

Non–Small Cell Lung Cancer, Version 4.2024

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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 for relapse, 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 molecular biomarkers.

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Overview

Lung cancer is the leading cause of cancer-related deaths in the United States.^{1,2} In 2024, an estimated 234,580 new cases (116,310 in males and 118,270 in females) of lung and bronchial cancer will be diagnosed, and 125,070 people (65,790 males and 59,280 females) will die because of the disease.¹ It is estimated that 25.4% of patients with lung and bronchial cancers are alive 5 years or more after diagnosis; this includes patients with non–small cell lung cancer (NSCLC) and those with small cell lung cancer (SCLC) in the United States from 2013 through 2019.³ The overall 5-year relative survival rate among those with adenocarcinoma histology was 32.2%.³ Since 2006, the incidence of lung cancer has decreased annually by 2.5% in males and 1% in females.¹ It is estimated that 81% of lung cancer deaths in 2024 will be caused directly by cigarette smoking.¹

There have been significant improvements in the treatment of lung cancer, including advances in screening; minimally invasive techniques for diagnosis and treatment; radiation therapy (RT), including stereotactic ablative radiotherapy (SABR); as well as new targeted therapies and immunotherapies.^{4–9} The

availability of these new treatments is associated with improved survival rates for patients with NSCLC. From 2015 to 2016, 2-year relative survival for NSCLC was 42% compared with 34% from 2009 to 2010.¹⁰ Patients with NSCLC who are eligible for targeted therapies or immunotherapies are now surviving longer; 5-year survival rates range from 15% to 62.5%, depending on the biomarker.^{9,11–27} Therefore, biomarker testing is critical to guide treatment selection and ensure optimal outcomes in patients with NSCLC, particularly for those with advanced or metastatic disease.

This selection from the NCCN Guidelines for NSCLC focuses on targeted therapy recommendations for patients with advanced or metastatic NSCLC with actionable molecular biomarkers (to view the complete and most recent version of these NCCN Guidelines, visit [NCCN.org](https://www.nccn.org)).

Advanced or Metastatic NSCLC

For patients with advanced or metastatic NSCLC, the NCCN Guidelines recommend that histologic subtype should be determined before therapy so that an appropriate treatment can be

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To view disclosures of external relationships for the NCCN Guidelines panel, go to <https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels>

The full NCCN Guidelines for Non–Small Cell Lung Cancer are not printed in this issue of *JNCCN*. The complete and most recent version of these guidelines is available free of charge at [NCCN.org](https://www.nccn.org).

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

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

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

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

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

All recommendations are category 2A unless otherwise indicated.

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

PLEASE NOTE

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

NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

selected. Smoking cessation counseling (if necessary) and palliative care should also be integrated into the disease management strategy. Data suggest that early palliative care is associated with higher quality of life in patients with metastatic NSCLC.²⁸

Molecular testing for somatic, disease-associated oncogenic driver mutations or alterations should be conducted as part of broad molecular profiling, which is strongly recommended by the panel. Broad molecular profiling is defined as molecular testing that identifies all actionable molecular biomarkers specified in the guidelines in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers. Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. The goal of broad molecular profiling is to identify driver alterations that can guide use of available targeted therapies or to appropriately counsel patients regarding potential clinical trials that may be available. Therefore, broad molecular profiling is considered a key component of improving care for patients with NSCLC.

Molecular testing via biopsy and/or plasma testing is recommended; combinations of tissue and plasma testing, either concurrently or in sequence, are acceptable. Evidence suggests that concurrent testing can improve time to test results and should be considered depending on the clinical situation.^{29–35} Negative results (defined as the absence of a definitive driver mutation) by one method suggest that a complementary method may be used.

Molecular testing for *EGFR*, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET* ex14 skipping, *RET*, and *ERBB2* (*HER2*) alterations is recommended in all patients with advanced or metastatic nonsquamous NSCLC (ie, adenocarcinoma, large cell carcinoma) and NSCLC not otherwise specified; *EGFR* mutation and *ALK* rearrangement testing are category 1 recommendations for patients with nonsquamous NSCLC or NSCLC not otherwise specified based on the data available to recommend targeted therapies for these biomarkers. As the cumulative incidence of targetable molecular alterations in squamous cell carcinoma across all alterations ranges from 2% to 10%,^{36–39} the same molecular testing should be considered in all patients with advanced or metastatic NSCLC squamous cell carcinoma, and not just those with certain clinical characteristics, such as never smoking status and mixed histology.

If a clinically actionable biomarker is found, the guidelines provide appropriate therapy recommendations. If results are unknown or pending, patients can be treated as if they do not have

driver oncogenes. However, retrospective data indicate that the availability of molecular testing before treatment initiation is associated with longer overall survival (OS) in patients with advanced nonsquamous NSCLC.⁴⁰ If patients require an urgent start to therapy, clinicians should consider holding immunotherapy for one cycle (ie, just use platinum-based chemotherapy regimens). Clinicians need to be aware of the long half-life of immune checkpoint inhibitors and the potential for higher rates of side effects when using certain targeted therapies, (such as osimertinib) in combination with or following checkpoint inhibitors.^{41–44}

If a clinical actionable biomarker is discovered during first-line systemic therapy, then the planned systemic therapy (including maintenance therapy) can be either interrupted or completed before switching to the appropriate targeted therapy. Factors that can be considered to guide this decision include the level of toxicity that the patient is experiencing and whether a clinical or radiographic response has been observed.

Upfront PD-L1 expression testing before first-line therapy is also a category 1 recommendation (regardless of histology) in patients with advanced or metastatic NSCLC to assess how immune checkpoint inhibitors (ICIs) could be used if no actionable molecular biomarkers are identified. Treatment options for advanced or metastatic NSCLC without actionable molecular biomarkers are stratified by PD-L1 level and include systemic therapy options such as immunotherapy with or without chemotherapy (see pages NSCL-37 and NSCL-38, available online, in these guidelines, at NCCN.org). Refer to the full guidelines at NCCN.org for complete treatment recommendations for advanced or metastatic NSCLC based on PD-L1 levels in the absence of a clinically actionable marker.

In the NCCN Guidelines, targeted therapies with a first-line indication are recommended as initial therapy (rather than first-line ICIs) for patients with advanced or metastatic NSCLC and some (but not all) oncogenic drivers, regardless of PD-L1 levels. The rationale is that targeted therapies typically yield higher response rates (eg, osimertinib, 80%) than ICIs (poor response rates) in the first-line setting, and targeted therapy is better tolerated.^{38,45–48} 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 NSCLC with *KRAS* G12C mutations are likely to benefit from immunotherapy (with or without chemotherapy) in the first-line

setting.^{38,49,50} Targeted therapies are recommended only in the second-line setting or later for those with *KRAS* G12C mutations.

