Non–Small Cell Lung Cancer, Version 4.2026

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Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer (NSCLC) provide recommendations for the treatment of patients with NSCLC, including diagnosis, primary disease management, surveillance, and subsequent treatment. The panel has updated the list of recommended targeted therapies based on recent FDA approvals and clinical data. This selection from the NCCN Guidelines for NSCLC focuses on treatment recommendations for advanced or metastatic NSCLC with actionable biomarkers.

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Overview

Experts estimate that 229,410 individuals will be diagnosed with lung cancer and 124,990 lung cancer-related deaths will occur within the United States in 2026.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 87% of lung cancers.[2] Survival rates for patients with NSCLC over the past few decades have improved, possibly due to increased screening, biomarker testing, and treatment advances.[3,4] Despite these improvements, lung cancer is projected to remain the leading cause of cancer-related death in the United States.[1] The 5-year overall survival (OS) rate for patients with NSCLC in the United States is approximately 32%.[5] However, survival is influenced by multiple factors, including histology, disease stage, age, and presence of actionable biomarkers.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC include recommendations for the treatment of patients with NSCLC. These NCCN Guidelines are updated by a multidisciplinary panel of NSCLC-focused experts that includes the areas of medical oncology, surgical oncology, pulmonary medicine, radiation oncology, pathology, radiology, and patient advocacy. This document describes clinical evidence supporting the recommendations related to systemic therapy for patients with advanced or metastatic NSCLC with an actionable biomarker.

Systemic Therapy for Advanced or Metastatic NSCLC with an Actionable Biomarker

Multiple classes of therapies are available for the treatment of advanced or metastatic NSCLC, including targeted therapy, immunotherapy, and chemotherapy. To identify the most appropriate initial treatment of each patient, the NCCN panel recommends establishing histologic subtype and conducting biomarker testing before starting systemic therapy. Real-world retrospective data indicate that the availability of biomarker testing results prior to treatment initiation is associated with longer OS in patients with advanced nonsquamous NSCLC.[6] Refer to Figure 1 and *Principles of Biomarker Analysis* in the NCCN Guidelines for NSCLC (available at NCCN.org) for detailed information about biomarker testing in patients with NSCLC.

Targeted therapies with a first-line indication (rather than first-line immune checkpoint inhibitors [ICIs]) are generally recommended as initial therapy for patients with advanced or metastatic NSCLC and certain oncogenic drivers, regardless of PD-L1 levels. The rationale is that targeted therapies typically yield

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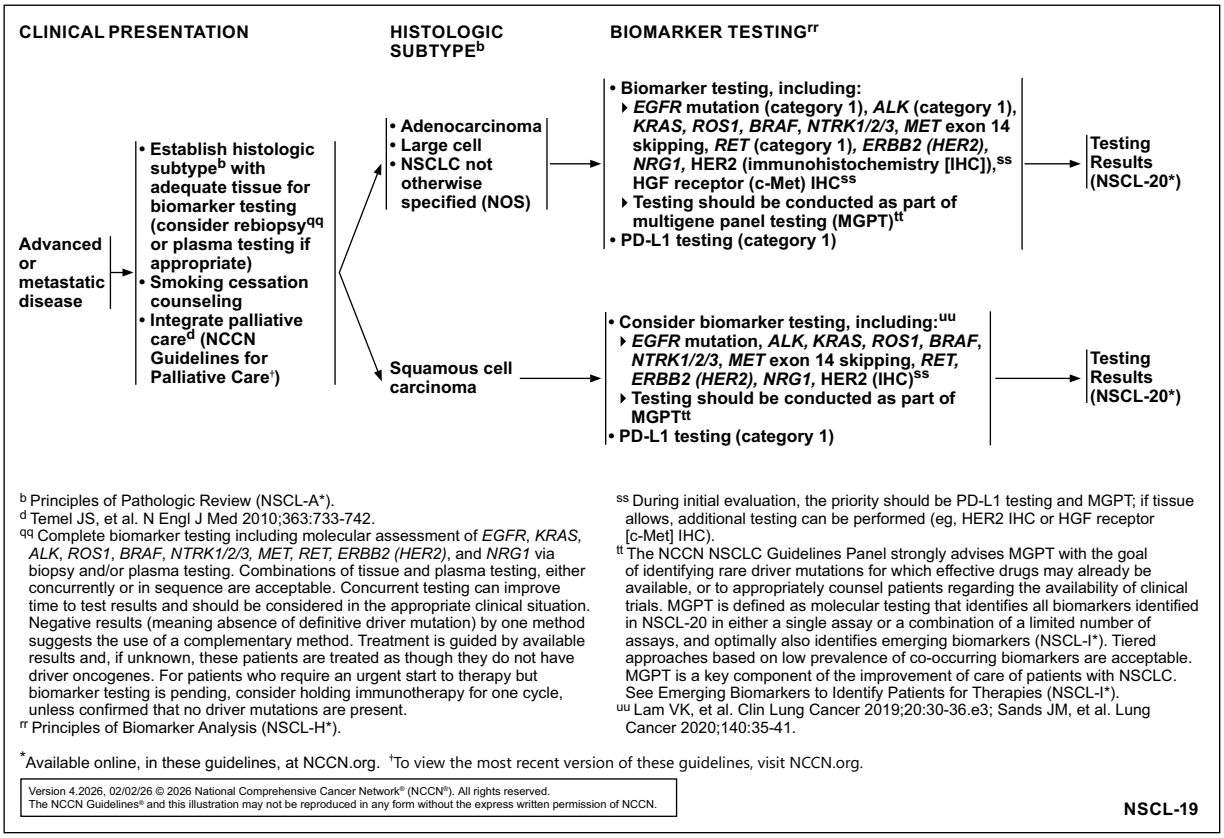
higher response rates than ICIs in the first-line setting, are better tolerated, and are often associated with better efficacy for disease in the central nervous system (CNS).[7–13] It should be noted that targeted therapies are not available or recommended for NSCLC with certain actionable biomarkers in the first-line setting. For instance, patients with *KRAS* G12C mutation-positive NSCLC are likely to benefit from immunotherapy (with or without chemotherapy) in the first-line setting.[7,14,15] Targeted therapies have been most well-studied in the second-line setting or later for those with a *KRAS* G12C mutation.

If an actionable biomarker is identified, refer to the appropriate section within the NCCN Guidelines for NSCLC for treatment recommendations. If patients require an urgent start to therapy and biomarker testing results are unknown or pending, clinicians should consider holding immunotherapy for one cycle (ie, use platinum-based chemotherapy regimens). Given the long half-life of ICIs, there is a potential for higher rates of side effects when using certain targeted therapies (such as osimertinib) in combination with or following ICIs.[16–19] Once it is confirmed that no driver mutations are



[b] Principles of Pathologic Review (NSCL-A*).
[d] Temel JS, et al. N Engl J Med 2010;363:733-742.
[qq] Complete biomarker testing including molecular assessment of *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, *ERBB2 (HER2)*, and *NRG1* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. Negative results (meaning absence of definitive driver mutation) by one method suggests the use of a complementary method. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes. For patients who require an urgent start to therapy but biomarker testing is pending, consider holding immunotherapy for one cycle, unless confirmed that no driver mutations are present.
[rr] Principles of Biomarker Analysis (NSCL-H*).
[ss] During initial evaluation, the priority should be PD-L1 testing and MGPT; if tissue allows, additional testing can be performed (eg, HER2 IHC or HGF receptor [c-Met] IHC).
[tt] The NCCN NSCLC Guidelines Panel strongly advises MGPT with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. MGPT is defined as molecular testing that identifies all biomarkers identified in NSCL-20 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I*). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. MGPT is a key component of the improvement of care of patients with NSCLC. See Emerging Biomarkers to Identify Patients for Therapies (NSCL-I*).
[uu] Lam VK, et al. Clin Lung Cancer 2019;20:30-36.e3; Sands JM, et al. Lung Cancer 2020;140:35-41.

*Available online, in these guidelines, at NCCN.org. [†]To view the most recent version of these guidelines, visit NCCN.org.

NSCL-19

Figure 1. NSCL-19. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

present, then patients can be treated as if they do not have an oncogenic driver mutation.

Best supportive care or enrollment in a clinical trial should be considered for all patients with NSCLC, if available. Smoking cessation counseling (if applicable) and palliative care should also be integrated into the disease management strategy. Early palliative care is associated with improved quality of life in patients with metastatic NSCLC.[20]

EGFR Exon 19 Deletion or L858R Mutation Positive

EGFR is a receptor tyrosine kinase that is altered in a subset of patients with NSCLC. The 2 most common *EGFR* mutations in NSCLC are exon 19 deletions and L858R; these represent approximately 85%–90% of all *EGFR* mutations in NSCLC.[21] Both result in activation of the tyrosine kinase domain and are associated with sensitivity to small-molecule EGFR tyrosine kinase inhibitors (TKIs).[22]

Clinical Data

Historically, first- and second-generation EGFR inhibitors (as monotherapy or part of combination therapy) were shown to have efficacy in patients with advanced or metastatic NSCLC and common *EGFR* mutations.[23–28] Currently, multiple appropriate first-line treatments for patients with *EGFR* exon 19 deletion or L858R mutation are available.

Osimertinib monotherapy and osimertinib in combination with platinum and pemetrexed chemotherapy are both indicated by the FDA for the first-line treatment of adults with metastatic NSCLC with *EGFR* exon 19 deletion or L858R mutation. The phase III randomized FLAURA trial assessed first-line therapy with osimertinib compared with either erlotinib or gefitinib in 556 patients with metastatic NSCLC and *EGFR* exon 19 deletion or L858R mutation.[11,29–31] The median progression-free survival (PFS) was longer with osimertinib than erlotinib or gefitinib (18.9 vs 10.2 months).[11] The median duration of response was longer with osimertinib compared with erlotinib or gefitinib (17.2 vs 8.5 months).[11] More recently, FLAURA2, a phase III randomized study, investigated first-line therapy with osimertinib in combination with chemotherapy (pemetrexed and either cisplatin or carboplatin) versus osimertinib monotherapy in 557 patients with advanced NSCLC with *EGFR* exon 19 deletion or L858R mutation.[32] Adenocarcinoma histology was reported in 99% of the patient population. The median investigator-assessed PFS was longer in the osimertinib plus chemotherapy group than in the osimertinib monotherapy group (25.5 vs 16.7 months). Based on the final analysis, the median OS was 47.5 months among patients who received osimertinib plus chemotherapy and 37.5 months among those who received osimertinib monotherapy (hazard ratio [HR], 0.77; $P=.02$).[33] The number of grade 3 adverse events (AEs) was higher with osimertinib plus chemotherapy than with osimertinib monotherapy and was primarily driven by known chemotherapy-related AEs.[32]

Antibody-based targeted therapies have recently become available for the treatment of *EGFR* mutation-positive advanced or metastatic NSCLC. Amivantamab-vmjw is a bispecific antibody against EGFR and hepatocyte growth factor (HGF) receptor (c-Met) that has been studied in a variety of contexts of NSCLC with *EGFR* mutations.[34] The phase III randomized MARIPOSA trial assessed amivantamab in combination with the third-generation EGFR TKI lazertinib (n=429) versus single-agent osimertinib (n=429) as first-line therapy in patients with *EGFR*-mutated locally advanced or metastatic NSCLC.[35] The median PFS was 23.7 months in the lazertinib + amivantamab group compared with 16.6 months for the osimertinib group. The objective response rates between the 2 groups were similar (86% vs 85%). There was a higher rate of discontinuation due to treatment-related AEs with lazertinib + amivantamab compared with osimertinib (10% vs 3%). Venous thromboembolic AEs were reported more frequently with lazertinib + amivantamab than with osimertinib (37% vs 9%). The final median OS was significantly longer in the lazertinib + amivantamab group than in the osimertinib group (not estimable [NE] vs 36.7 months; HR, 0.75; $P=.005$).[36] One group of patients in the MARIPOSA trial received single-agent lazertinib as a first-line treatment (n=216).[35] The median PFS for this group was 18.5 months.[35] Based on an exploratory analysis from this trial, the efficacy and safety of lazertinib were comparable to osimertinib in this setting.[37] Based on these data, amivantamab-vmjw in combination with lazertinib is approved by the FDA for the first-line treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or L858R substitution mutations.[38] However, lazertinib monotherapy is not currently FDA approved for these patients. In general, amivantamab and hyaluronidase-lpuj subcutaneous injection may be substituted for intravenous amivantamab-vmjw. Amivantamab and hyaluronidase-lpuj has different dosing, administration, and premedication instructions compared with intravenous amivantamab-vmjw.[38]

Amivantamab-vmjw has been studied in combination with carboplatin and pemetrexed for the treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletion or L858R mutation, whose disease has progressed on or after treatment with an EGFR TKI, and is approved in this indication.[38] This approval was based on data from the phase III randomized MARIPOSA-2 trial, which evaluated the efficacy of amivantamab-vmjw in combination with chemotherapy (carboplatin and pemetrexed) as subsequent therapy compared with chemotherapy in patients with advanced NSCLC and *EGFR* exon 19 deletion or L858R mutation whose disease progressed on or after osimertinib monotherapy.[39] The median PFS was longer for the amivantamab-vmjw plus chemotherapy group than the chemotherapy group (6.3 vs 4.2 months). The objective response rate was 64% with amivantamab-vmjw plus chemotherapy versus 36% with chemotherapy alone. The most common grade 3 or higher AEs were neutropenia, thrombocytopenia, anemia, and leukopenia. In the second interim analysis, it was reported that the median OS was numerically longer with amivantamab + chemotherapy than chemotherapy alone; however, this difference was not statistically significant (17.7 vs 15.3 months; HR, 0.73; $P=.039$).[40]

Amivantamab-vmjw in combination with lazertinib as subsequent therapy following progression on osimertinib was also evaluated in a cohort of 45 patients with advanced *EGFR* exon 19 deletion or L858R mutation-positive NSCLC from the phase I CHRYSALIS study.[41] The overall response rate was 36%, with a median PFS of 4.9 months. In this cohort, 80% of patients experienced rash-related AEs. Strategies for mitigating dermatologic toxicities related to lazertinib and amivantamab treatment in patients with *EGFR*-mutated NSCLC have been investigated in a randomized trial.[42]

Datopotamab deruxtecan is a Trop-2 directed antibody and topoisomerase inhibitor conjugate that was granted accelerated

approval by the FDA for the treatment of patients with locally advanced or metastatic *EGFR*-mutated NSCLC who have received prior *EGFR*-directed therapy and platinum-based chemotherapy.[38] The efficacy and safety of datopotamab deruxtecan was evaluated in a pooled analysis of the phase II TROPION-Lung05 and phase III randomized TROPION-Lung01 trials that included 117 patients with *EGFR* mutation-positive advanced or metastatic NSCLC who received prior targeted therapy and platinum-based chemotherapy.[43] The most common mutations were exon 19 deletion (51%) and L858R (32%); T790M was identified in 27% of patients. The median number of prior lines of therapy used to treat advanced or metastatic NSCLC in the trial was 3; 99% previously received platinum-based chemotherapy and 82% previously received osimertinib. The confirmed objective response rate was 43% and the median OS was 15.6 months. Similar efficacy outcomes were reported between patients who were previously treated with osimertinib and the overall study population. Grade 3 or higher treatment-related AEs were reported in 23% of the patients. Oral mucositis and stomatitis were among the most common AEs of special interest (69%). Ocular surface events (any grade) were reported in 32% of patients, while drug-related interstitial lung disease (ILD) or pneumonitis occurred in 4%.

