease progression during or after first-line targeted therapy with cetirinib, crizotinib, or entrectinib. The different options depend on whether the progression is asymptomatic or symptomatic and on the site of progression. The panel deleted single-agent vandetanib (category 2B) as a first-line therapy option for patients with RET rearrangement-positive metastatic NSCLC because other therapy options are better.221,222
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### Individual Disclosures for the NCCN Non–Small Cell Lung Cancer Panel

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<td>Apans Hegle, MBBS</td>
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<td>Rudy P. Lecker, MD</td>
<td>None</td>
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<td>Michael Lavat, MD</td>
<td>None</td>
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<td>Julie Lin, MD</td>
<td>Genentech, Inc.; Novartis Pharmaceuticals Corporation</td>
<td>None</td>
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<td>Intuitive Surgical, Inc.; Lung Bronchopneumology</td>
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<td>Billy W. Loo, Jr., MD, PhD*</td>
<td>None</td>
<td>None</td>
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<td>Christine M. Lough, MD, PhD</td>
<td>Roche Laboratories, Inc.</td>
<td>None</td>
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<td>Silvia K. Madrigal, MD, MS</td>
<td>AbbVie, Inc.; ARAID Pharmaceuticals, Inc.; ArisZena Pharmaceuticals LP; Boston Biomedical; Bristol-Myers Squibb Company; Daichii- Seiki Co., El Lilly and Company; Genentech, Inc.; Glaxosmithline, Janssen Pharmaceuticals Products, LP; Kta Pharma, Merck &amp; Co., Inc.; Pfizer Inc.; TaiBda Pharmaceuticals North America, Inc.</td>
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<td>Fabian Mahonkak, MD</td>
<td>None</td>
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<td>Gracia Massarik, MD, PhD, MS</td>
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<td>Daniel Morgenstern, MD</td>
<td>AbbVie, Inc.; Arcus; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; El Lilly and Company; Epcrion, Insite Corporation; Merck &amp; Co., Inc.; NaczeninTech; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Surface</td>
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<td>Thomas Ng, MD</td>
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<td>Gregory Ottenwenger, MD</td>
<td>ARAID, Inc.; Ametite Pharma US, LLC; ArisZena Pharmaceuticals LP; BeGene, Bristol-Myers Squibb Company; Genentech, Inc.; Ixcellence; licensee pharmacological; Nascure</td>
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<td>Jose M. Pacheco, MD</td>
<td>Checkpoint Therapeutics, Daisho- Sendai Co., Harris Pharmaceuticals, Immunomedicine, Inc.; Mobi Therapeutics; Revolution Medicines</td>
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<td>Gregory J. Ratl, MD, PhD</td>
<td>Daichii- Sendai Co.; Flaton Health, Inc.; Mori; TaiBda Pharmaceuticals North America, Inc.</td>
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<td>Jonathan Ries, MD</td>
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<td>Steven E. Schild, MD</td>
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<td>Theresa A. Shapiro, MD, PhD</td>
<td>WHO/UNITAD</td>
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<td>James Stever, MD</td>
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<td>Ahsan Tariq, MD</td>
<td>Boston Scientific Corporation; Johnson &amp; Johnson</td>
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<td>Towse Turaygon, MD, MPH</td>
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<td>Douglas Wood, MD, FACS, FRCSIEd</td>
<td>Delphi Diagnostics, QGI Foundation, National Lung Cancer Roundtable</td>
<td>None</td>
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<tr>
<td>Jane Yagcioglu, MD*</td>
<td>DSM</td>
<td>Legal firm</td>
<td>Conference – Great Debates and Updates in Electrophysiology</td>
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<td>Stephen C. Yang, MD</td>
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<td>Edwin Yau, MD, PhD</td>
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</table>

The NCCN Guidelines Staff have no conflicts to declare.

*The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

- Dara Aizer, MD, PhD*; GOAL Consortium
- Billy W. Loo, Jr., MD, PhD; TaiBda Pharmaceuticals North America, Inc.
- June Yagcioglu, MD; ICONA