Monitoring is recommended during initial therapy with response assessment with CT (with or without contrast) of known or high-risk sites of disease (such as chest, abdomen, and pelvis) after 2 cycles and then every 2 to 4 cycles. Likewise, monitoring of known or high-risk sites of disease is also recommended during maintenance or subsequent therapy with CT (with or without contrast) every 6 to 12 weeks.

For complete treatment recommendations for advanced or metastatic NSCLC, see Figure 1.

NSCLC With *EGFR* Alterations

Epidermal growth factor receptor (*EGFR*) is a receptor tyrosine kinase that is altered in a subset of patients with NSCLC. The two most common *EGFR* alterations in NSCLC are deletions in exon 19 (with conserved deletion of the LREA sequence) and a point mutation in exon 21 (L858R); these represent approximately 85%–90% of all *EGFR* alterations in NSCLC.⁵¹ Both result in activation of the tyrosine kinase domain and are associated with sensitivity to small-molecule *EGFR* tyrosine kinase inhibitors (TKIs).⁵² These *EGFR* alterations are found in approximately 10% of white patients with NSCLC and up to 19% of Black and 50% of Asian patients.^{53–55}

Other less common *EGFR* mutations (approximately 10%) include exon 20 S768I, exon 21 L861Q, and/or exon 18 G719X.^{51,56} These mutations have varying degrees of sensitivity to first- (erlotinib/gefitinib), second- (afatinib/dacomitinib), and third- (osimertinib) generation *EGFR* TKIs.^{51,56–60}

EGFR T790M is an *EGFR* exon 20 mutation associated with acquired resistance to *EGFR* TKI therapy and has been reported in about 60% of patients with disease progression after initial response to afatinib, erlotinib, or gefitinib.^{61–68} If *EGFR* T790M is identified in the absence of prior *EGFR* TKI therapy, genetic counseling and possible germline genetic testing are warranted. Identification of germline *EGFR* T790M confers a high risk for lung cancer regardless of smoking status.^{69–71}

EGFR exon 20 insertion mutations are the third most common group of *EGFR* mutations; they occur in approximately 2% of patients with NSCLC and 4%–12% of patients with *EGFR* mutations.^{72–75} *EGFR* exon 20 insertion mutations are a heterogeneous group; while NSCLC with these variants generally have low response rates to early-generation *EGFR* TKIs, variable levels of response with newer therapies have been reported, depending on the variant.^{72,76–78}

Clinical Data: NSCLC With *EGFR* Exon 19 Deletion or Exon 21 L858R Mutations

Osimertinib is a third-generation oral *EGFR* TKI that is approved by the US FDA for the treatment of NSCLC with *EGFR* alterations.^{79,80} Osimertinib monotherapy and osimertinib in combination with platinum and pemetrexed chemotherapy are both indicated for the first-line treatment of adults with metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutation.

FLAURA, a phase III randomized trial, assessed first-line therapy with osimertinib compared with either erlotinib or gefitinib in patients with metastatic NSCLC and *EGFR* mutations (exon 19 deletion or L858R).^{18,48,81,82} The median progression-free survival

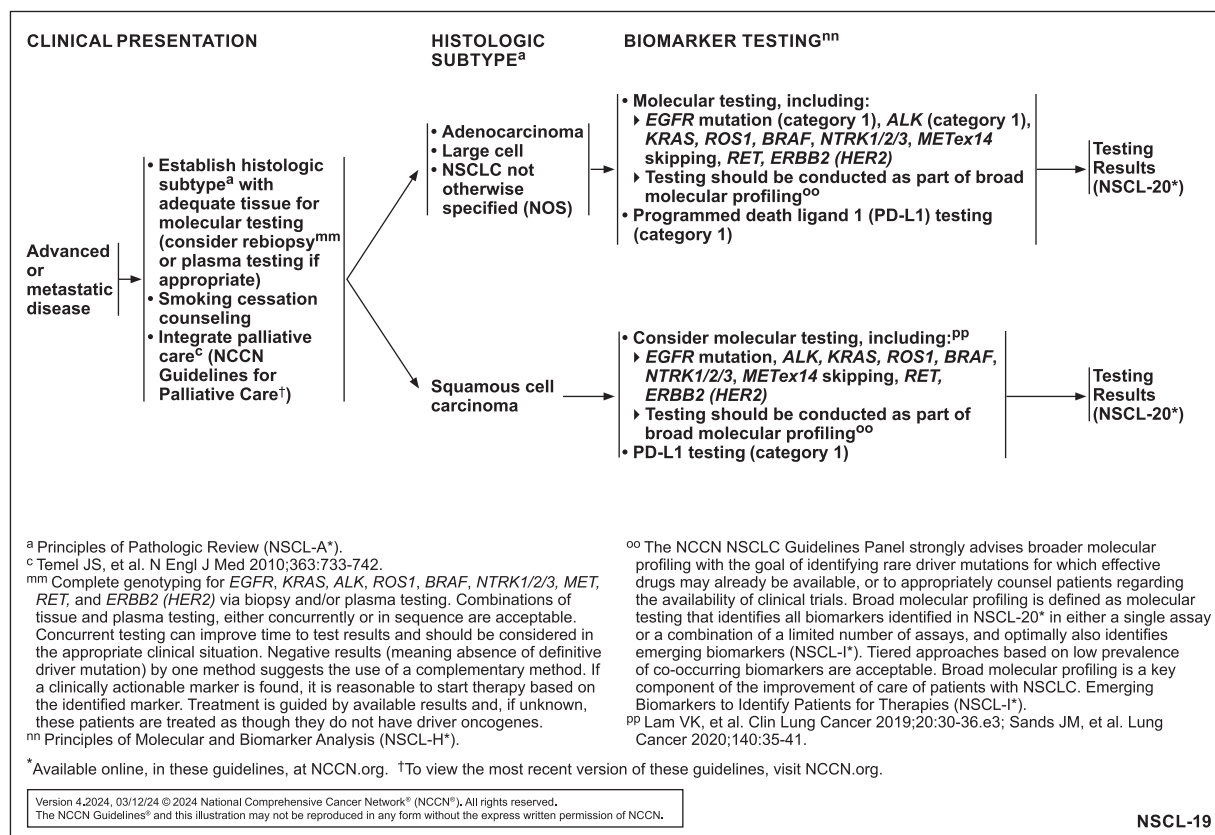


Figure 1. NSCLC-19. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

(PFS) was longer with osimertinib compared with either erlotinib or gefitinib (18.9 months vs 10.2 months; hazard ratio [HR], 0.46; $P < .001$).⁴⁸ The median duration of response was longer with osimertinib compared with erlotinib or gefitinib (median response, 17.2 vs 8.5 months).⁴⁸ Only 6% of patients receiving osimertinib had central nervous system (CNS) progression events when compared with 15% of those receiving erlotinib or gefitinib.⁴⁸ Grade 3 or higher adverse events (AEs) were reported in 34% of patients receiving osimertinib and 45% of those receiving erlotinib or gefitinib.⁴⁸ An updated analysis showed that median OS was 38.6 months with osimertinib compared with 31.8 months for either erlotinib or gefitinib (HR, 0.8; $P = .046$).¹⁸