Several studies have reported that PD-1/PD-L1 inhibitor monotherapy in the second-line setting is less effective in *EGFR* exon 19 deletion or L858R mutation-positive NSCLC, regardless of PD-L1 expression.[9,44–46] Recent data also suggest that a PD-1 inhibitor (such as pembrolizumab or nivolumab) in combination with chemotherapy as subsequent therapy does not have an OS or PFS benefit compared with chemotherapy alone in patients with metastatic NSCLC and an *EGFR* exon 19 deletion or L858R mutation.[47,48]

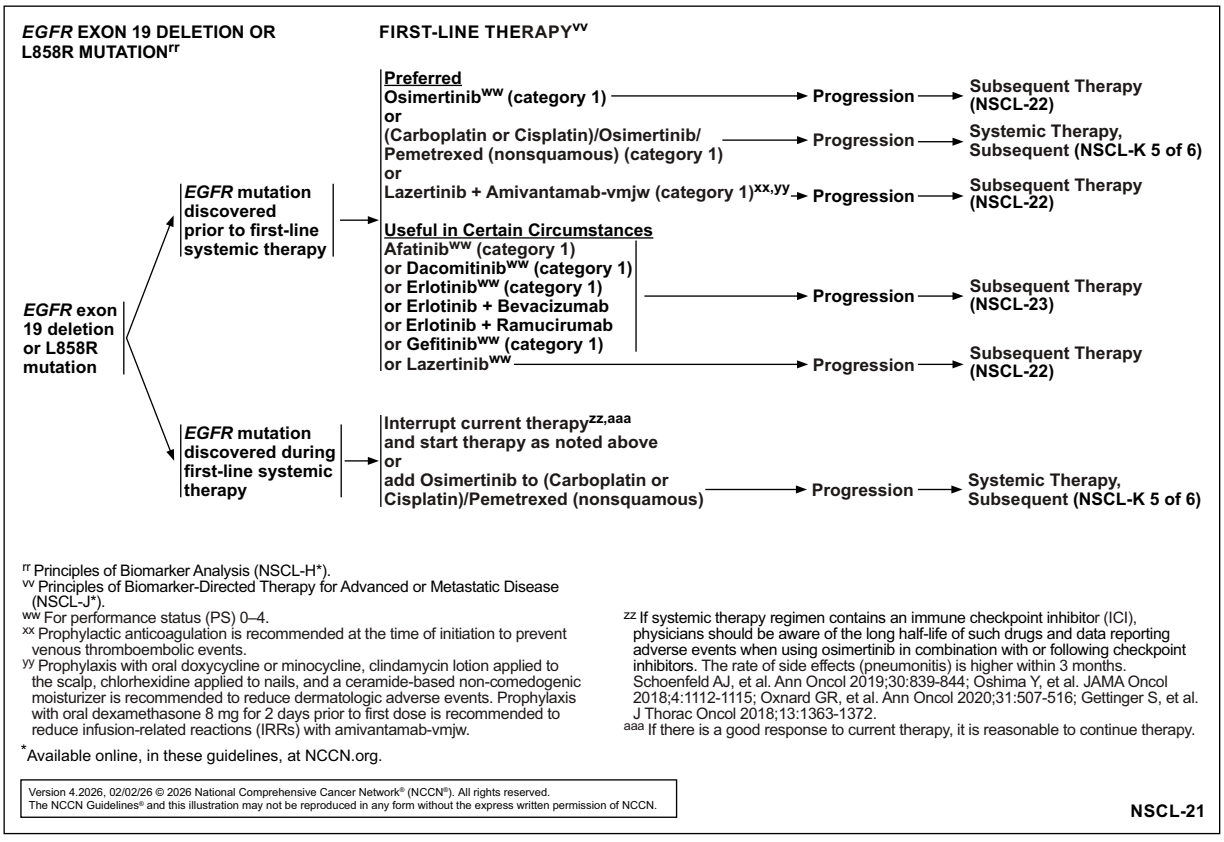
NCCN Recommendations

In the first-line setting, the NCCN NSCLC panel recommends the following as preferred and category 1 options for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletion or L858R mutation: single-agent osimertinib, osimertinib in combination with (carboplatin or cisplatin)/pemetrexed (for nonsquamous histology), or lazertinib + amivantamab-vmjw (Figures 2–4).

Single-agent afatinib, dacomitinib, erlotinib, gefitinib, or lazertinib are first-line treatment options that may be useful in certain circumstances. Erlotinib in combination with bevacizumab (if nonsquamous and no recent history of hemoptysis) or erlotinib in combination with ramucirumab are also first-line treatment options that may be useful in certain circumstances.

If an *EGFR* exon 19 deletion or L858R mutation is discovered during first-line systemic therapy, the NCCN panel recommends interrupting the current therapy and initiating one of the targeted therapies noted previously; alternatively, osimertinib can be added to (carboplatin or cisplatin)/pemetrexed for those with nonsquamous histology. For patients receiving first-line ICIs with or without chemotherapy, oncologists should be aware of the long half-life of the ICI and potential AEs when using osimertinib (or other TKIs) in combination with or after ICIs.[16–19] For example, the rate of AEs, such as pneumonitis, is higher when osimertinib is initiated within 3 months of treatment with certain ICIs.[16]

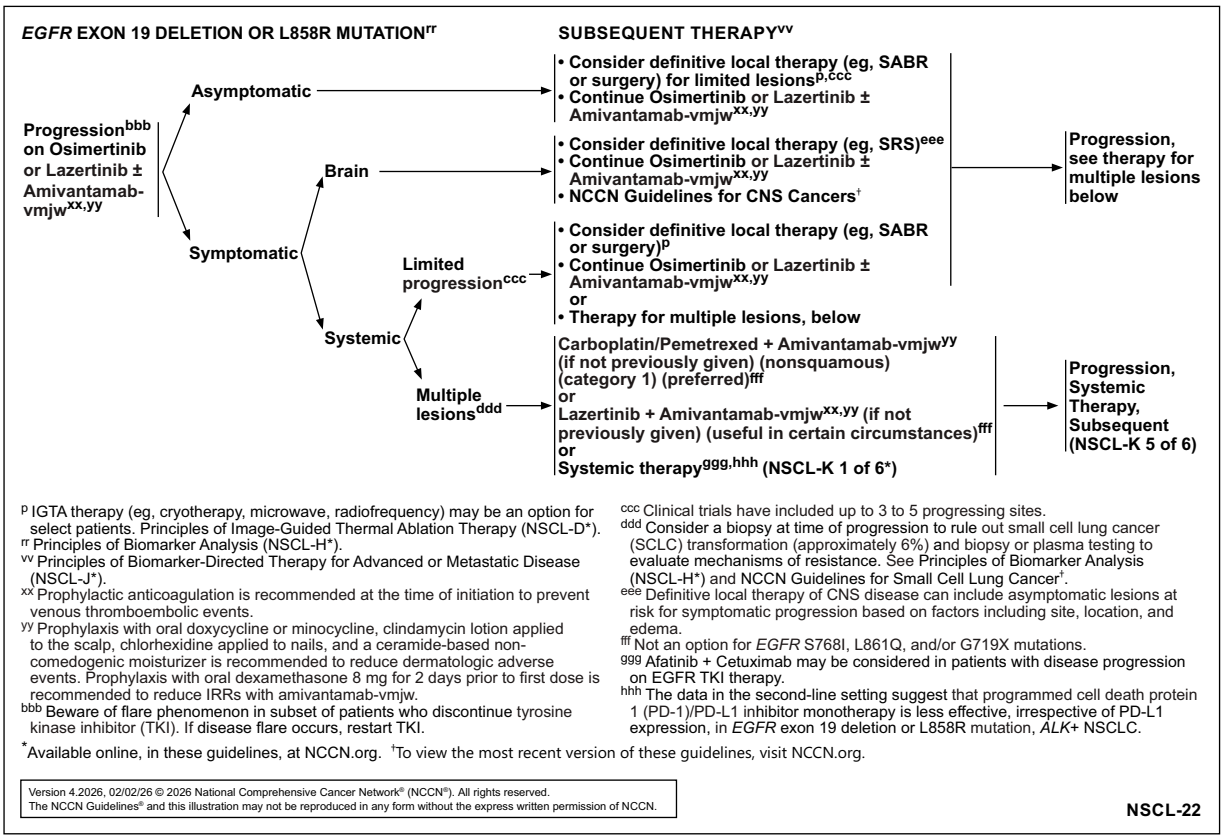
In patients who experience disease progression after receiving first-line osimertinib monotherapy or lazertinib (with or



[rr] Principles of Biomarker Analysis (NSCL-H*).
[vv] Principles of Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J*).
[ww] For performance status (PS) 0–4.
[xx] Prophylactic anticoagulation is recommended at the time of initiation to prevent venous thromboembolic events.
[yy] Prophylaxis with oral doxycycline or minocycline, clindamycin lotion applied to the scalp, chlorhexidine applied to nails, and a ceramide-based non-comedogenic moisturizer is recommended to reduce dermatologic adverse events. Prophylaxis with oral dexamethasone 8 mg for 2 days prior to first dose is recommended to reduce infusion-related reactions (IRRs) with amivantamab-vmjw.
[zz] If systemic therapy regimen contains an immune checkpoint inhibitor (ICI), physicians should be aware of the long half-life of such drugs and data reporting adverse events when using osimertinib in combination with or following checkpoint inhibitors. The rate of side effects (pneumonitis) is higher within 3 months. Schoenfeld AJ, et al. Ann Oncol 2019;30:839-844; Oshima Y, et al. JAMA Oncol 2018;4:1112-1115; Oxnard GR, et al. Ann Oncol 2020;31:507-516; Gettinger S, et al. J Thorac Oncol 2018;13:1363-1372.
[aaa] If there is a good response to current therapy, it is reasonable to continue therapy.
*Available online, in these guidelines, at NCCN.org.

NSCL-21

Figure 2. NSCL-21. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.



[p] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D*).
[rr] Principles of Biomarker Analysis (NSCL-H*).
[vv] Principles of Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J*).
[xx] Prophylactic anticoagulation is recommended at the time of initiation to prevent venous thromboembolic events.
[yy] Prophylaxis with oral doxycycline or minocycline, clindamycin lotion applied to the scalp, chlorhexidine applied to nails, and a ceramide-based non-comedogenic moisturizer is recommended to reduce dermatologic adverse events. Prophylaxis with oral dexamethasone 8 mg for 2 days prior to first dose is recommended to reduce IRRs with amivantamab-vmjw.
[bbb] Beware of flare phenomenon in subset of patients who discontinue tyrosine kinase inhibitor (TKI). If disease flare occurs, restart TKI.
[ccc] Clinical trials have included up to 3 to 5 progressing sites.
[ddd] Consider a biopsy at time of progression to rule out small cell lung cancer (SCLC) transformation (approximately 6%) and biopsy or plasma testing to evaluate mechanisms of resistance. See Principles of Biomarker Analysis (NSCL-H*) and NCCN Guidelines for Small Cell Lung Cancer[†].
[eee] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.
[fff] Not an option for *EGFR* S768I, L861Q, and/or G719X mutations.
[ggg] Afatinib + Cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[hhh] The data in the second-line setting suggest that programmed cell death protein 1 (PD-1)/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or L858R mutation, *ALK*+ NSCLC.

*Available online, in these guidelines, at NCCN.org. [†]To view the most recent version of these guidelines, visit NCCN.org.

NSCL-22

Figure 3. NSCL-22. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

without amivantamab-vmjw), decisions about subsequent therapies are guided by disease symptoms as well as sites of progression. A change in systemic therapy is generally recommended if patients have symptomatic systemic progression and/or multiple lesions. When considering second-line systemic therapy, ideally patients should undergo repeat biopsy to rule out transformation to small cell histology, a phenomenon that occurs in approximately 6% of EGFR TKI-resistant tumors.[49,50] Amivantamab-vmjw in combination with carboplatin and pemetrexed is a preferred treatment option for patients with multiple lesions. Lazertinib + amivantamab-vmjw may also be useful in certain circumstances, if not previously given.

Systemic therapy options such as chemotherapy are also recommended for patients with symptomatic systemic progression (see "Principles of Systemic Therapy for Advanced or Metastatic Disease," Figure 5 and in these guidelines [available at NCCN.org]). Data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective in *EGFR* exon 19 deletion or L858R mutation positive-NSCLC, irrespective of PD-L1 expression.[9,44–46]

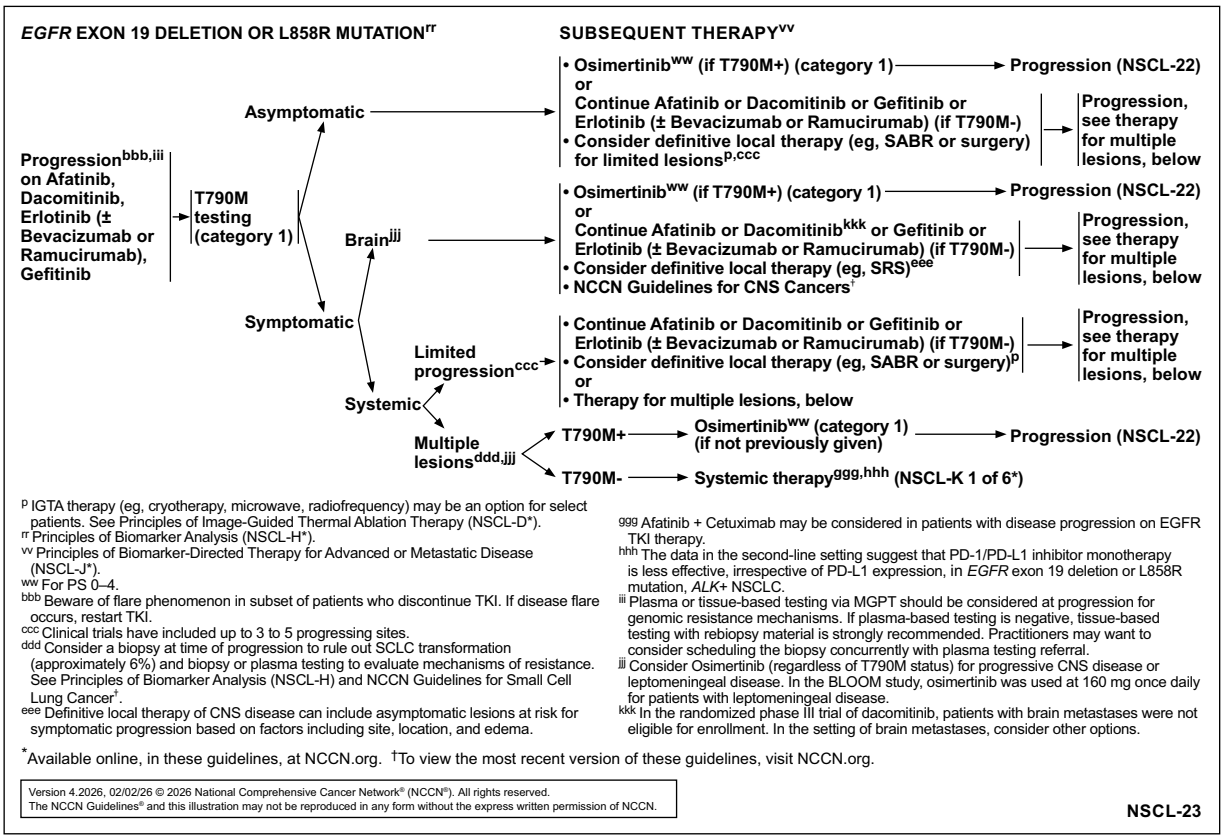
If disease progresses after treatment with osimertinib in combination with chemotherapy with pemetrexed and either cisplatin or carboplatin, then the subsequent therapy options listed on NSCL-K 5 of 6 (Figure 5) can be considered. Datopotamab deruxtecan-dlnk is included on this page as a subsequent therapy option for patients with nonsquamous NSCLC with *EGFR* mutations, including exon 19 deletions or L858R mutation. Based on the FDA prescribing information, patients should be informed about the need for eye exams during datopotamab deruxtecan-dlnk treatment due to the potential for ocular AEs.[38]

Definitive local therapy has a role in the treatment of metastatic *EGFR*-positive NSCLC. Local therapy may be an appropriate subsequent therapy option for certain patients with persistent disease or who have progressed after initial therapy with an EGFR TKI. For those with asymptomatic progression or symptomatic systemic progression that is limited in nature (oligoprogression), definitive local therapy (eg, stereotactic ablative radiotherapy [SABR] or surgery) should be considered for limited lesions regardless of prior TKI therapy; image-guided thermal ablation (IGTA) therapy may also be an option (see "Principles of Image-Guided Thermal Ablation Therapy" [NSCL-D] in these NCCN Guidelines [available at NCCN.org]).

Patients with *EGFR* mutations are considered at higher risk for brain metastases than those with wild-type *EGFR*.[51,52] For those with CNS progression, definitive local therapy (eg, stereotactic radiosurgery [SRS] with or without surgical resection, whole brain radiation therapy [WBRT]) should be considered for symptomatic lesions, and SRS should be considered for asymptomatic lesions at risk for symptomatic progression based on factors including size, location, and edema. See also the NCCN Guidelines for CNS Cancers (available at NCCN.org) for additional recommendations.

EGFR S768I, L861Q, and/or G719X Mutation Positive

Other less common *EGFR* mutations (approximately 10% of *EGFR* mutations observed in patients with NSCLC) include S768I, L861Q, and/or G719X.[21,53] These mutations have varying



[p] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D*).
[rr] Principles of Biomarker Analysis (NSCL-H*).
[vv] Principles of Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J*).
[ww] For PS 0–4.
[bbb] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[ccc] Clinical trials have included up to 3 to 5 progressing sites.
[ddd] Consider a biopsy at time of progression to rule out SCLC transformation (approximately 6%) and biopsy or plasma testing to evaluate mechanisms of resistance. See Principles of Biomarker Analysis (NSCL-H) and NCCN Guidelines for Small Cell Lung Cancer†.
[eee] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.
[ggg] Afatinib + Cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
[hhh] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or L858R mutation, *ALK*+ NSCLC.
[iii] Plasma or tissue-based testing via MGPT should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.
[jjj] Consider Osimertinib (regardless of T790M status) for progressive CNS disease or leptomeningeal disease. In the BLOOM study, osimertinib was used at 160 mg once daily for patients with leptomeningeal disease.
[kkk] In the randomized phase III trial of dacomitinib, patients with brain metastases were not eligible for enrollment. In the setting of brain metastases, consider other options.

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NSCL-23

Figure 4. NSCL-23. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

degrees of sensitivity to first- (erlotinib or gefitinib), second- (afatinib or dacomitinib), and third- (osimertinib) generation EGFR TKIs.[21,53–57]

Clinical Data

For patients with the less common *EGFR* S768I, L861Q, and/or G719X mutations, treatment recommendations are based on nonrandomized studies. Afatinib is a second-generation oral TKI that irreversibly inhibits the ErbB/HER family of receptors including EGFR and HER2.[58,59] Afatinib is approved by the FDA for the first-line treatment of patients with metastatic NSCLC whose tumors have nonresistant *EGFR* mutations.[38] A posthoc analysis of several LUX-Lung trials (LUX-Lung 2, 3, and 6) assessed afatinib in patients with advanced NSCLC and certain uncommon *EGFR* mutations (including L861Q, G719X, and S768I).[54] Median OS was 19.4 months. A response to afatinib was reported in 8 patients (100%) with *EGFR* S768I mutations. Among those with *EGFR* G719X mutations, an objective response to afatinib was reported in 14 patients (77.8%), while a response to afatinib was reported in 9 patients (56.3%) of those with *EGFR* L861Q.

Osimertinib has also been studied in patients with less common *EGFR* mutations, including S768I, L861Q, and G719X. KCSG-LU15-09, a phase II trial based in Korea, assessed first-line therapy with osimertinib in patients with metastatic or recurrent NSCLC and these mutations.[55] The median PFS was 8.2 months and the objective response rate was 50%. An objective response with osimertinib was observed in 78% (7/9) of those with *EGFR* L861Q, 53% (10/19) of those with *EGFR* G719X, and 38% (3/8) of those with *EGFR* S768I). The median PFS was 15.2 months, 8.2 months, and 12.3 months in the L861Q, G719X and S768I groups, respectively. The most common AEs included rash, pruritus, decreased appetite, diarrhea, and dyspnea.[55]

Retrospective data suggest that the clinical response to osimertinib versus afatinib may differ, depending on the exact *EGFR* mutation identified.[54,60,61] For example, afatinib may be more effective for some mutations (such as G719X) while osimertinib may be more appropriate for classic-like mutations such as L861Q).[62]

Datopotamab deruxtecan-dlnk is also a subsequent therapy option based on the pooled analysis of the TROPION-Lung05 and TROPION-Lung01 trials.[43] The patient population included 6 patients with *EGFR* G719X mutations and 5 patients with L861Q mutations; some of these patients experienced a treatment response with datopotamab deruxtecan.

NCCN Recommendations

The panel recommends afatinib or osimertinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC with *EGFR* S768I, L861Q, and/or G719X mutations. Dacomitinib, erlotinib, and gefitinib are other recommended first-line treatment options. All are appropriate for patients with a performance status (PS) 0–4 (Figure 6).

Subsequent treatment approaches for advanced or metastatic NSCLC with *EGFR* S768I, L861Q, and/or G719X mutations that progressed after first-line treatment with afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib are similar as for the more

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)	SQUAMOUS CELL CARCINOMA (PS 0–2)
Preferred (no previous IO) Systemic ICIs • Nivolumab (category 1) • Pembrolizumab[k] (category 1) • Atezolizumab (category 1) Preferred (*EGFR* mutations[l]) • Datopotamab deruxtecan-dlnk Other Recommended (*EGFR* exon 19 deletion or L858R mutation) • Lazertinib + Amivantamab-vmjw[m,n] Other Recommended (no previous immuno-oncology [IO] or previous IO)[n] • Docetaxel • Pemetrexed • Gemcitabine • Docetaxel + Ramucirumab • Albumin-bound Paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+) • Telisotuzumab vedotin-tllv (HGF receptor [c-Met] ≥50% IHC 3+ and *EGFR* wild-type)	Preferred (no previous IO) Systemic ICIs • Nivolumab (category 1) • Pembrolizumab[k] (category 1) • Atezolizumab (category 1) Other Recommended (no previous IO or previous IO)[n] • Docetaxel • Gemcitabine • Docetaxel + Ramucirumab • Albumin-bound Paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+)
ADENOCARCINOMA, LARGE CELL, NSCLC NOS, SQUAMOUS CELL CARCINOMA (PS 3–4)	
Best supportive care (NCCN Guidelines for Palliative Care[†])	

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – PROGRESSION[n,o]

ADENOCARCINOMA, LARGE CELL, NSCLC NOS	SQUAMOUS CELL CARCINOMA
• Options for PS 0–2: Nivolumab, Pembrolizumab, or Atezolizumab; Datopotamab deruxtecan-dlnk (*EGFR* mutations[l]); Lazertinib + Amivantamab-vmjw[m] (*EGFR* exon 19 deletion or L858R mutation); Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+); Telisotuzumab vedotin-tllv (HGF receptor [c-Met] ≥50% IHC 3+ and *EGFR* wild-type); Docetaxel (category 2B); Pemetrexed (category 2B); Gemcitabine (category 2B); Docetaxel + Ramucirumab (category 2B); or Albumin-bound Paclitaxel (category 2B) • PS 3–4: Best supportive care	• Options for PS 0–2: Nivolumab, Pembrolizumab, or Atezolizumab; Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+); Docetaxel (category 2B); Gemcitabine (category 2B); Docetaxel + Ramucirumab (category 2B); or Albumin-bound Paclitaxel (category 2B) • PS 3–4: Best supportive care

General Principles and Monitoring

[k] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.
[l] *EGFR* mutations include: exon 19 deletion, L858R, S768I, L861Q, G719X mutations and exon 20 insertion.
[m] If progression on (Carboplatin or Cisplatin)/Osimertinib/Pemetrexed.
[n] If not previously given.
[o] Options for further progression are best supportive care or clinical trial.
[†] To view the most recent version of these guidelines, visit NCCN.org.

References

NSCL-K 5 OF 6

Figure 5. NSCL-K 5 of 6. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

common *EGFR* mutations described previously and in Figures 3 and 4.

In addition to chemotherapy-based regimens, datopotamab deruxtecan-dlnk is included on NSCL-K 5 of 6 as a subsequent therapy option for patients with nonsquamous NSCLC and *EGFR* mutations, including S768I, L861Q, and G719X (Figure 5). Based on the FDA prescribing information, patients should be informed about the need for eye exams during datopotamab deruxtecan-dlnk treatment due to the potential for ocular AEs.[38]

EGFR Exon 20 Insertion Mutation Positive

EGFR exon 20 insertion mutations are the third most common group of *EGFR* mutations; these heterogenous mutations occur in approximately 2% of patients with NSCLC and 4%–12% of patients with *EGFR* mutations.[63–65]

Clinical Data

For patients with NSCLC and *EGFR* exon 20 insertion mutations, treatment with typical EGFR TKIs has generally not been associated with disease response.[34,63,66] However, other types of targeted therapies have demonstrated clinical efficacy in patients with *EGFR* exon 20 insertion mutations in recent years.

Amivantamab-vmjw in combination with carboplatin and pemetrexed is approved by the FDA for the first-line treatment of adults with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations.[38] PAPILLON, a phase III randomized trial, assessed first-line amivantamab plus chemotherapy (pemetrexed and carboplatin) versus chemotherapy alone in 308 patients with advanced NSCLC with *EGFR* exon 20 insertion mutations who had not previously received systemic therapy.[67] The median PFS was longer in the amivantamab plus chemotherapy group than in the chemotherapy alone group (11.4 vs 6.7 months). The objective response rate was higher for those who received amivantamab plus chemotherapy than those treated with chemotherapy only (73% and 47%). Based on the interim OS analysis, the HR for amivantamab plus chemotherapy versus chemotherapy alone was 0.67 (P=.11). The most common AEs reported with amivantamab plus chemotherapy were hematologic effects and skin-related EGFR-related toxic events.

Single-agent amivantamab-vmjw is FDA-approved for the treatment of adults with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.[38] The phase I CHRYSALIS trial assessed subsequent therapy with amivantamab in 81 patients with *EGFR* exon 20 insertion-positive metastatic NSCLC who had received one or more previous lines of therapy.[34] The overall response rate was 40%, with 3 complete responses. The median PFS was 8.3 months. Common treatment-related AEs included cutaneous reactions, infusion-related reactions, and paronychia; common grade 3 to 4 AEs included hypokalemia, pulmonary embolism, neutropenia, diarrhea, and rash.

Sunvozertinib is an oral EGFR TKI that was granted accelerated approval by the FDA for the treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.[38] Sunvozertinib as a subsequent therapy in patients

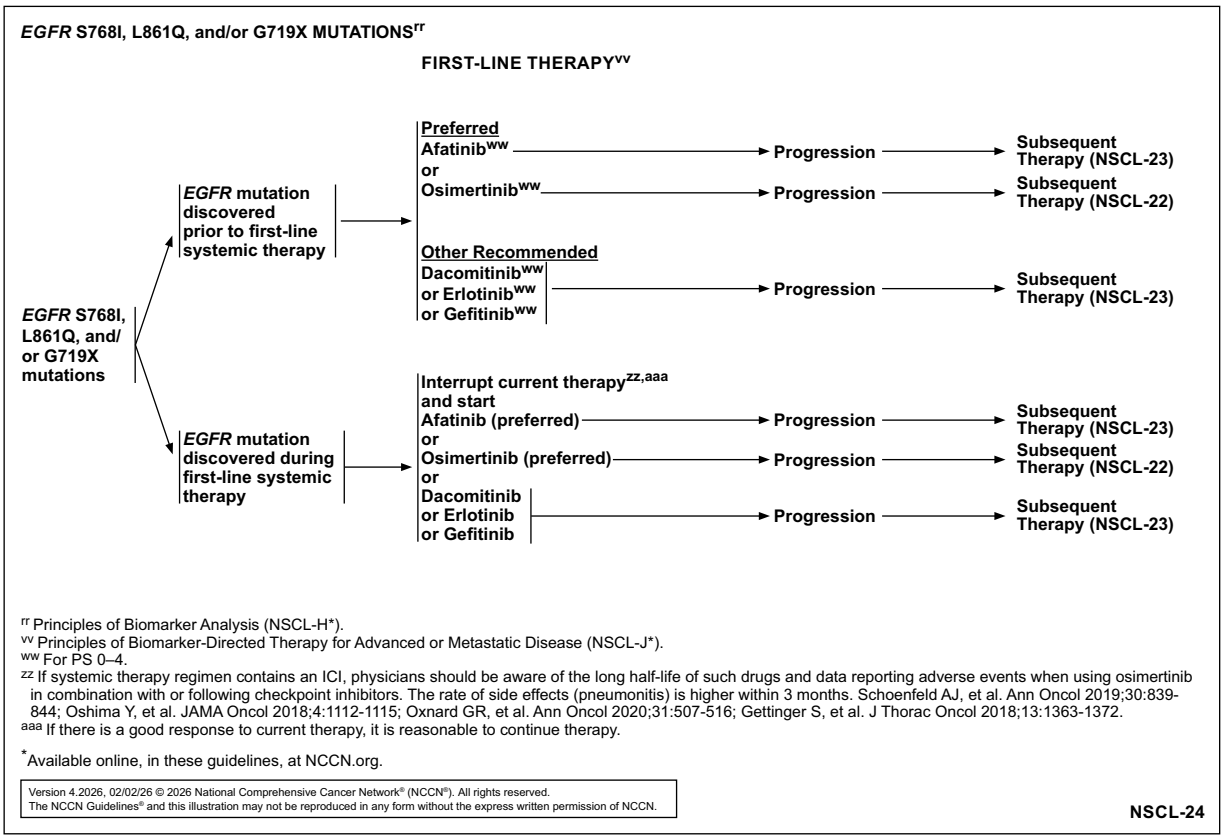


Figure 6. NSCL-24. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

with NSCLC and *EGFR* exon 20 insertion mutations was evaluated in the phase II WU-KONG1B trial.[68,69] All patients in the study previously received platinum-based chemotherapy; ~14% previously received amivantamab.[69] The objective response rate was approximately 46% among the 3 cohorts evaluated in the study. The disease control rate was approximately 90%. Twelve-month OS rate ranged from 62.1% to 73.7% among the 3 cohorts evaluated. Commonly reported treatment-related AEs included diarrhea, skin rash, and increased creatine phosphokinase.

Datopotamab deruxtecan-dlnk is also a subsequent therapy option based on the pooled analysis of the TROPION-Lung05 and TROPION-Lung01 trials.[43] The patient population included just 5 patients with *EGFR* exon 20 insertion mutations in the analysis and some experienced a treatment response. Based on the FDA prescribing information, patients should be informed about the need for eye exams during datopotamab deruxtecan-dlnk treatment due to the potential for ocular AEs.[38]

NCCN Recommendations

The panel recommends amivantamab-vmjw in combination with carboplatin and pemetrexed as a category 1 and preferred first-line treatment option for patients with advanced or metastatic nonsquamous *EGFR* exon 20 insertion mutation-positive NSCLC. Amivantamab and hyaluronidase-lpuj subcutaneous injection may be substituted for intravenous amivantamab-vmjw. Amivantamab and hyaluronidase-lpuj has different dosing, administration, and premedication instructions compared with intravenous amivantamab-vmjw (Figure 7).

Other systemic therapy regimens (eg, chemotherapy) listed in the "Principles of Systemic Therapy for Advanced or Metastatic Disease" (page NSCL-K) in the NCCN Guidelines for NSCLC (available at NCCN.org) are also recommended as first-line treatment options. Data indicate that ICI monotherapy is associated with low activity in NSCLC with *EGFR* mutations.[7,70]

The NCCN NSCLC Panel recommends single-agent amivantamab-vmjw or sunvozertinib (if available) as subsequent therapy options (if not given previously) for patients with *EGFR* exon 20 insertion mutation-positive advanced or metastatic NSCLC. Other systemic therapy options recommended in the subsequent setting are listed on NSCL-K 5 of 6 (Figure 5). Datopotamab deruxtecan-dlnk is included on NSCL-K 5 of 6 as a subsequent therapy option for patients with nonsquamous NSCLC and *EGFR* mutations, including exon 20 insertion mutations.