FLAURA2, a phase III open-label randomized study, evaluated 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.⁸³ The histology was adenocarcinoma in 99% of the patient population. The median investigator-assessed PFS was longer in patients who received osimertinib in combination with chemotherapy compared with those who received only osimertinib (25.5 vs 16.7 months; HR, 0.62; $P < .001$). The median duration of response was also longer with osimertinib plus chemotherapy compared with osimertinib alone (24.0 vs 15.3 months). The number of grade 3 AEs was higher with osimertinib plus chemotherapy than with osimertinib monotherapy and was primarily driven by known chemotherapy-related AEs.

Amivantamab-vmjw is a bispecific human antibody to *EGFR* and *MET* that has been studied in a variety of contexts of NSCLC with *EGFR* mutations.⁷⁶ For patients with advanced NSCLC and *EGFR* exon 19 deletion or L858R mutation whose disease progressed on or after osimertinib monotherapy, MARIPOSA-2, a phase III randomized trial, evaluated the efficacy of amivantamab-vmjw in combination with chemotherapy (carboplatin and pemetrexed) as subsequent therapy compared with chemotherapy.⁸⁴ The median PFS was longer for the amivantamab-vmjw plus chemotherapy group than the chemotherapy group (6.3 vs 4.2 months; HR, 0.48; $P < .001$). The objective response rate was 64% with amivantamab-vmjw plus chemotherapy versus 36% with chemotherapy alone. No statistically significant difference in OS was reported in the interim analysis. The most common grade 3 or higher AEs were neutropenia, thrombocytopenia, anemia, and leukopenia.

Multiple studies have shown that other single-agent *EGFR* inhibitors and combination regimens also have efficacy in patients with advanced or metastatic NSCLC and *EGFR* alterations.^{85–90} Erlotinib, gefitinib, and dacomitinib have all been approved by the FDA for the treatment of metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (L858R) substitution mutations.^{91–93} Erlotinib in combination with either ramucirumab⁹⁴ or bevacizumab^{90,95} can also be considered as options.

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 exon 21 L858R-positive NSCLC, regardless of PD-L1 expression.^{46,96–98} Recent data also suggest that PD-1 inhibitor (pembrolizumab) in combination with chemotherapy as subsequent therapy may not have an OS or PFS benefit compared with chemotherapy alone in patients with metastatic NSCLC and *EGFR* exon 19 deletion or exon 21 L858R.⁹⁹

NCCN Recommendations: Advanced or Metastatic NSCLC With *EGFR* Exon 19 Deletion or Exon 21 L858R Mutations

This section discusses Figures 2–4. In the first-line setting, the NCCN NSCLC Panel recommends single-agent osimertinib as a preferred treatment option for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutations. Single-agent erlotinib, afatinib, gefitinib, or dacomitinib are other recommended first-line treatment options. All of these are category 1 recommendations and are appropriate for patients with performance status 0–4.

The following combination regimens are also included in the guidelines as “other recommended” options for advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R mutations in the first-line setting: osimertinib in combination with pemetrexed and either cisplatin or carboplatin (category 1; nonsquamous), erlotinib in combination with bevacizumab (nonsquamous and no recent history of hemoptysis), or erlotinib in combination with ramucirumab. An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Targeted therapies are also recommended as an option if an *EGFR* exon 19 deletion or *EGFR* exon 21 L858R mutation is discovered during first-line systemic therapy. 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 following ICIs.^{41–44} For example, the rate of AEs, such as pneumonitis, is higher when osimertinib is initiated within 3 months of treatment with certain ICIs.⁴¹

In patients who experience disease progression after receiving first-line osimertinib, decisions about subsequent therapies are guided by disease symptoms as well as sites of progression. Changes in systemic therapy are generally recommended if patients have symptomatic systemic progression and/or multiple lesions. When considering second-line systemic therapy, ideally patients should be rebiopsied to rule out transformation to small cell histology, a phenomenon that occurs in approximately 5% *EGFR* TKI-resistant tumors.^{63,100} Amivantamab-vmjw in combination with carboplatin and pemetrexed is a category 1 and preferred treatment option for patients with multiple lesions (if nonsquamous). Systemic therapy options such as chemotherapy (see, algorithm pages NSCL-K 1 of 5 or NSCL-K 2 of 5, available online, in these guidelines, at NCCN.org) are also recommended for patients with symptomatic systemic progression. Data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective in *EGFR* exon 19 deletion or exon 21 L858R NSCLC, irrespective of PD-L1 expression.^{46,96–98}

Definitive local therapy has a role in the treatment of metastatic *EGFR*-positive NSCLC. For patients with a limited number of initial sites of metastasis (oligometastasis; limited number is not universally defined, but clinical trials have included 3–5 metastases), definitive local therapy (eg, SABR or surgery) should be considered as consolidation after initiating *EGFR* TKI therapy (local consolidative therapy) if not given before *EGFR* TKI therapy (see “Principles of Radiation Therapy,” NSCL-C and NSCL-15, available online, in these guidelines, at NCCN.org). Local therapy may also be an appropriate subsequent therapy option for certain patients 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, SABR or surgery) should be considered for