KRAS G12C Mutation Positive

KRAS is a protein with intrinsic GTPase activity that is commonly mutated in lung cancers; these mutations can result in unregulated signaling through the MAPK pathway.[71,72] *KRAS* G12C is an activating mutation that results in activation of downstream oncogenic pathways.[73] Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have a *KRAS* mutation.[74–78] Some, but not all, *KRAS* mutations are associated with cigarette smoking.[79,80]

Clinical Data

KRAS-targeted therapies are not recommended as first-line treatment options for advanced or metastatic NSCLC with a

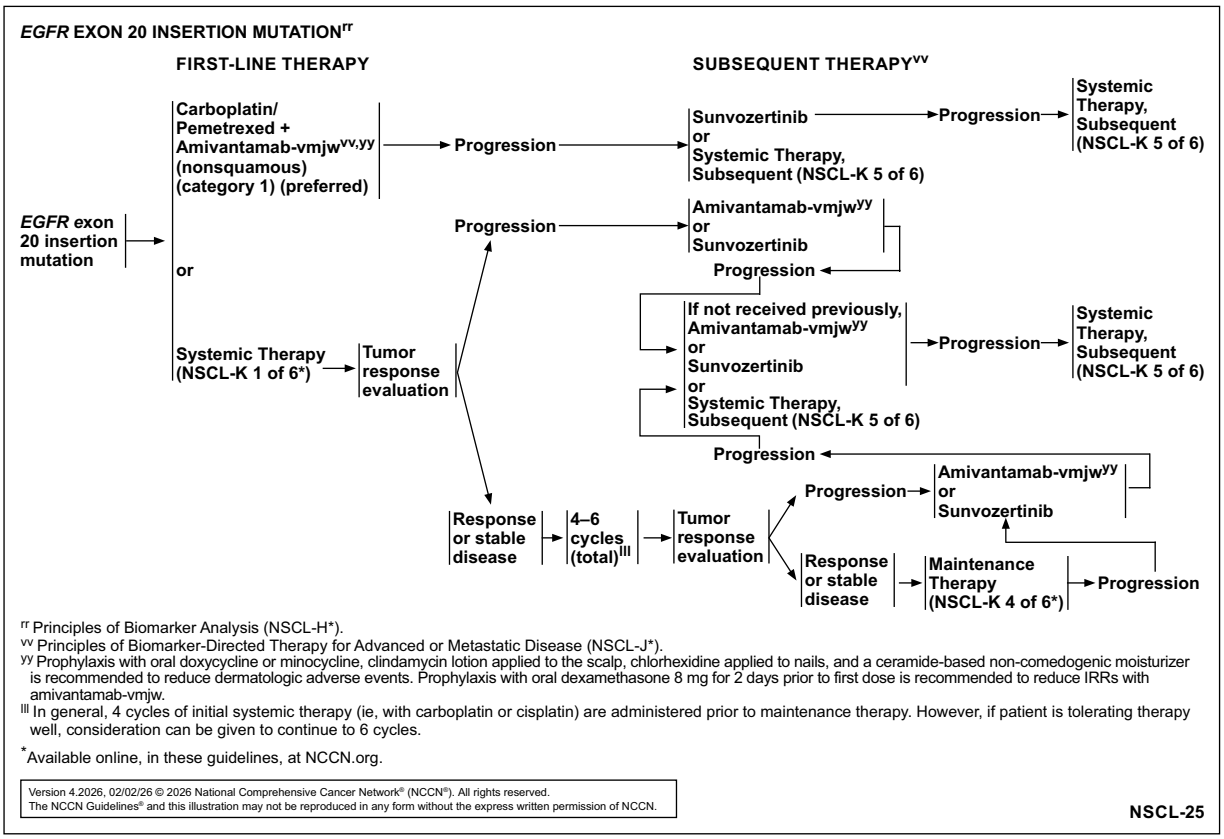


Figure 7. NSCL-25. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

KRAS G12C mutation. Data indicate that patients with advanced or metastatic NSCLC and *KRAS* mutations are likely to derive benefit from immunotherapy-based regimens in the first-line setting.[14,15] One study reported a positive association between PFS and PD-L1 expression in patients with advanced NSCLC and *KRAS* mutations who received ICI monotherapy.[7]

Two targeted therapies are available as subsequent therapy options for NSCLC with *KRAS* G12C mutations. Adagrasib and sotorasib are oral small molecules that target *KRAS* G12C and have both been granted accelerated approval by the FDA for the treatment of adults with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who received at least one prior systemic therapy.[38]

The randomized phase III CodeBreaK 200 trial compared subsequent therapy with sotorasib to treatment with docetaxel in 345 patients with *KRAS* G12C mutation-positive advanced NSCLC who had previously received platinum-based chemotherapy plus a PD-1 or PD-L1 inhibitor.[81] Median PFS was 5.6 months in patients receiving sotorasib compared with 4.5 months in those receiving docetaxel. The median OS was 10.6 months in the sotorasib group versus 11.3 months in the docetaxel group; no statistically significant difference was reported. The most common treatment-related AEs associated with sotorasib that were grade 3 or higher included diarrhea and increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels.

Adagrasib (versus docetaxel) was assessed in the phase III KRYSTAL-12 trial.[82] In this study, 453 patients with locally advanced or metastatic NSCLC with *KRAS* G12C mutations who previously received platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor were randomized to receive either adagrasib or docetaxel. The median PFS was longer in the adagrasib group than in the docetaxel group (5.5 months vs 3.8 months; $P<.0001$). Among patients with baseline brain metastases, the intracranial response rate was 24% with adagrasib compared with 11% with docetaxel. There were 4 treatment-related deaths among the patients who received adagrasib (epilepsy, hepatic failure, hepatic ischemia, and unknown cause), compared with one in the docetaxel group (sepsis).

NCCN Recommendations

The panel recommends using PD-L1 expression level to guide selection of first-line systemic therapy regimen (such as immunotherapy and/or chemotherapy) for patients with advanced or metastatic NSCLC with *KRAS* G12C mutations. See pages NSCL-38 and NSCL-39 in the algorithm in the full NCCN Guidelines for NSCLC at NCCN.org for treatment recommendations based on PD-L1 level (Figure 8).

The panel recommends adagrasib or sotorasib as subsequent therapy options for patients who experience disease progression after treatment with first-line systemic therapy. Adagrasib or sotorasib may also be used as third-line therapy or beyond if the patient has not previously received a *KRAS* G12C-targeted therapy. The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended.

After further progression, systemic therapy options listed on NSCL-K 5 of 6 are recommended (Figure 5).

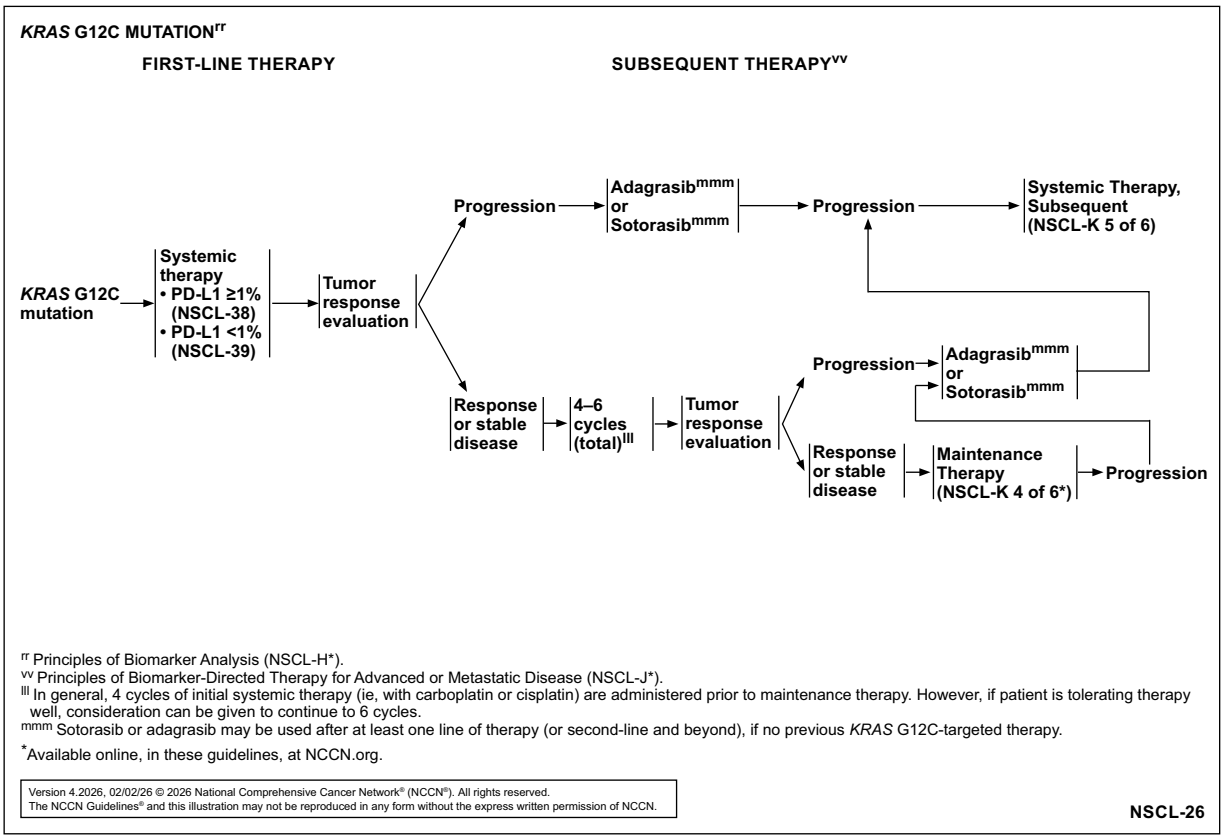


Figure 8. NSCL-26. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

ALK Gene Fusion Positive

An *ALK* gene fusion is present in about 5% of patients with NSCLC.[83,84] *ALK* gene fusions can lead to the dysregulation of ALK signaling, resulting in oncogenicity.[83]

Clinical Data

Initial studies demonstrated that single-agent ALK inhibitors (crizotinib and ceritinib) are superior to chemotherapy in patients with advanced or metastatic NSCLC with *ALK* gene fusion.[85–87] First-generation ALK TKI crizotinib and second-generation ALK TKI ceritinib are FDA approved for the treatment of adults with *ALK*-positive metastatic NSCLC;[38] however, subsequent studies have shown superior efficacy for newer ALK inhibitors.

Alectinib is a second-generation ALK inhibitor that is approved by the FDA for the treatment of patients with *ALK*-positive metastatic NSCLC.[38,88] ALEX, a phase III randomized trial, assessed first-line therapy with alectinib versus crizotinib in 303 patients with *ALK* gene fusion-positive advanced NSCLC, including those with asymptomatic CNS disease.[89] Disease progression or death occurred in a lower proportion of patients receiving alectinib compared with crizotinib (41% vs 68%). Investigator-assessed PFS rate was higher with alectinib than crizotinib (68.4% vs 48.7%). The objective response rates were 82.9% in the alectinib group versus 75.5% in the crizotinib group. Fewer patients receiving alectinib had CNS progression (12%) versus crizotinib (45%). Patients receiving alectinib had fewer grade 3 or higher AEs than those who received crizotinib (41% vs 50%, respectively) even though patients received alectinib for a longer duration than crizotinib (median, 17.9 vs 10.7 months). The final analysis of the trial reported that the median OS was 81.1 months with alectinib and 54.2 months with crizotinib (HR, 0.78; $P=.13$).[90]

Brigatinib is also a second-generation ALK inhibitor that is approved by the FDA for the treatment of adults with *ALK*-positive metastatic NSCLC.[38,88] ALTA-1L, a phase III randomized trial, assessed brigatinib versus crizotinib in 275 patients with *ALK*-positive metastatic NSCLC who had not previously received an ALK-targeted therapy.[91] At the 3-year analysis, the PFS was higher in the brigatinib group versus the crizotinib group (43% vs 19%).[92] A pooled analysis of 169 patients with *ALK* gene fusion-positive advanced or metastatic NSCLC who received brigatinib from the ALTA-1L trial and the phase II J-ALTA trial found that the 3-year OS rate was 74%.[93] The intracranial objective response rate among 47 patients with any brain metastases at baseline was 66%. Approximately 80% of patients experienced a grade 3 treatment-related AE.

Ensartinib is a second-generation ALK inhibitor approved by the FDA for the treatment of patients with *ALK*-positive locally advanced or metastatic NSCLC.[38] The phase III randomized eXalt3 trial assessed the efficacy and safety of ensartinib versus crizotinib in 290 patients with advanced, recurrent, or metastatic *ALK*-positive NSCLC who had not previously received an ALK inhibitor.[94] The median PFS was 25.8 months in the ensartinib group compared with 12.7 months in the crizotinib group. The intracranial response rate was higher with ensartinib than crizotinib (63.6% vs 21.1%) among those with brain metastases at baseline.

Lorlatinib is a third-generation ALK inhibitor approved by the FDA for the treatment of adults with *ALK*-positive metastatic

NSCLC.[38] CROWN, a phase III randomized trial, assessed lorlatinib versus crizotinib as first-line therapy in 296 patients with *ALK*-positive advanced NSCLC.[95] At 12 months, 78% of patients were alive without disease progression in the lorlatinib group versus 39% in the crizotinib group. The objective response rate was 76% for patients receiving lorlatinib and 58% for those receiving crizotinib. For patients with measurable brain metastases, an intracranial response was reported in 82% of those receiving lorlatinib and 23% of those receiving crizotinib; a complete intracranial response was achieved in 71% of those who received lorlatinib. More grade 3 or 4 AEs (mainly altered lipid levels) occurred with lorlatinib than with crizotinib (72% vs 56%). Peripheral neuropathy occurred in 34% of the lorlatinib group and 15% of the crizotinib group. Cognitive effects, such as memory impairment, disturbance in attention, confusion, amnesia, cognitive disorder, and delirium, were reported in 21% of patients treated with lorlatinib (compared with 6% in the crizotinib group). Long-term data from the CROWN trial demonstrated that the 5-year PFS rate was 60% with lorlatinib and 8% with crizotinib in the first-line setting.[96]

Data have suggested that lorlatinib can be used as subsequent therapy in patients with disease progression after treatment with other ALK inhibitors, including those with CNS metastases.[97,98] A phase II trial assessed lorlatinib in patients with *ALK* or *ROS1* gene fusion-positive advanced NSCLC and disease progression after ALK inhibitor therapy; many patients had asymptomatic CNS metastases.[97] In the cohort of *ALK*-positive patients who had previously received at least one ALK inhibitor, objective responses were achieved in 47% of patients. In those with measurable baseline CNS lesions, an objective intracranial response was observed in 63% of patients. Lorlatinib was effective in patients who had received up to three previous ALK inhibitors. Treatment-related peripheral neuropathy was reported in over a quarter of patients who received lorlatinib; cognitive effects occurred in over 17% of those treated with lorlatinib. Grade 3 to 4 treatment-related AEs included hypercholesterolemia and hypertriglyceridemia.

Data from this trial also showed 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.[99] The objective response rate with lorlatinib was 62% when using plasma circulating tumor DNA (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. However, data from other studies suggest that lorlatinib may not be effective in NSCLC with resistant compound *ALK* mutations (eg, combination of L1196M and G1202R).[99–101]

NCCN Recommendations

The panel recommends alectinib, brigatinib, ensartinib, or lorlatinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC and *ALK* gene fusion. Ceritinib and crizotinib are recommended as treatment options that may be useful in certain circumstances. All targeted therapy options are appropriate for patients with PS 0–4 and are category 1 recommendations if an *ALK* gene fusion is discovered prior to first-line systemic therapy (Figures 9–11).

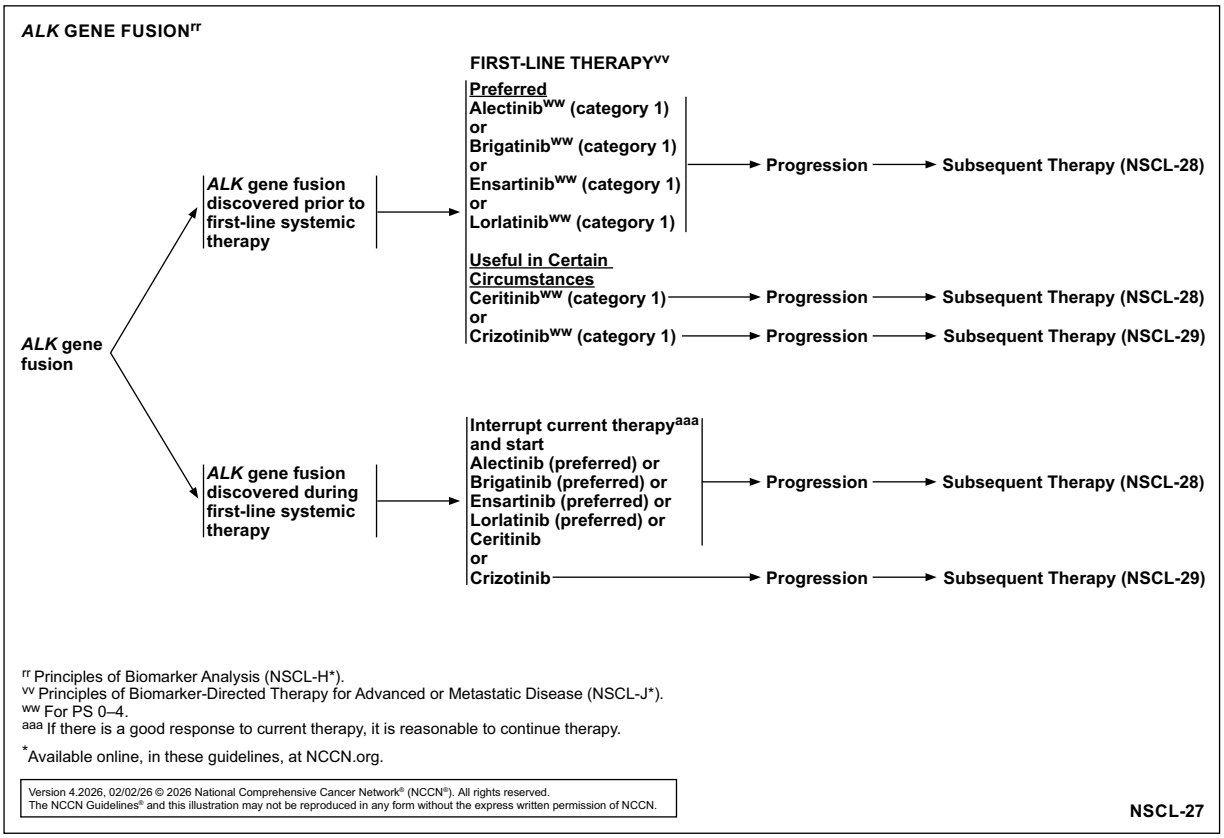
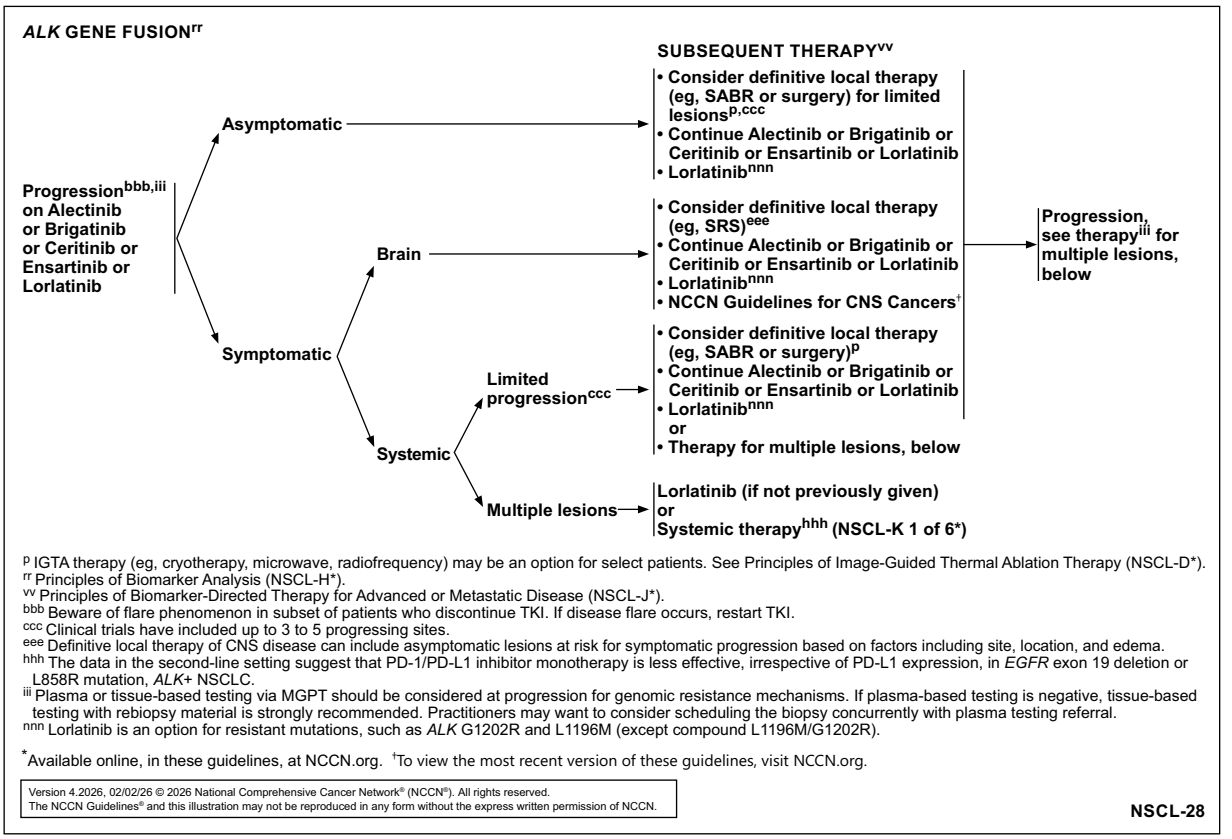