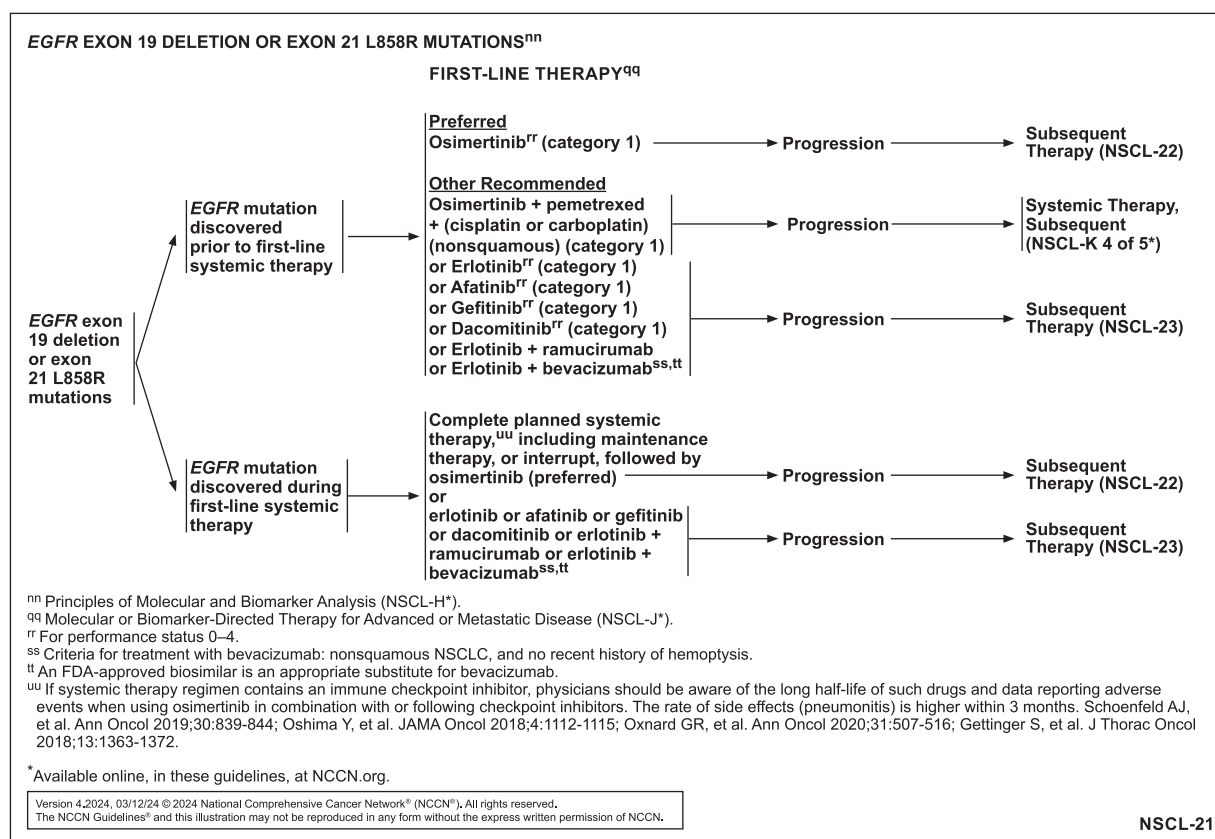


Figure 2. NSCL-21. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

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], available online, in these guidelines, at NCCN.org). For those with CNS progression, definitive local therapy (eg, stereotactic radiosurgery [SRS] with or without surgical resection) 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.

If the patient experiences disease progression after treatment with osimertinib as well as chemotherapy with pemetrexed and either cisplatin or carboplatin then the subsequent therapy options listed on NSCL-K 4 of 5 (available online, in these guidelines, at NCCN.org; such as chemotherapy) can be considered.

Clinical Data: NSCLC With EGFR S768I, L861Q, and/or G719X Mutations

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.^{101,102} Afatinib is approved by the FDA for the first-line treatment of metastatic NSCLC whose tumors have some EGFR mutations.¹⁰³ A posthoc analysis of several LUX-Lung trials (LUX-Lung 2, 3, and 6) assessed afatinib in

patients with advanced NSCLC and the most frequent uncommon EGFR mutations (L861Q, G719X, and S768I).⁵⁷ 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.⁵⁸ 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. Manageable AEs included rash, pruritus, decreased appetite, diarrhea, and dyspnea.⁵⁸

Retrospective data suggest that the clinical response to osimertinib versus afatinib may differ, depending on the exact EGFR mutation identified; for example, NSCLC with EGFR L861Q may be more likely to respond to osimertinib than afatinib.^{57,104,105}

NCCN Recommendations: Advanced or Metastatic NSCLC With EGFR S768I, L861Q, and/or G719X Mutations

The NCCN NSCLC Panel recommends afatinib or osimertinib as preferred first-line therapy options for patients with advanced or

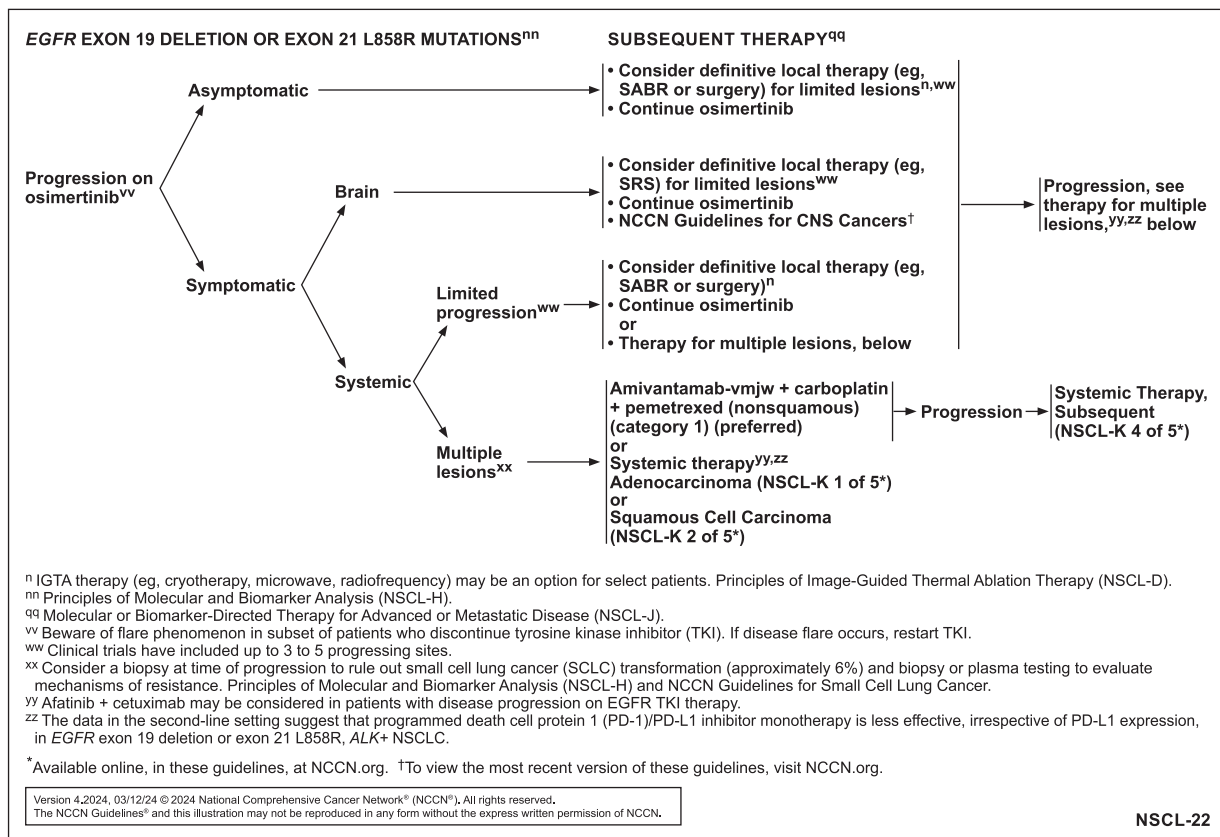


Figure 3. NSCL-22. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

metastatic NSCLC with the less common *EGFR* S768I, L861Q, and/or G719X mutations (Figure 5). All are appropriate for patients with performance status 0–4.