Figure 9. NSCL-27. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.



[p] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients. See Principles of Image-Guided Thermal Ablation Therapy (NSCL-D*).
[rr] Principles of Biomarker Analysis (NSCL-H*).
[vv] Principles of Biomarker-Directed Therapy for Advanced or Metastatic Disease (NSCL-J*).
[bbb] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.
[ccc] Clinical trials have included up to 3 to 5 progressing sites.
[eee] Definitive local therapy of CNS disease can include asymptomatic lesions at risk for symptomatic progression based on factors including site, location, and edema.
[hhh] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR* exon 19 deletion or L858R mutation, *ALK*+ NSCLC.
[iii] Plasma or tissue-based testing via MGPT should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.
[nnn] Lorlatinib is an option for resistant mutations, such as *ALK* G1202R and L1196M (except compound L1196M/G1202R).

*Available online, in these guidelines, at NCCN.org. [†]To view the most recent version of these guidelines, visit NCCN.org.

NSCL-28

Figure 10. NSCL-28. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

On disease progression, consideration of plasma and/or tissue-based testing using multigene panel testing is recommended to determine genomic resistance mechanisms and guide selection of subsequent therapy options.[99]

After progression on alectinib, brigatinib, ceritinib, or ensartinib, the panel recommends a switch in treatment to lorlatinib. Continuing lorlatinib is an option for those who experienced disease progression on or after lorlatinib given in the first-line setting. Lorlatinib can be used for NSCLC with resistant mutations such as *ALK* G1202R or L1196M, but not if compound-resistant mutations are detected (ie, both L1196M and G1202R). Continuing the same TKI that was used in the first-line setting is another option, except for those with symptomatic systemic progression and multiple lesions. If disease progression occurs after first-line crizotinib treatment, switching to a different TKI is recommended.

Systemic therapy options such as chemotherapy are recommended as additional subsequent therapy options for patients with symptomatic systemic progression and multiple lesions (see "Principles of Systemic Therapy for Advanced or Metastatic Disease" [NSCL-K] in these NCCN Guidelines [available at NCCN.org]). Data suggest that PD-1/PD-L1 inhibitor monotherapy is less effective in *ALK*-positive NSCLC, irrespective of PD-L1 expression.[7,9,70]

Definitive local therapy has a role in the treatment of metastatic *ALK*-positive NSCLC and may be an appropriate subsequent therapy option for certain patients with persistent disease or who have progressed after initial therapy with an ALK TKI. For those with asymptomatic progression or symptomatic systemic progression that is limited in nature (oligoprogression), definitive local therapy (eg, SABR or surgery) should be considered for limited lesions; IGTA therapy (eg, cryotherapy, microwave ablation, radiofrequency ablation) may also be an option for certain patients (see "Principles of Image-Guided Thermal Ablation Therapy" [NSCL-D] in these NCCN Guidelines [available at NCCN.org]).

For patients with CNS progression, definitive local therapy (eg, SRS with or without surgical resection, WBRT) should be considered for symptomatic lesions, and SRS should be considered for asymptomatic lesions at risk for symptomatic progression based on factors including size, location, and edema. See also the NCCN Guidelines for CNS Cancers (available at NCCN.org) for additional recommendations.

ROS1 Gene Fusion Positive

ROS1 gene fusions are estimated to occur in about 1%–2% of patients with NSCLC.[102–104] *ROS1* gene fusion can result in ROS1 kinase dysregulation and increased signaling.[104] Although ROS1 is a distinct receptor tyrosine kinase, it is similar to ALK and members of the insulin receptor family.[105,106]

Clinical Data

Crizotinib is a first-generation oral TKI that inhibits ALK, ROS1, and HGF receptor (c-Met).[107] Crizotinib is approved for the treatment of adults with *ROS1*-positive or *ALK*-positive metastatic NSCLC.[38] Multiple studies have shown that crizotinib is effective for patients with *ROS1* gene fusion, with response rates of about 70%–80%—including complete responses.[106,108–111] The phase I PROFILE 1001 study, which included treatment-naïve and pretreated patients,

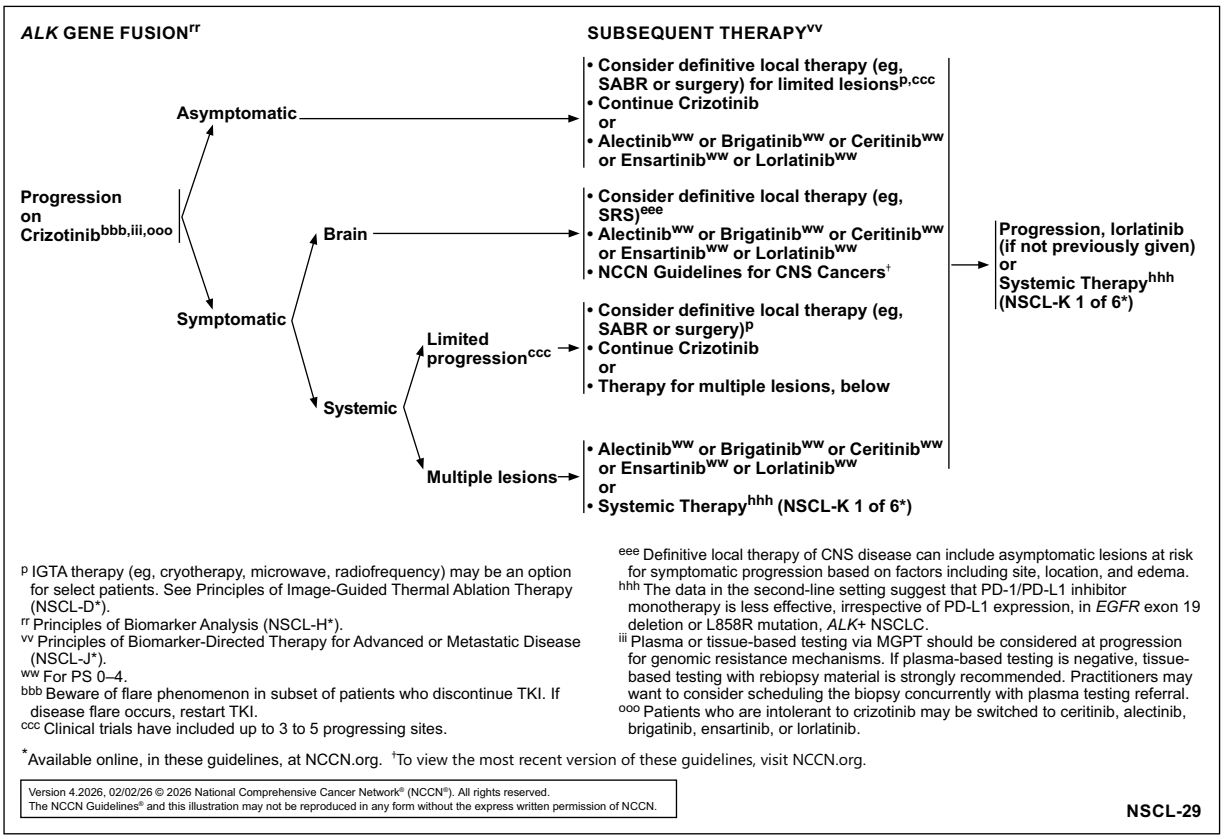


Figure 11. NSCL-29. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

reported that the median OS with crizotinib was 51.4 months.[112] No grade 4 or higher treatment-related AEs were reported.

Entrectinib is an oral TKI that inhibits several kinases (including ROS1, ALK, and TRK) and is approved by the FDA for the treatment of *ROS1*-positive metastatic NSCLC.[38,113,114] Entrectinib has been assessed in several trials in patients with *ROS1*-positive metastatic solid tumors (ie, phase 2 STARTRK 2-trial, phase 1 STARTRK-1 trial, phase 1 ALKA-372-001 trial).[115] Pooled data from these three trials in 53 patients with *ROS1*-positive metastatic NSCLC who had not been treated with a ROS1 TKI showed that entrectinib treatment was associated with an objective response rate of 77% and a median PFS of 19.0 months.[115] The intracranial overall response rate was 55% among the 20 patients with baseline CNS metastases.[115] Grade 3 or 4 treatment-related AEs were reported in 34% of patients who received at least a one dose of entrectinib among all the studies. Reported serious AEs included nervous system disorders and cardiac disorders.

Repotrectinib is a next-generation ROS1, TRK, and ALK TKI that is approved by the FDA for the treatment of adults with locally advanced or metastatic *ROS1*-positive NSCLC.[38,116] The phase I and II TRIDENT-1 trial evaluated repotrectinib in 71 patients with *ROS1* fusion-positive NSCLC who had not previously received a ROS1 TKI and 56 patients with *ROS1* fusion-positive NSCLC who had previously received one ROS1 TKI (crizotinib, entrectinib, or ceritinib) and never received chemotherapy.[117] The confirmed objective response with repotrectinib was 79% among those who had not received a ROS1 TKI, with a median PFS of 35.7 months. The objective response rate was 38% among those who had received one ROS1 TKI, with a median PFS of 9.0 months. For those with measurable brain metastases at baseline, the intracranial objective response with repotrectinib was 89% (8/9) among those who had no previous ROS1 TKI and 38% (5/13) among those who had one previous ROS1 TKI and no chemotherapy. Among the 17 patients with the known resistance mutation *ROS1* G2032R who had previously received a ROS1 TKI, repotrectinib treatment resulted in a 59% response rate. The most common treatment-related AEs were dizziness, dysgeusia, and paresthesia. Treatment-related AEs that were grade 3 or higher occurred in 29% of patients.

Taletrectinib is a next-generation ROS1 TKI that was recently approved by the FDA for the treatment of patients with locally advanced or metastatic *ROS1*-postive NSCLC.[38] This approval was based on pooled data from the phase II TRUST-I and TRUST-II trials, which assessed taletrectinib in 273 patients with locally advanced or metastatic *ROS1*-positive NSCLC; the patient population included those that were TKI-naïve as well as patients pretreated with a ROS1 TKI.[118] The objective response rate was 88.8% for the TKI-naïve group and 55.8% for the TKI-pretreated group. The median PFS was 45.6 months and 9.7 months for the TKI-naïve and TKI-pretreated groups, respectively. The intracranial objective response rate was 76.5% in the TKI-naïve group and 65.6% in the TKI-pretreated group. Among the 13 patients with a *ROS1* G2032R resistance mutation at baseline, the objective response rate was 61.5%. The most common treatment-related AEs included gastrointestinal events and AST or ALT elevation. Grade 3 or higher treatment-related AEs were reported in 33% of patients.

Lorlatinib is an oral TKI approved for the treatment of *ALK*-positive metastatic NSCLC; however, it can target both ALK and ROS1 and penetrate the blood-brain barrier.[38,119] A phase I/II trial assessed lorlatinib in 69 patients with *ROS1*-positive metastatic NSCLC.[120] Many patients (58%) had previously received crizotinib; some patients were TKI-naïve (30%). Objective response rates of 35% and 62% were reported in patients who previously received crizotinib and in those who were TKI-naïve, respectively. An intracranial response was observed in 50% of patients who previously received crizotinib and in 64% of the TKI-naïve group. Serious treatment-related AEs occurred in 7% of patients. Peripheral neuropathy was reported in more than one-third of patients treated with lorlatinib, while cognitive effects occurred in approximately a quarter of the patient population.

NCCN Recommendations

The panel recommends crizotinib, entrectinib, repotrectinib, or taletrectinib as preferred first-line treatment options for patients with *ROS1* gene fusion-positive advanced or metastatic NSCLC. All are appropriate for patients with PS 0–4; however, entrectinib, repotrectinib, or taletrectinib may be better for patients with brain metastases (Figures 12 and 13).

On disease progression, consideration of plasma- or tissue-based testing via multigene panel testing should be considered to identify genomic resistance mechanisms. If plasma-based testing is negative, the panel strongly recommends tissue-based testing with rebiopsy material. If a resistant mutation (such as *ROS1* G2032R) is identified, then repotrectinib or taletrectinib are recommended treatment options.

For asymptomatic progression on first-line targeted therapy, the panel recommends repotrectinib, taletrectinib, or lorlatinib as subsequent therapy options, if not previously given.

For patients with CNS progression, repotrectinib, taletrectinib, or lorlatinib are preferred options (if not previously given). Entrectinib can be considered in this setting if the patient was previously treated with crizotinib. A clinical trial, if available, is also recommended. See the NCCN Guidelines for CNS Cancers at NCCN.org for additional recommendations. For symptomatic systemic progression with multiple systemic lesions, repotrectinib, taletrectinib, or lorlatinib are recommended targeted therapy options (if not previously given). Systemic therapies (such as chemotherapy) can be considered in this setting as well (see the "Principles of Systemic Therapy for Advanced or Metastatic Disease" [NSCL-K] in the NCCN Guidelines for NSCLC [available at NCCN.org]). Data indicate that ICI monotherapy is less effective in NSCLC with *ROS1* gene fusion.[7,70]

Continuation of entrectinib, crizotinib, repotrectinib, or taletrectinib is also an option for certain patients with disease progression; continuation of these therapies is not recommended for those with symptomatic systemic progression and either multiple lesions or brain metastases.