Subsequent treatment options for advanced or metastatic NSCLC with *EGFR* S768I, L861Q, and/or G719X alterations that progressed following first-line treatment with afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib are the same as for the more common *EGFR* alterations – refer to Figures 3 and 4 (NSCL-22 and NSCL-23) and the subsequent therapy treatment recommendations for advanced or metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R detailed previously.

Clinical Data: NSCLC With *EGFR* Exon 20 Insertion Mutation

For patients with NSCLC and *EGFR* exon 20 insertions, treatment with early-generation *EGFR* TKIs has generally not been associated with disease response.^{72,76,77} Patients with *EGFR* exon 20 insertion-positive metastatic NSCLC have frequently been treated with first-line platinum-based chemotherapy.^{106,107} The response rates (0%–25%) to immunotherapy regimens vary, depending on the specific *EGFR* exon 20 insertion mutation.^{72,108} Mobocertinib, an *EGFR* TKI developed specifically for patients with *EGFR* exon 20 insertions, was previously granted accelerated approval by the FDA in the United States. However, mobocertinib was withdrawn from the United States market in 2023 and is no longer recommended as a subsequent treatment option by the panel based on data from the phase III EXCLAIM-2 trial, which compared first-line mobocertinib to platinum-based chemotherapy, as the primary endpoint was not met.^{109,110}

Single-agent amivantamab-vmjw is FDA-approved for the treatment of adults with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.¹¹¹ CHRYSALIS, a phase I study, assessed subsequent therapy with amivantamab-vmjw in 81 patients with *EGFR* exon 20 insertion-positive metastatic NSCLC who had received one or more previous lines of therapy.⁷⁶ 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. The most common grade 3 to 4 AEs included hypokalemia as well as pulmonary embolism, neutropenia, diarrhea, and rash. Eight deaths were reported in the safety assessment (7%).

Amivantamab-vmjw in combination with carboplatin and pemetrexed is also approved by the FDA for the treatment of adults with locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations.¹¹¹ PAPILON, a phase III randomized trial, assessed the efficacy and safety of first-line amivantamab-vmjw plus chemotherapy (pemetrexed and carboplatin) versus chemotherapy alone in 308 patients with advanced NSCLC with *EGFR* exon 20 insertions who had not previously received systemic therapy.¹¹² The median PFS was longer in the amivantamab-vmjw plus chemotherapy group than in the chemotherapy alone group (11.4 vs 6.7 months; HR, 0.40; $P < .001$). Based on the interim OS analysis, the HR for amivantamab-vmjw plus chemotherapy versus chemotherapy alone was 0.67 ($P = .11$). The most common AEs reported with amivantamab-vmjw plus chemotherapy were

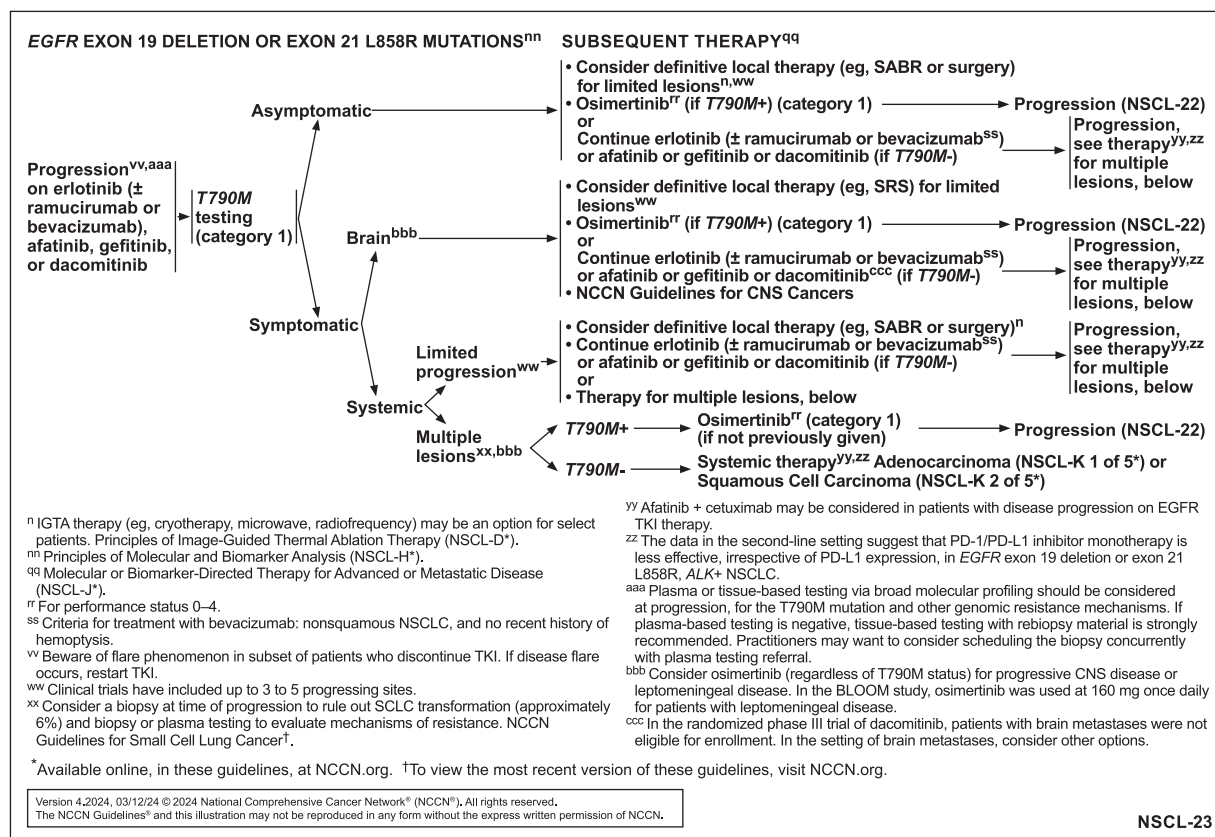


Figure 4. NSCL-23. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

hematologic effects and skin-related EGFR-related toxic events (eg, rash, paronychia, dermatitis acneiform).