Definitive local therapy has a role in the treatment of metastatic *ROS1* gene fusion-positive NSCLC and may be an appropriate subsequent therapy option for certain patients with persistent disease or who have progressed after initial therapy

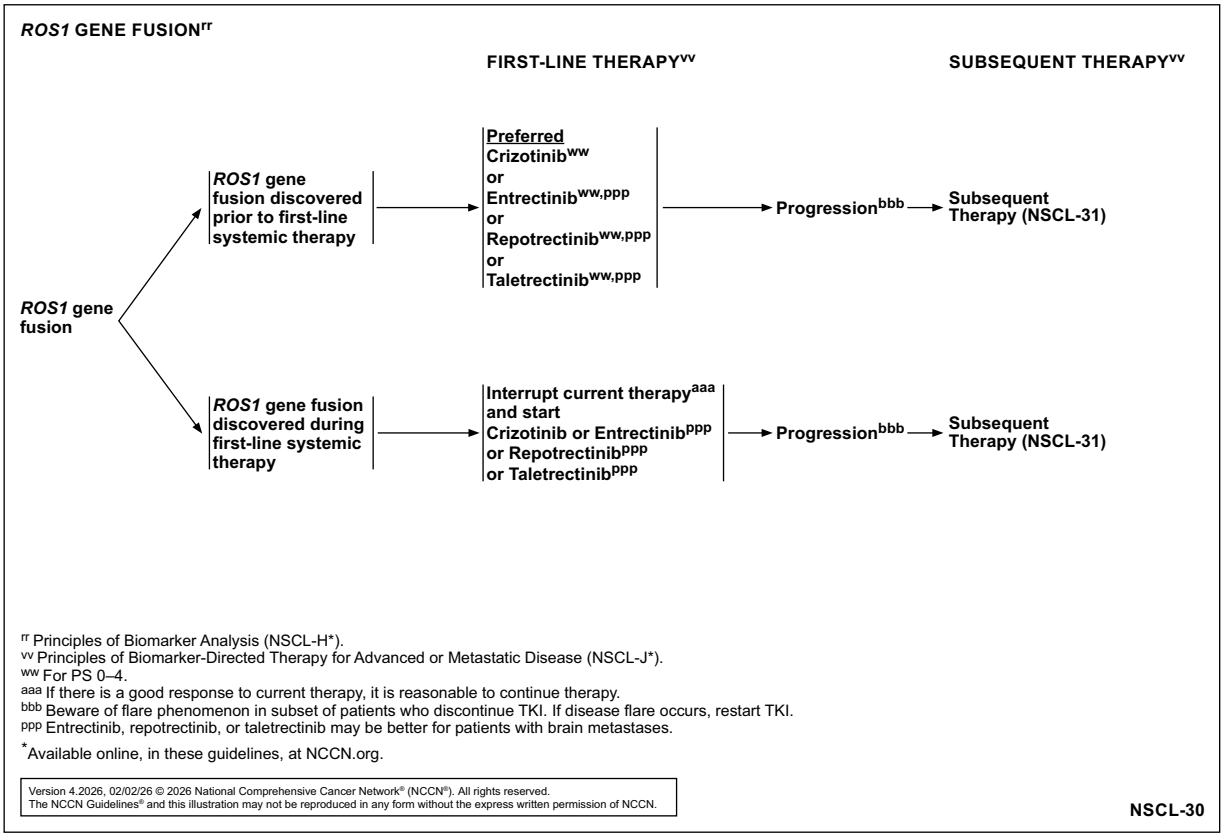


Figure 12. NSCL-30. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

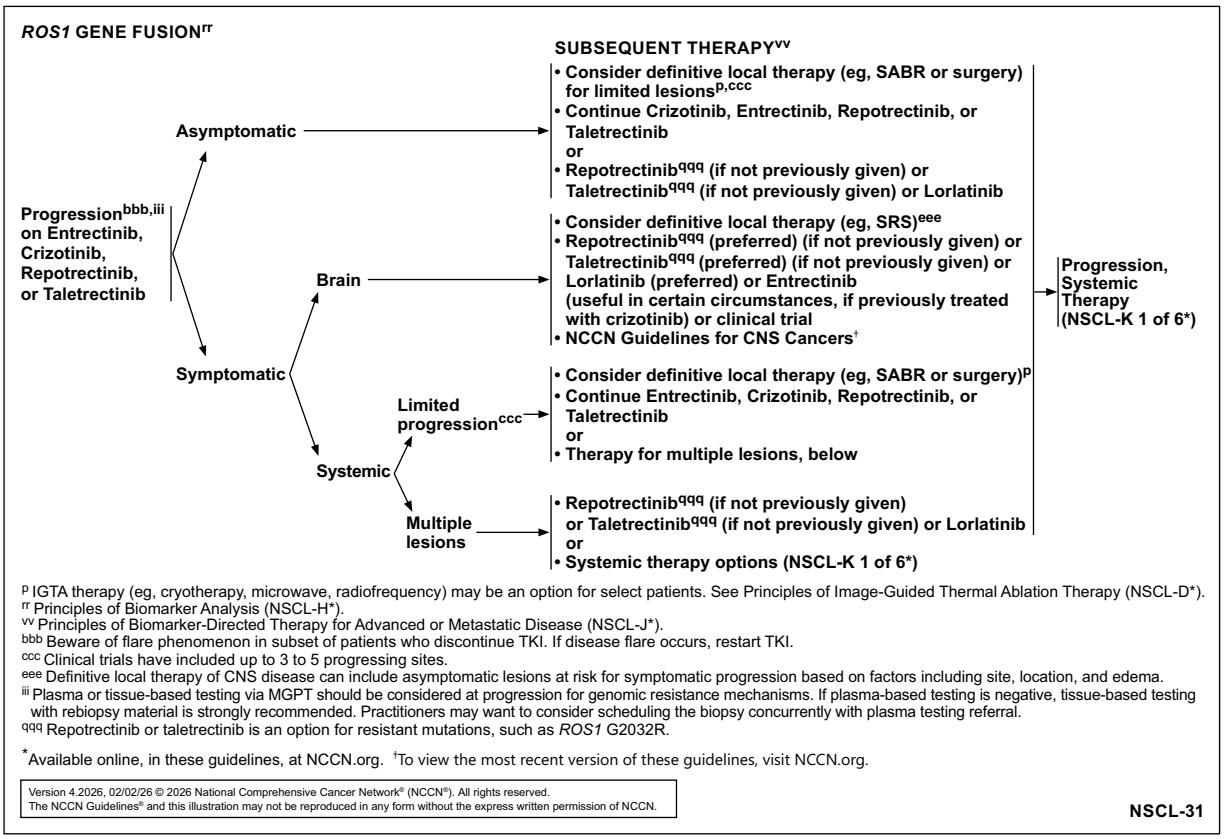


Figure 13. NSCL-31. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

with a ROS1 TKI. For patients with asymptomatic or symptomatic systemic progression that is limited in nature (oligoprogression), definitive local therapy (eg, SABR or surgery) should be considered. IGTA therapy, such as cryotherapy, microwave ablation, or radiofrequency ablation, may also be an option for select patients; see "Principles of Image-Guided Thermal Ablation Therapy" (NSCL-D) in the NCCN Guidelines for NSCLC (available at NCCN.org) for additional information.

For those with CNS progression, definitive local therapy (eg, SRS with or without surgical resection, WBRT) should be considered for symptomatic lesions, and SRS should be considered for asymptomatic lesions at risk for symptomatic progression based on factors including size, location, and edema. See also the NCCN Guidelines for CNS Cancers (at NCCN.org) for additional recommendations.

BRAF V600E Mutation Positive

The *BRAF* V600E mutation occurs in 1%–2% of patients with lung adenocarcinoma and is the most common of the *BRAF* mutations.[121,122] The *BRAF* gene encodes for BRAF, a serine/threonine kinase; activating mutations in *BRAF* result in unregulated signaling through the MAPK pathway.[123]

Clinical Data

Dabrafenib and encorafenib are both oral BRAF kinase inhibitors. Dabrafenib, in combination with the MEK1/2 inhibitor trametinib, is approved by the FDA for the treatment of metastatic NSCLC with *BRAF* V600E mutation.[38] Encorafenib, in combination with the MEK1/2 inhibitor binimetinib, is FDA-approved for the treatment of metastatic NSCLC with a *BRAF* V600E mutation.[38]

A phase II trial assessed dabrafenib in combination with trametinib as first-line therapy in 36 patients with metastatic NSCLC and *BRAF* V600E mutations.[124,125] The overall response rate with dabrafenib plus trametinib as first-line therapy was 63.9%; the median OS was 17.3 months.[124] The same trial also assessed the dabrafenib plus trametinib regimen as subsequent therapy in 57 patients with advanced NSCLC and *BRAF* V600E mutations and disease progression on chemotherapy.[124,126] The overall response rate was 68.4% and the median OS was 18.2 months with dabrafenib/trametinib as subsequent therapy.[124] The most frequent AE reported in the trial was pyrexia.[124]

A phase II PHAROS study evaluated encorafenib in combination with binimetinib in patients with *BRAF* V600E-positive metastatic NSCLC in both the first-line (n=59) and subsequent therapy (n=39) settings.[127,128] The updated analysis reported that the objective response rate was 75% in treatment-naïve patients and 49% in previously treated patients.[128] The median OS was 47.6 months among the treatment-naïve patients and 22.7 months for the previously treated group.[128] The most common treatment-related AEs were nausea, diarrhea, and fatigue. One grade 5 treatment-related AE (intracranial hemorrhage) was reported.

Data suggest that treatment with a single-agent BRAF inhibitor, such as vemurafenib, can also be used to treat patients with metastatic NSCLC and *BRAF* V600E.[129] Results from retrospective studies indicate that patients with advanced NSCLC and *BRAF* mutations may also derive benefit from PD-1/PD-L1

inhibitors.[7,130] Therefore, first-line treatment with an ICI-based regimen can be considered, particularly for those with a minimal burden of disease and/or high PD-L1 levels.

NCCN Recommendations

The panel recommends dabrafenib/trametinib or binimetinib/encorafenib as preferred first-line therapy options for patients with *BRAF* V600E mutation-positive advanced or metastatic NSCLC. The panel also recommends dabrafenib/trametinib or binimetinib/encorafenib as subsequent therapy options if the patient with a *BRAF* V600E mutation did not previously receive a BRAF inhibitor. Both regimens are appropriate for patients with a PS of 0–4 (Figure 14).

Other first-line therapy options include systemic therapy regimens (such as immunotherapy with or without chemotherapy) listed in the "Principles of Systemic Therapy for Advanced or Metastatic Disease" in the NCCN Guidelines for NSCLC (available at NCCN.org); these are designated as "other recommended" options. These regimens can also be used as subsequent therapy options for patients whose disease progressed after receiving a first-line therapy that included a BRAF inhibitor.

NTRK1/2/3 Gene Fusion Positive

NTRK1/2/3 gene fusions encode TRK fusion proteins that act as oncogenic drivers for multiple types of solid tumors, including NSCLC.[131] It is estimated that *NTRK1/2/3* gene fusions occur in <1% of patients with NSCLC and do not typically overlap with other known oncogenic drivers.[132]

Clinical Data

Entrectinib, larotrectinib, and repotrectinib are oral TRK inhibitors that were granted accelerated approval by the FDA for the treatment of patients with solid tumors that have an *NTRK* gene fusion.[38] Entrectinib and repotrectinib are also approved for the treatment of *ROS1*-positive metastatic NSCLC (see the *ROS1 Gene Fusion Positive* section for more information).[38]

The efficacy of entrectinib was evaluated in an analysis of data pooled from 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).[133] Updated data in 51 patients with *NTRK*-positive locally advanced or metastatic NSCLC found that the objective response rate was 62.7%; the median OS was 41.5 months.[134] Among the patients with CNS metastases at baseline, the intracranial objective response rate was 64.3%. Most treatment-related AEs were grade 1 or 2.

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 (by independent review) of 75%.[135] In an analysis of 15 patients with *NTRK* gene fusion-positive lung cancer, the objective response rate by investigator assessment was 73%.[136] The median OS was 40.7 months and the median PFS was 35.4 months. Among those with CNS metastases at baseline, the objective response rate was 63%. Most of the treatment-related AEs were grade 1 or 2.

The efficacy and safety of repotrectinib in patients with *NTRK* gene fusion-positive locally advanced or metastatic solid

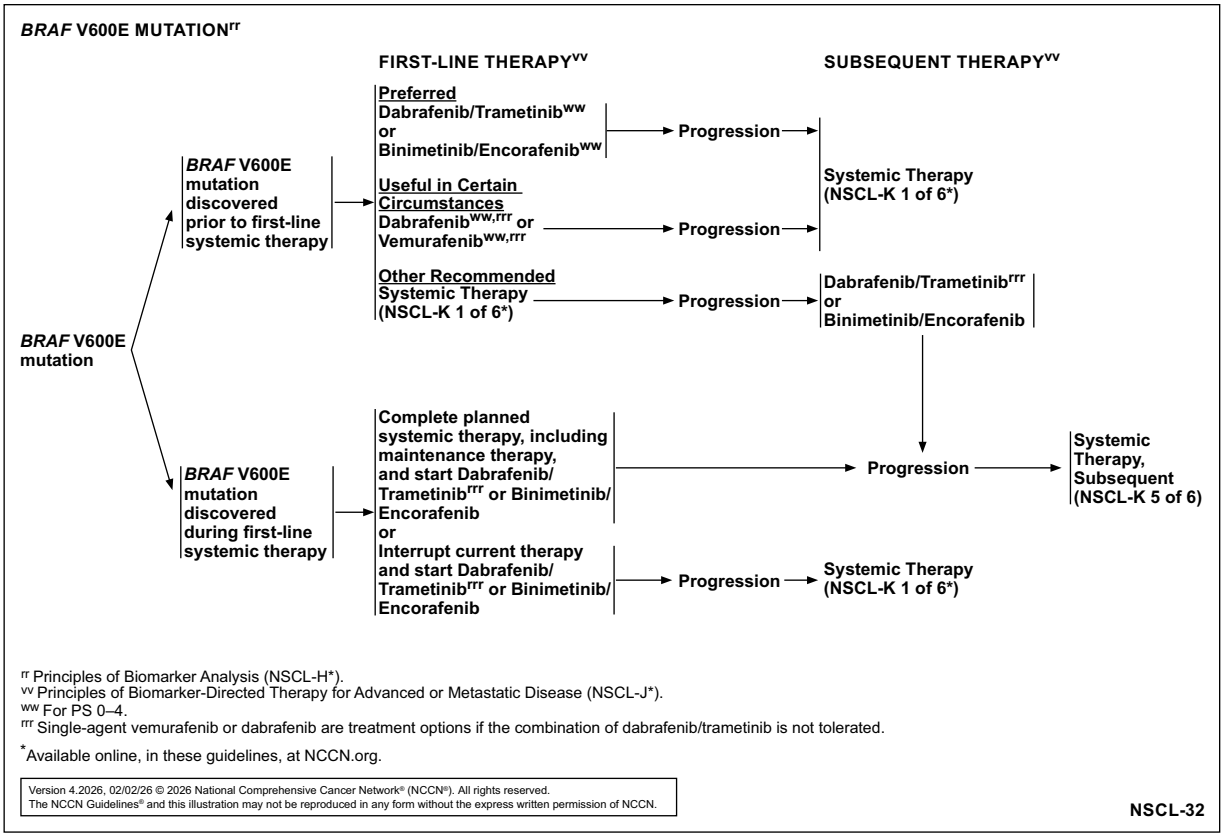


Figure 14. NSCL-32. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

tumors were investigated as part of the phase I/II TRIDENT-1 trial.[137] NSCLC was the most common tumor type represented. In the initial analysis, the confirmed objective response rates were 62% and 42% in the TKI-naïve NSCLC and TKI pretreated NSCLC groups, respectively. The 12-month PFS rate was 64% for the TKI-naïve NSCLC group and 23% for the TKI-pretreated NSCLC group. Dizziness was the most common treatment-emergent AE among all patients in the study (including all tumor types). Half of the patients in the study experienced a grade 3 or higher treatment-emergent AE.

NCCN Recommendations

The panel recommends entrectinib, larotrectinib, or repotrectinib as preferred first-line therapy options for patients with *NTRK1/2/3* gene fusion-positive advanced or metastatic NSCLC (PS 0–4). Repotrectinib can be used as a subsequent therapy if entrectinib or larotrectinib were given previously (Figure 15).

Other systemic therapies (such as chemotherapy with or without immunotherapy) are listed within the "Principles of Systemic Therapy for Advanced or Metastatic Disease" (NSCL-K) in the NCCN Guidelines for NSCLC (available at NCCN.org) and are categorized as first-line treatment options that may be useful in certain circumstances for NTRK1/2/3-positive advanced or metastatic NSCLC. These systemic therapies are also recommended as subsequent therapy options for patients whose disease progressed after treatment with entrectinib, larotrectinib, or repotrectinib. For patients who did not receive a TKI in the first-line setting, recommended subsequent therapy options are entrectinib, larotrectinib, or repotrectinib.

MET Exon 14 Skipping Mutation Positive

MET exon 14 skipping mutations occur in 3%–4% of patients with lung adenocarcinoma and approximately 2% of patients with other NSCLC histologies.[138–140] *MET* exon 14 skipping mutations lead to dysregulation of the HGF receptor (c-Met) tyrosine kinase and inappropriate signaling.[141] The presence of this type of mutation is associated with responsiveness to oral HGF receptor (c-Met) TKIs. The NCCN Guidelines recommend testing for *MET* exon 14 skipping mutations as part of multigene panel testing given the availability of FDA-approved targeted therapies for this biomarker.