NCCN Recommendations: Advanced or Metastatic NSCLC With EGFR Exon 20 Insertion Mutation

The NCCN NSCLC Panel recommends amivantamab-vmjw in combination with carboplatin and pemetrexed as a category 1 and preferred treatment option for patients with advanced or metastatic nonsquamous EGFR exon 20 insertion mutation-positive NSCLC (Figure 6). Other systemic therapy regimens (eg, chemotherapy) listed on NSCL-K 1 of 5 or NSCL-K 2 of 5 in the guidelines (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 alterations.^{38,113}

The NCCN NSCLC Panel recommends amivantamab-vmjw as a subsequent therapy option for patients with EGFR exon 20 insertion mutation-positive advanced or metastatic NSCLC and disease progression who were not previously treated with amivantamab-vmjw. For patients whose disease progressed after first-line treatment with amivantamab-vmjw in combination with chemotherapy, subsequent therapy options listed on NSCL-K 4 of 5 in the guidelines are recommended.

NSCLC With KRAS G12C Mutation

KRAS is a protein with intrinsic GTPase activity that is commonly mutated in lung cancers; these mutations can result in unregulated signaling through the MAP/ERK pathway.^{114,115}

KRAS G12C is an activating mutation that results in increased activation of downstream oncogenic pathways.¹¹⁶ Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have a KRAS mutation, the most common mutation in this population.^{117–121} Some, but not all, KRAS mutations are associated with cigarette smoking, unlike many of the other actionable mutations (eg, EGFR mutations, ALK rearrangements).^{122,123}

Clinical Data

Targeted therapies are not recommended as first-line treatment options for advanced or metastatic NSCLC with a KRAS G12C mutation, unlike most other actionable alterations. 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.^{49,50} Additionally, one study reported a positive association between PFS and PD-L1 expression in patients with advanced NSCLC and KRAS mutations who received ICI monotherapy.³⁸

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.^{124–126}

A phase II study assessed sotorasib as subsequent therapy in 126 patients with KRAS G12C mutation-positive advanced

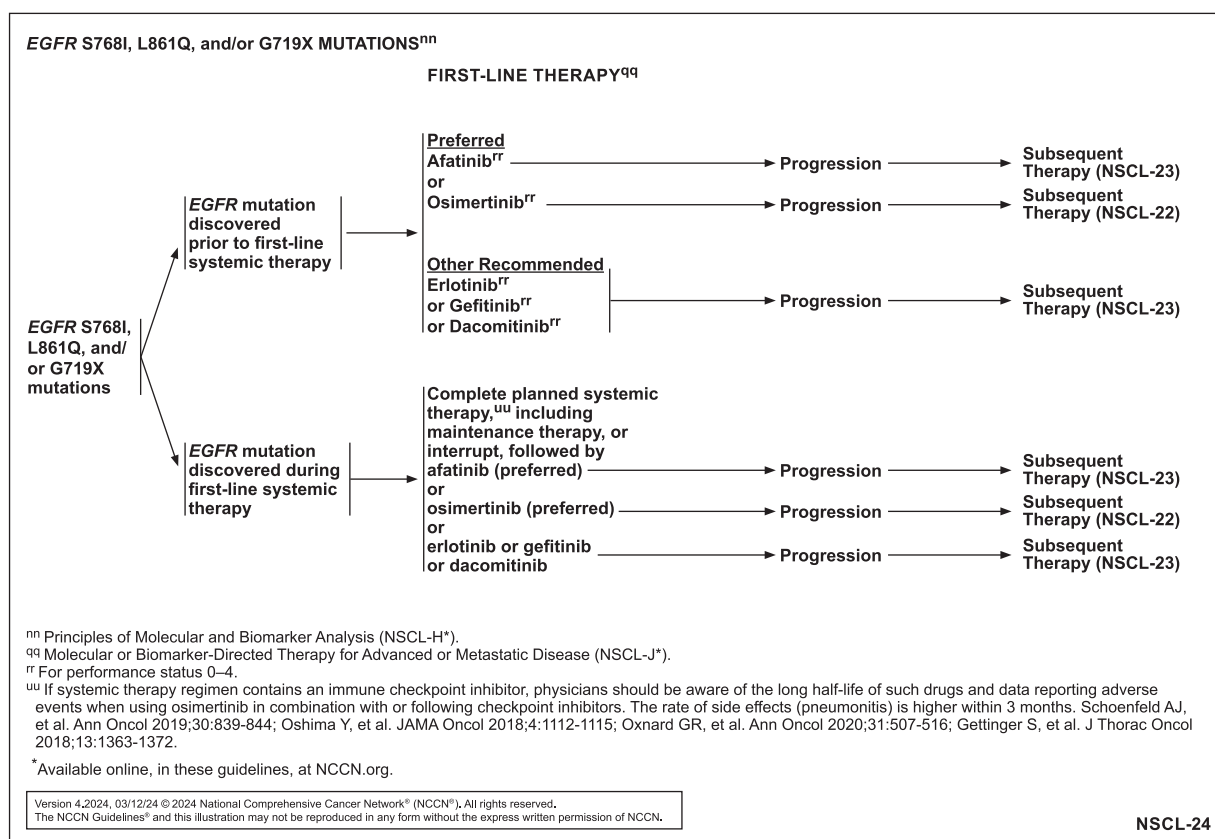


Figure 5. NSCL-24. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

NSCLC who had previously received platinum-based chemotherapy ($\pm$ PD-1 or PD-L1 immunotherapy).¹¹⁶ The median OS was 12.5 months and the objective response rate was 37.1%; a complete response was reported in 4 patients. Treatment-related grade 3 AEs occurred in 19.8% of patients, including diarrhea, and increased alanine transaminase and aspartate transferase levels; one treatment-related grade 4 event occurred (dyspnea and pneumonitis).

A phase II study evaluated adagrasib as subsequent therapy in 116 patients with *KRAS* G12C mutation-positive advanced NSCLC who had previously received at least one platinum-based chemotherapy and immunotherapy.¹²⁶ The median OS was 12.6 months and the objective response rate was 42.9%. The intracranial response rate was 33.3%. Grade 3 or higher AEs occurred in 44.8% of patients, including anemia, pneumonia, dyspnea, acute kidney injury, hyponatremia, fatigue, nausea, and increased alanine transaminase and aspartate transferase levels. There were two deaths (cardiac failure and pulmonary hemorrhage).