Clinical Data

Capmatinib and tepotinib are oral TKIs that selectively inhibit HGF receptor (c-Met) kinase and are both approved by the FDA for the treatment of adults with metastatic NSCLC whose tumors have a *MET* exon 14 skipping mutation.[38,142]

The phase II GEOMETRY study assessed capmatinib in different cohorts of patients with *MET* genomic alterations, including those with *MET* exon 14 skipping mutations; patients had stage IIIB or IV NSCLC and were wild-type for *EGFR* and *ALK*.[143] First-line capmatinib resulted in an overall response rate of 68% in 28 patients with *MET* exon 14 skipping mutations; the median PFS was 12.4 months.[143] Subsequent therapy with capmatinib yielded an overall response rate of 41% in 69 patients with *MET* exon 14 skipping mutations; the median PFS was 5.4 months.[143] Common treatment-related AEs for patients with *MET* exon 14 skipping mutations across all cohorts included peripheral edema, nausea, and vomiting and increased blood creatinine levels.[143]

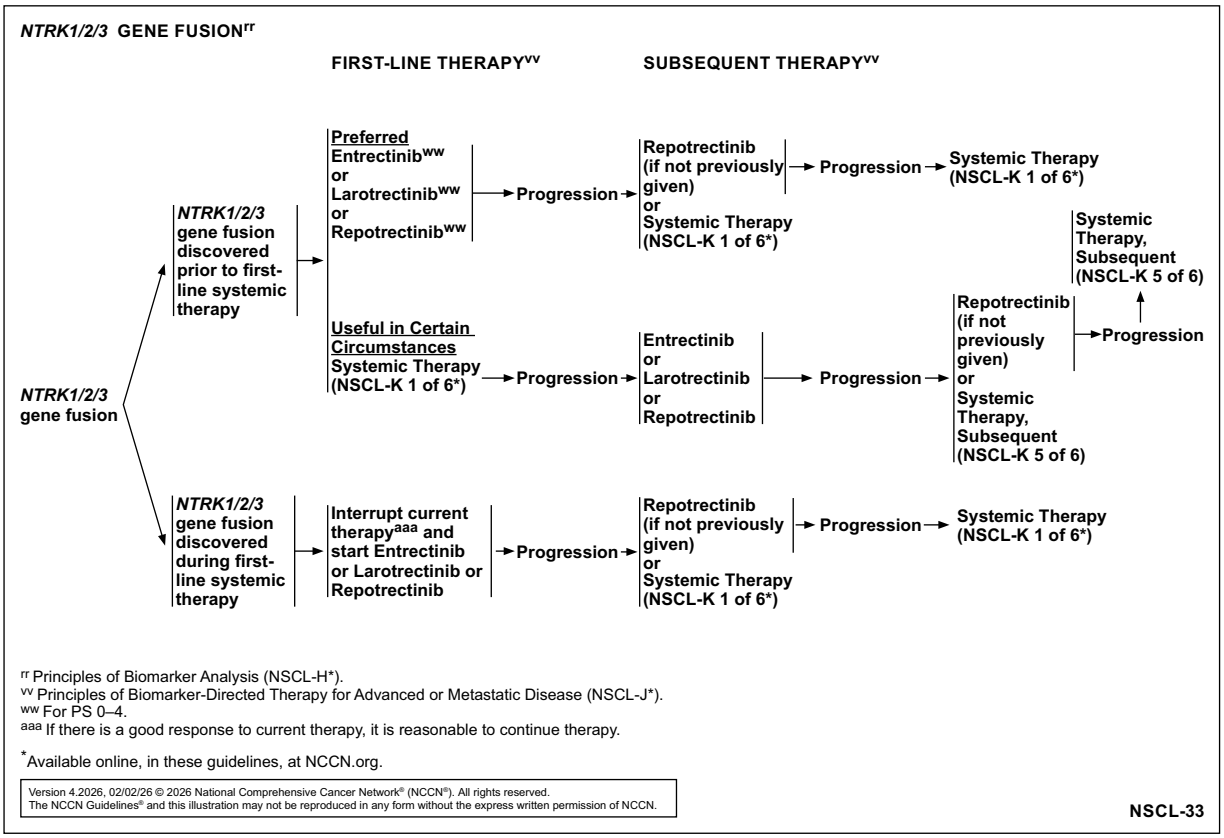


Figure 15. NSCL-33. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

The phase II VISION trial assessed tepotinib in patients with *MET* exon 14 skipping mutation-positive locally advanced or metastatic NSCLC and wild-type *EGFR* and *ALK*.[144–146] Based on the 18-month analysis, the objective response rate with tepotinib was 57.3% in the treatment-naïve group and 45.0% among previously treated patients.[146] The median OS was 21.3 months for the treatment-naïve group and 19.3 months for the previously treated group. Peripheral edema was the most common treatment-related AE.

Data suggest that crizotinib, an oral TKI that inhibits multiple kinases, is also a viable targeted therapy option for patients with advanced NSCLC and a *MET* exon 14 skipping mutation.[147]

NCCN Recommendations

The panel recommends capmatinib, tepotinib, or crizotinib as first-line targeted therapy options for patients with advanced or metastatic NSCLC and a *MET* exon 14 skipping mutation. These are also recommended as subsequent therapy options, if the patient was not previously treated with capmatinib, tepotinib, or crizotinib. Capmatinib and tepotinib are categorized as preferred, while crizotinib is considered "Useful in certain circumstances." The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended (Figure 16).

Other systemic therapy regimens listed in the "Principles of Systemic Therapy for Advanced or Metastatic Disease" (NSCL-K) in these NCCN Guidelines (available at NCCN.org) are recommended as "Useful in certain circumstances" for first-line therapy. These are also recommended as subsequent therapy options in patients whose disease progressed following treatment with capmatinib, tepotinib, or crizotinib. Data indicate that ICI monotherapy may be less effective in NSCLC with *MET* alterations.[7,70]

RET Gene Fusion Positive

RET gene fusions occur in about 1%–2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology.[148–152] Rearrangements may occur between *RET* and other genes, including *KIF5B* and *CCDC6*, which can lead to dysregulation of RET kinase and inappropriate signaling.[148,149]

Clinical Data

Selpercatinib and pralsetinib are oral TKIs that inhibit RET and are both approved by the FDA for the treatment of metastatic NSCLC with *RET* gene fusion.[38,153]

LIBRETTO-431, a randomized phase III trial, evaluated selpercatinib versus control (platinum-based chemotherapy with or without pembrolizumab) as first-line therapy in 212 patients with advanced NSCLC and *RET* gene fusion.[154] Based on the interim analysis, the median PFS was longer with selpercatinib than with the control treatment (24.8 months vs 11.2 months). The objective response rate of the selpercatinib group was higher than the control group (84% vs 65%). Among those with brain metastases at baseline, a higher proportion of patients in the selpercatinib group experienced an intracranial response compared with those in the control group (82% vs 58%). The

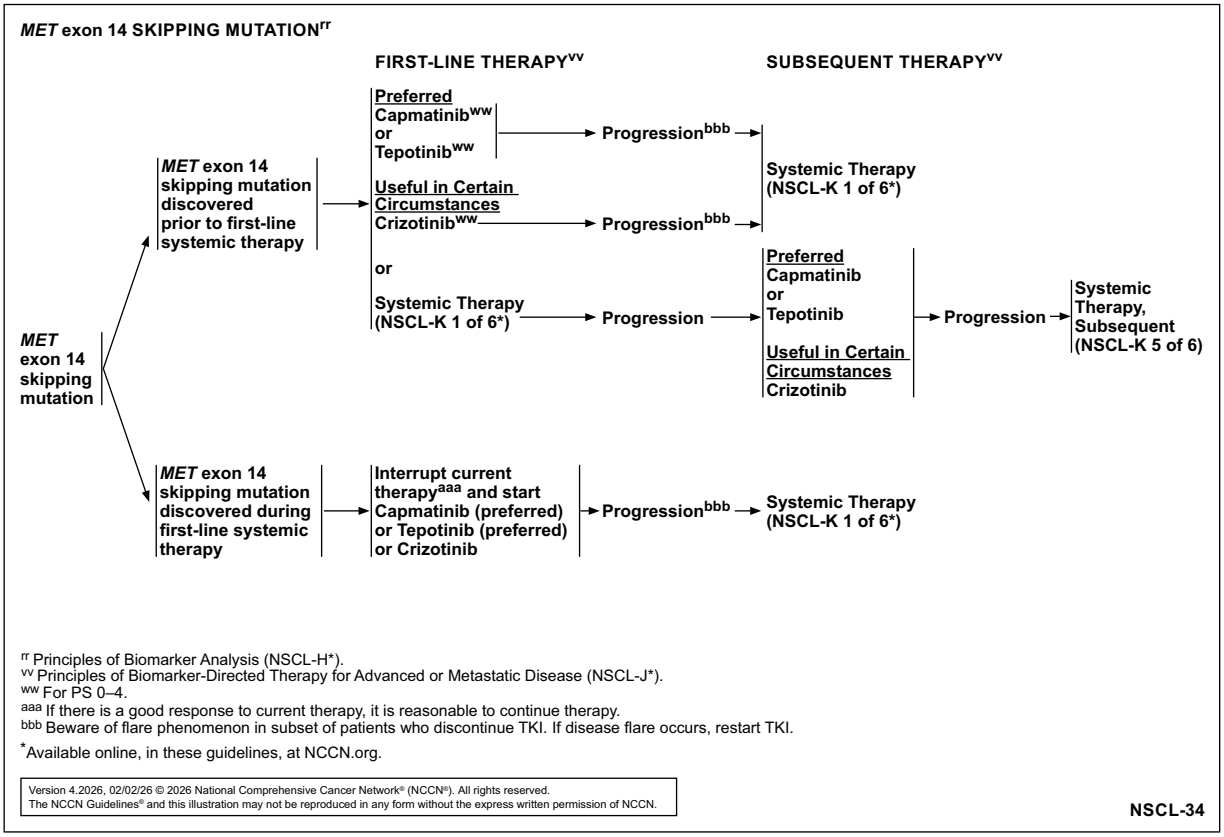


Figure 16. NSCL-34. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

incidence of grade 3 or higher AEs was 70% with selpercatinib compared with 57% in the chemotherapy (with or without pembrolizumab) group. Common AEs that occurred with selpercatinib included increases in AST or ALT levels, hypertension, diarrhea, edema, dry mouth, and increase in blood bilirubin. An analysis of patient-reported outcomes from the LIBRETTO-431 trial reported that selpercatinib was associated with lower symptom burden and side effect bother than the control treatment (platinum chemotherapy with pembrolizumab).[155]

ARROW, a phase I/II study, assessed pralsetinib in patients with metastatic NSCLC and *RET* gene fusion.[156] First-line therapy with pralsetinib resulted in an overall response rate of 70% (19/27), while second-line therapy with pralsetinib resulted in an overall response rate of 61% (53/87). Grade 3 or higher AEs with pralsetinib included anemia, neutropenia, and hypertension. Common AEs with pralsetinib included increased AST levels, increased ALT levels, anemia, hypertension, constipation, and neutropenia. Updated data from the ARROW trial showed that the overall response rate with pralsetinib was 72% for those who were treatment-naïve and 59% for those who previously received platinum-based chemotherapy.[157] Among the 10 patients with intracranial metastases (all who previously received systemic therapy), the intracranial response rate was 70%.

Data suggest that cabozantinib, an oral kinase inhibitor active against multiple receptor tyrosine kinases, including RET, HGF receptor (c-Met), VEGFR2, and others,[153] is another viable treatment option for patients with *RET* gene fusion-positive metastatic NSCLC.[158–160]

NCCN Recommendations

The panel recommends pralsetinib or selpercatinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC and *RET* gene fusion; both are appropriate for a PS of 0–4. Cabozantinib is recommended as a subsequent therapy option. Selpercatinib is a category 1 recommendation, while pralsetinib and cabozantinib are category 2A. The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended (Figure 17).

Other systemic therapies (such as chemotherapy) listed within the "Principles of Systemic Therapy for Advanced or Metastatic Disease" (NSCL-K) in the NCCN Guidelines for NSCLC (available at NCCN.org) are recommended as subsequent therapy options for *RET* gene fusion-positive advanced or metastatic NSCLC in patients whose disease progressed after treatment with pralsetinib, selpercatinib, or cabozantinib. Data indicate that ICI monotherapy may be less effective in NSCLC with *RET* gene fusions.[7,70]

ERBB2 (HER2) Mutation Positive

The *ERBB2* gene (also commonly referred to as *HER2*) encodes for HER2, a receptor tyrosine kinase found on the surface of normal epithelial cells that is often overexpressed or mutated in a variety of human malignancies.[161] Up to 5% of NSCLC may have a mutation in *ERBB2 (HER2)*.[162,163] The most common mutations are those within the tyrosine kinase domain.[164] Resources are available to assess whether a specific *ERBB2 (HER2)* mutation is oncogenic or likely to be oncogenic (such as www.oncoKB.org).

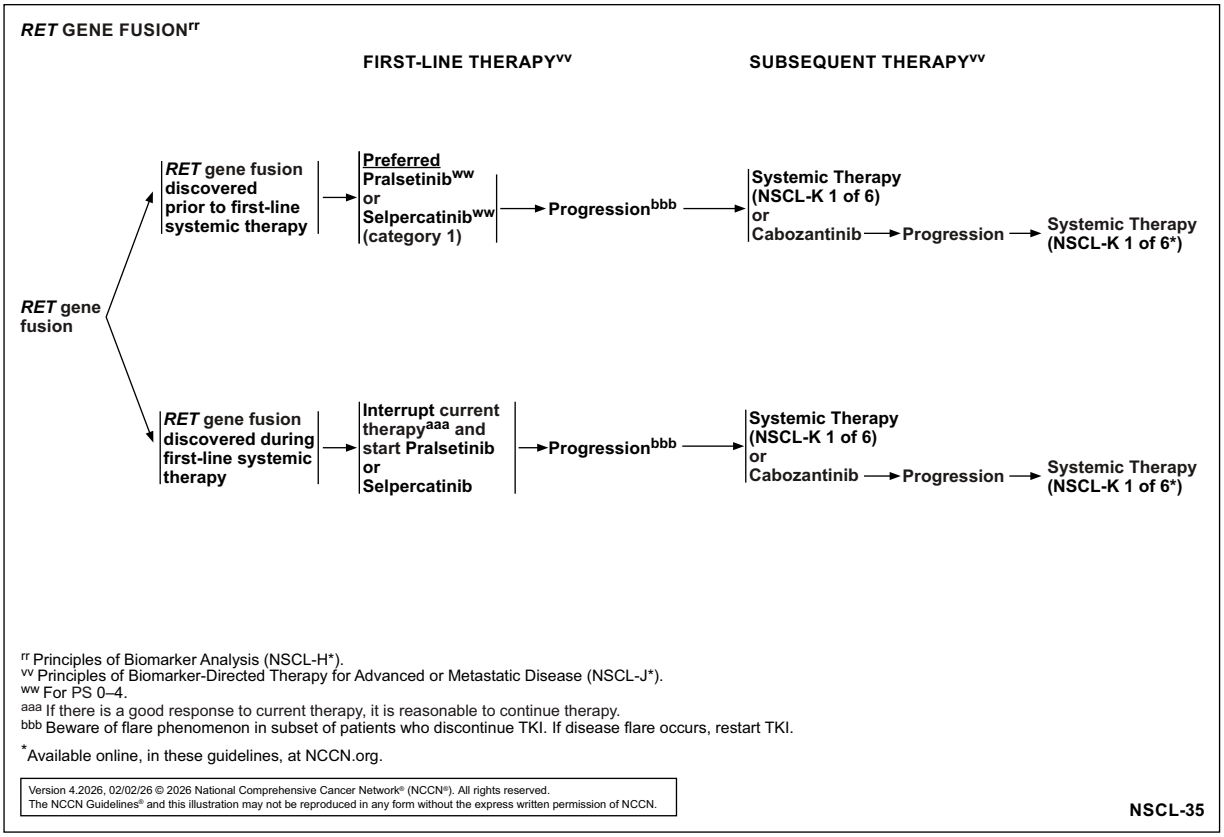


Figure 17. NSCL-35. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

Clinical Data

Fam-trastuzumab deruxtecan-nxki was granted accelerated approval by the FDA for the treatment of adults with unresectable or metastatic NSCLC tumors that have activating *ERBB2 (HER2)* mutations, and who received a prior systemic therapy.[38] Fam-trastuzumab deruxtecan-nxki is a humanized monoclonal antibody drug conjugate (ADC) consisting of an antibody targeting HER2 and a topoisomerase I inhibitor.[165]

The phase II DESTINY-Lung01 study assessed fam-trastuzumab deruxtecan-nxki in 91 patients with metastatic nonsquamous NSCLC and *ERBB2* mutations.[165–167] Most patients had *ERBB2 (HER2)* exon 20 insertion mutations (86%).[165] The objective response rate with fam-trastuzumab deruxtecan-nxki was 55%; most patients had received prior treatment.[165] Median OS was 17.8 months.[165] Grade 3 or higher AEs occurred in 46% of patients including neutropenia (19%). Treatment-related ILD was reported in 26% (24/91) of patients, resulting in 2 deaths.