A randomized phase III 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.¹²⁷ Median PFS was 5.6 months in patients receiving sotorasib compared with 4.5 months in those receiving docetaxel (HR, 0.66; $P = .0017$). No difference in OS was reported.

NCCN Recommendations

The NCCN NSCLC Panel recommends using PD-L1 level to determine the appropriate first-line systemic therapy regimen (such as

immunotherapy and/or chemotherapy) for patients with advanced or metastatic NSCLC with *KRAS* G12C mutations (Figure 7). See NSCL-37 and NSCL-38 in the full guidelines at NCCN.org for treatment recommendations based on PD-L1 level.

The panel recommends sotorasib or adagrasib as subsequent therapy options for patients who experience disease progression after treatment with first-line systemic therapy. Sotorasib or adagrasib 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.

NSCLC With *ALK* Rearrangement

About 5% of patients with NSCLC have *ALK* gene rearrangements leading to gene fusions.¹²⁸ These events can result in dysregulation and inappropriate *ALK* signaling.¹²⁹

Clinical Data

Initial studies have shown that single-agent *ALK* inhibitors (crizotinib and ceritinib) are superior to chemotherapy in patients with advanced or metastatic NSCLC with *ALK* rearrangements.^{130–133} Both crizotinib and ceritinib are FDA-approved for the treatment of adults with *ALK*-positive metastatic NSCLC.^{134,135} Subsequent trials have compared newer agents to crizotinib.

Alectinib is an *ALK* inhibitor that is approved by the FDA for the treatment of patients with *ALK*-positive metastatic NSCLC.^{136,137} ALEX, a phase III randomized trial, assessed first-line therapy

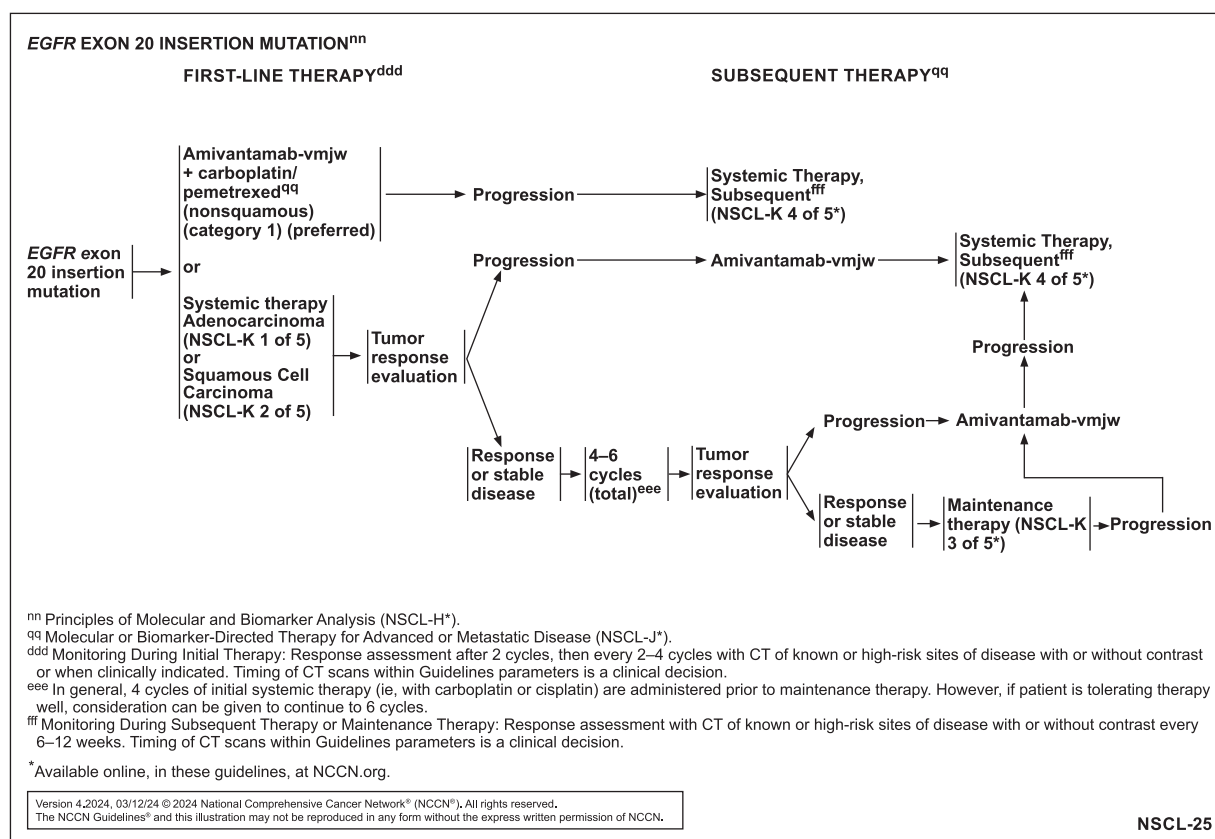


Figure 6. NSCL-25. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

with alectinib versus crizotinib in 303 patients with *ALK*-positive advanced NSCLC including those with asymptomatic CNS disease.¹³⁰ Disease progression or death occurred in a lower proportion of patients receiving alectinib when compared with crizotinib (41% vs 68%). Investigator-assessed PFS rate was higher with alectinib versus crizotinib (68.4% vs 48.7%; HR, 0.47; $P < .001$). The median PFS was not reached for alectinib when compared with crizotinib at 11.1 months. Fewer patients receiving alectinib had CNS progression (12%) versus crizotinib (45%). Response rates were 82.9% in the alectinib group versus 75.5% in the crizotinib group ($P = .09$). 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). Fewer deaths were reported with alectinib (3.3%) versus crizotinib (4.6%); two treatment-related deaths were reported with crizotinib and none with alectinib. An updated analysis of the trial reported that the 5-year OS rate was 62.5% with alectinib and 45.5% with crizotinib.¹⁴

J-ALEX, a phase III open-label randomized trial, assessed first-line therapy with alectinib versus crizotinib in 207 Japanese patients with *ALK*-positive advanced NSCLC who were *ALK* inhibitor-naïve.¹³⁸ Median PFS was not reached with alectinib versus 10.2 months with crizotinib (HR, 0.34; stratified log-rank $P < .0001$). Grade 3 or 4 AEs were less frequent with alectinib (26%) than with crizotinib (52%). Fewer patients stopped taking alectinib (9%) because of an AE when compared with crizotinib (20%).