Data have shown that ado-trastuzumab emtansine, a HER2-directed ADC, also has efficacy in this patient population; however, this agent is not FDA approved in the setting of *ERBB2 (HER2)*-positive NSCLC.[168,169]

More recently, two oral TKIs received accelerated approval by the FDA for the treatment of patients with *ERBB2 (HER2)*-mutated NSCLC.[38]

Zongertinib is an irreversible HER2-selective TKI indicated by the FDA for the treatment of patients with unresectable or metastatic nonsquamous NSCLC whose tumors have *ERBB2* (*HER2*) tyrosine kinase domain (TKD) activating mutations and who have received prior systemic therapy.[38,170] The phase Ib multicohort Beamion LUNG-1 trial evaluated the efficacy and safety of zongertinib in patients with advanced or metastatic *ERBB2* (HER2)-mutated nonsquamous NSCLC who had been previously treated.[170] Among the 75 patients with a mutation in the tyrosine kinase domain, 71% experienced an objective response, with a median PFS of 12.4 months. In an exploratory analysis of 20 patients with NSCLC and *ERBB2* non-TKD mutations, a 30% objective response rate was reported with zongertinib. The most common AE reported in the previously treated cohort was diarrhea in 56%. Elevations in aspartate aminotransferase occurred in 24%.

Sevabertinib is a reversible HER2 and EGFR TKI indicated by the FDA for the treatment of patients with locally advanced or metastatic nonsquamous NSCLC whose tumors have *ERBB2 (HER2)* TKD activating mutations and who have received a prior systemic therapy.[38,171] The efficacy and safety of sevabertinib in 209 patients with locally advanced or metastatic NSCLC with *ERBB2 (HER2)* mutations was assessed in the phase I–II SOHO-01 trial.[171] More than 90% of the patients in the study had an *ERBB2* (*HER2*) TKD mutation. Among the 81 patients previously treated with a non–HER2-targeted therapy, the objective response rate with sevabertinib was 64% and the median PFS was 8.3 months. Based on an exploratory biomarker analysis of this group, a higher proportion of patients with an *ERBB2* TKD mutation experienced an objective response with sevabertinib than those with a non-TKD mutation (70% vs 14%). Among the 55 patients who previously received a HER2-targeted ADC, the objective response rate was 38% and the median PFS was 5.5 months. The most common AE reported in the study was diarrhea, which was experienced by 84%–91% of patients across cohorts.

NCCN Recommendations

The NCCN NSCLC Panel recommends systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed in the "Principles of Systemic Therapy for Advanced or Metastatic Disease" (NSCL-K) in these NCCN Guidelines (available at NCCN.org) for the first-line treatment of advanced or metastatic NSCLC with *ERBB2 (HER2)* mutation (Figure 18). Data indicate that ICI monotherapy may be less effective in NSCLC with an *ERBB2 (HER2)* mutation.[7,70]

At disease progression, fam-trastuzumab deruxtecan-nxki, zongertinib, or sevabertinib are recommended as preferred subsequent therapy options, while ado-trastuzumab emtansine is designated as "Useful in certain circumstances." Other subsequent therapy options are listed on NSCL-K 5 of 6 (Figure 5). The panel notes that switching between agents with a similar mechanism of action (eg, zongertinib and sevabertinib) at progression is not recommended. However, given the slightly different toxicity profile of zongertinib and sevabertinib, switching between these agents due to toxicity in the absence of progression may be reasonable.

Some patients may have overexpression of HER2 protein rather than *ERBB2 (HER2)* mutations. Refer to the "HER2 (IHC 3+) Positive" subsequent section for treatment options.

NRG1 Gene Fusion Positive

The NRG1 protein, encoded by the *NRG1* gene, is a member of the neuregulin family that includes EGF-like proteins involved in nervous system and cardiac development and homeostasis.[172,173] *NRG1* gene fusions are rare and estimated to occur in <1% of patients diagnosed with NSCLC.[174,175] Invasive mucinous lung adenocarcinoma are associated with higher rates of *NRG1* gene fusion.[174] The resulting NRG1 fusion proteins are considered oncogenic drivers as they result in inappropriate signaling via the ERBB family receptor tyrosine kinase pathway.[172,173]

Clinical Data

Zenocutuzumab is a bispecific HER2- and HER3-directed antibody that has been granted accelerated approval by the FDA for the treatment of advanced, unresectable, or metastatic NSCLC with an *NRG1* gene fusion with disease progression on or after prior systemic therapy.[38]

The accelerated approval was based on data from a phase II trial that evaluated zenocutuzumab in patients with advanced or metastatic solid tumors with *NRG1* gene fusion.[176] Patients with NSCLC represented 58% (94 of 161) of the primary efficacy population. Within the NSCLC group, 87% were previously treated with systemic therapy; 76% received platinum-based chemotherapy and 56% received immunotherapy. The overall response rate based on investigator assessment was 29% in the NSCLC group; the median duration of response was 12.7 months. Grade 3 or 4 treatment-related AEs occurred in 7% of all patients who received zenocutuzumab; diarrhea and anemia were the most common in this group.

NCCN Recommendations

The panel recommends systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed in the "Principles of Systemic Therapy for Advanced or Metastatic Disease" (NSCL-K) pages in these NCCN Guidelines (available at NCCN.org) for the first-line treatment of advanced or metastatic NSCLC with an *NRG1* gene fusion (Figure 19).

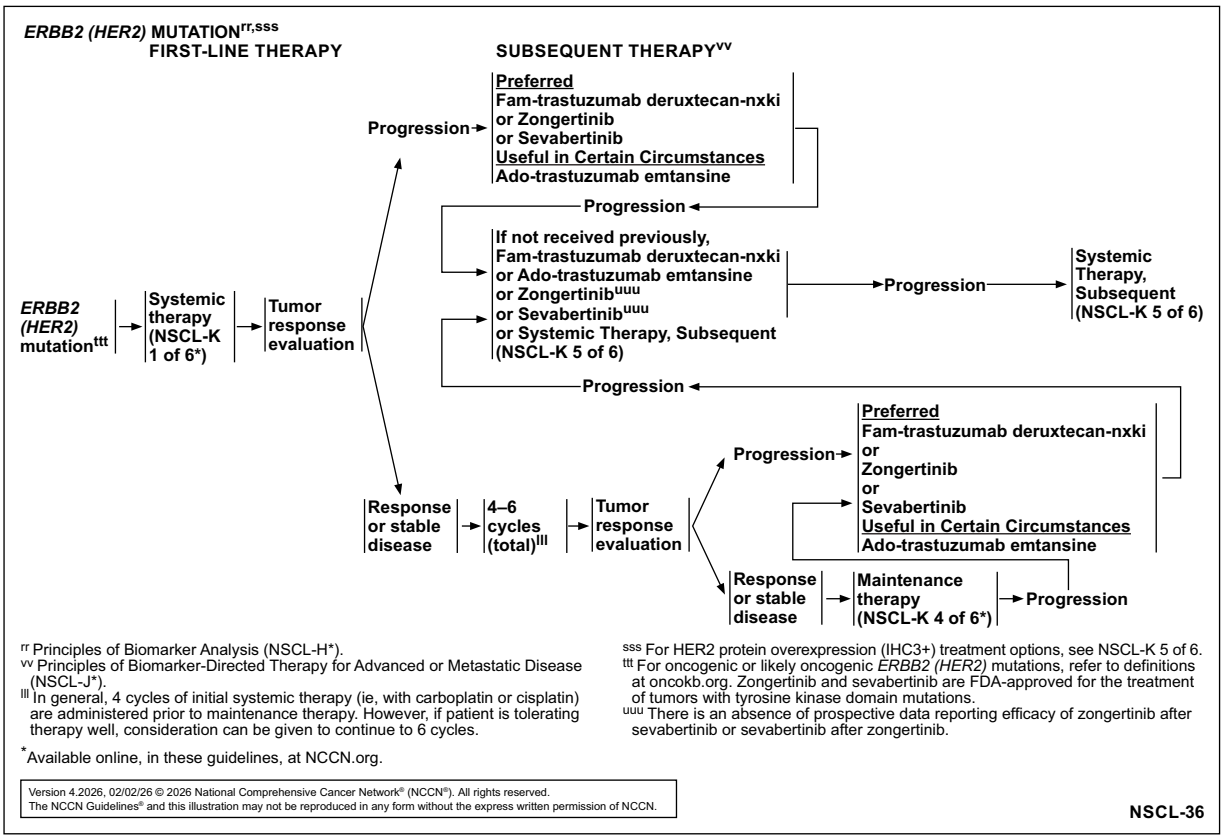


Figure 18. NSCL-36. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

Zenocutuzumab-zbco is recommended as a subsequent therapy option for those with *NRG1* gene fusion-positive advanced or metastatic NSCLC. After progression on zenocutuzumab-zbco, additional systemic therapy options are detailed on NSCL-K 5 of 6 (Figure 5).

HER2 (IHC 3+) Positive

HER2 protein overexpression occurs in many types of solid tumors, including NSCLC, and is often associated with poor outcomes.[177]

Clinical Data

Fam-trastuzumab deruxtecan-nxki was granted accelerated approval by the FDA for the treatment of patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative options.[38] This approval is applicable to patients with NSCLC based on positive data from the phase II single-arm DESTINY-Lung01 trial, which included 90 patients with unresectable or metastatic HER2-overexpressing (IHC 3+ or 2+) NSCLC who received fam-trastuzumab deruxtecan-nxki as subsequent therapy (cohorts 1 [6.4 mg/kg] and 1A [5.4 mg/kg]).[178] The objective response rates were 26.5% and 34.1% in cohort 1 and cohort 1A, respectively. One death was attributed to treatment-emergent pneumonitis by the investigator. Drug-related ILD or pneumonitis (based on independent adjudication) occurred in 20% of patients in cohort 1 (including 3 grade 5 events) and 5% of cohort 1A (including one grade 5 event).

NCCN Recommendations

The panel recommends fam-trastuzumab deruxtecan-nxki as a subsequent therapy option for patients with advanced or metastatic NSCLC with HER2 (IHC 3+). Fam-trastuzumab deruxtecan-nxki is appropriate for patients with a PS of 0–2, regardless of histology (Figure 5).

HGF Receptor (c-Met)-Positive (≥50% IHC 3+ and EGFR Wild-Type)

HGF receptor (commonly referred to as c-Met) is a receptor tyrosine kinase encoded by the *MET* gene that is found on the surface of normal epithelial cells.[179] HGF receptor (c-Met) overexpression in patients with NSCLC is associated with worse prognosis.[179,180]

Clinical Data

Telisotuzumab vedotin-tllv is an HGF receptor (c-Met)-directed ADC that was granted accelerated approval by the FDA for the treatment of adults with locally advanced or metastatic nonsquamous NSCLC with high HGF receptor (c-Met) protein overexpression (≥50% of tumor cells with strong [3+] staining) who have received a prior systemic therapy.[38]

The phase II LUMINOSITY trial was a 2-stage study that evaluated telisotuzumab vedotin-tllv in patients with locally advanced or metastatic NSCLC with HGF receptor (c-Met) overexpression.[181] The optimal candidates for telisotuzumab vedotin-tllv were first identified as those with nonsquamous *EGFR* wild-type NSCLC and HGF receptor (c-Met) overexpression; telisotuzumab vedotin-tllv was then further assessed in an expanded

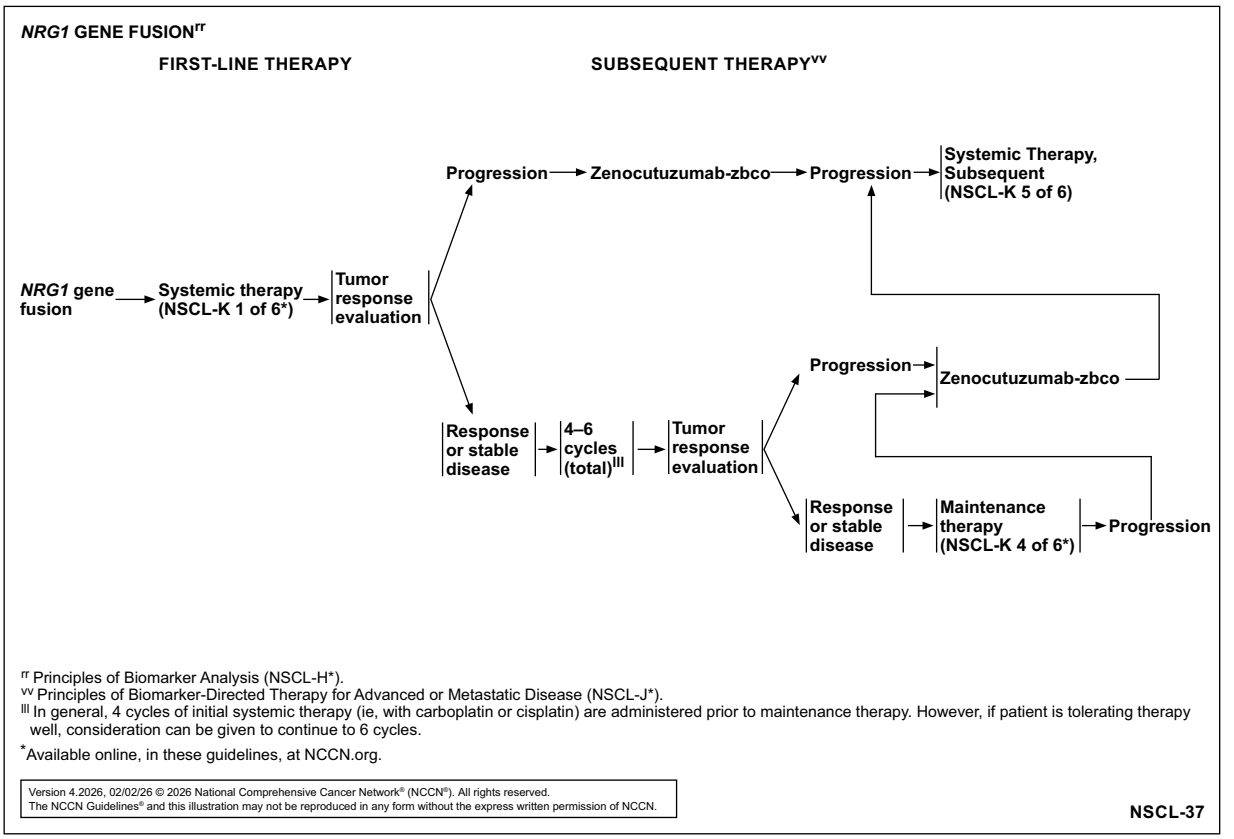


Figure 19. NSCL-37. NCCN Clinical Practice Guidelines in Oncology for Non-Small Cell Lung Cancer, Version 4.2026.

group of patients with these disease characteristics. The overall response rates were 34.6% for 78 patients with HGF receptor (c-Met) ≥50% IHC 3+ and 22.9% among 83 patients ≥25% to <50% IHC 3+. The median OS was 14.6 months and 14.2 months for the HGF receptor (c-Met) ≥50% IHC 3+ and ≥25% to <50% IHC 3+ groups, respectively. The most common treatment-related AEs were peripheral sensory neuropathy, peripheral edema, and fatigue. Treatment-related pneumonitis (any grade) was reported in 10.5% of patients with HGF receptor (c-Met) overexpression. Adjudicated ILD events were reported in 9.9% of patients.

NCCN Recommendations

The panel recommends telisotuzumab vedotin-tllv as a subsequent therapy option for patients with advanced or metastatic nonsquamous NSCLC with HGF receptor (c-Met) ≥50% IHC 3+ and wild-type *EGFR*. Telisotuzumab vedotin-tllv is appropriate for patients with a PS of 0–2 (Figure 5).

Summary

The NCCN Guidelines for NSCLC outline treatment strategies for patients diagnosed with NSCLC. For advanced or metastatic disease, systemic therapy is the primary treatment modality; however, definitive local therapy may also be used for certain patients. Biomarker testing should be incorporated into the treatment plan for most patients with NSCLC to identify the most appropriate systemic therapy options. The panel will continue to update the NCCN Guidelines for NSCLC based on clinical evidence and consensus.

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