Brigatinib is an *ALK* inhibitor that is approved by the FDA for the treatment of adults with *ALK*-positive metastatic NSCLC.^{139,140} ALTA-1L, a phase III randomized trial, assessed brigatinib versus crizotinib as first-line therapy in 275 patients with *ALK*-positive metastatic NSCLC.¹⁴¹ At the first interim analysis, PFS rate was higher in patients receiving brigatinib (67%) than in those receiving crizotinib (43%) (HR, 0.49; $P < .001$). The rate of intracranial response was also higher with brigatinib (78%) versus crizotinib (29%).¹⁴¹ At the second interim analysis (24.9 months of median follow-up), brigatinib continued to show improved blinded independent review committee-assessed PFS when compared with crizotinib (48% vs 26%; HR, 0.49; $P < .0001$).¹⁴² After 3 years, the PFS was 43% for brigatinib versus 19% for crizotinib (HR, 0.48). The median OS was not reached in either arm; however, a posthoc analysis suggested a survival benefit for patients with intracranial metastasis (HR, 0.43; 95% CI, 0.21–0.89).¹⁴³

Lorlatinib is an *ALK* inhibitor that is approved by the FDA for the treatment of adults with *ALK*-positive metastatic NSCLC.¹⁴⁴ CROWN, a phase III randomized trial, assessed lorlatinib versus crizotinib as first-line therapy in 296 patients with *ALK*-positive advanced NSCLC.¹⁴⁵ At 12 months, 78% of patients were alive without disease progression in the lorlatinib group versus 39% in the crizotinib group (HR, 0.28; $P < .001$). 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

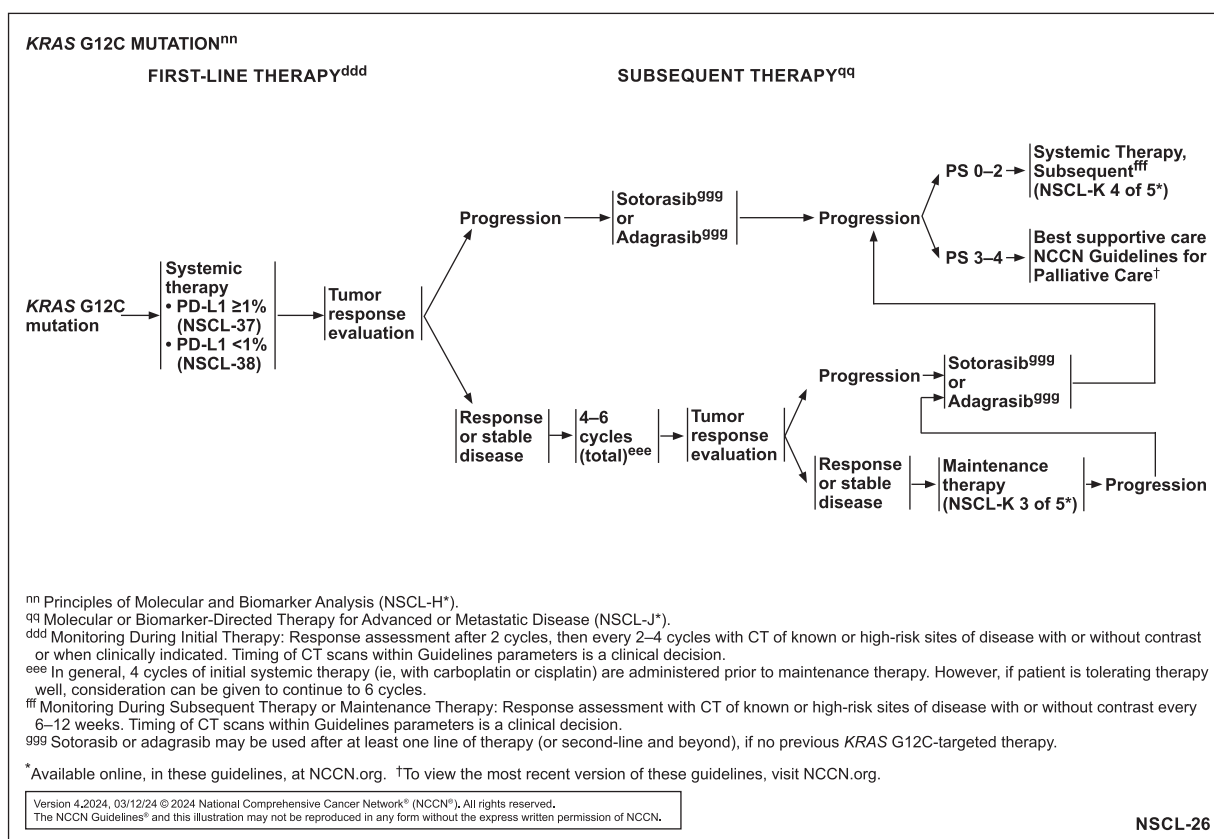


Figure 7. NSCL-26. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

lorlatinib. Hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects were the most common AEs seen with lorlatinib. More grade 3 or 4 AEs (mainly altered lipid levels) occurred with lorlatinib than with crizotinib (72% vs 56%, respectively). A post hoc analysis of the CROWN study showed that in patients with brain metastases at baseline, the 12-month cumulative incidence of CNS progression was 7% with lorlatinib compared with 72% with crizotinib; the 12-month PFS rates were 78% versus 22%, respectively.¹⁴⁶ In patients without brain metastases at baseline, the 12-month cumulative incidence of CNS progression was 1% with lorlatinib compared with 18% with crizotinib; the 12-month PFS rates were 78% versus 45%, respectively.¹⁴⁶ Updated data from the CROWN trial demonstrated that the 3-year PFS rate was 64% with lorlatinib and 19% with crizotinib.¹⁴⁷ Additionally, the HR for time to intracranial progression for lorlatinib in comparison with crizotinib was 0.10 among those with baseline brain metastases and 0.02 among those without brain metastases at baseline.

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.^{148,149} A phase II trial assessed lorlatinib in patients with ALK-positive or ROS1-positive advanced NSCLC and disease progression after ALK inhibitor therapy; many patients had asymptomatic CNS metastases.¹⁴⁸ In the cohort of ALK-positive patients who had received at least one previous ALK inhibitor, objective responses were achieved in 47% of patients; there were 4 complete responses and 89 partial responses. In those with

measurable baseline CNS lesions, an objective intracranial response was observed in 63% of patients. Lorlatinib was effective in patients who had received up to 3 previous ALK inhibitors. Grade 3 to 4 AEs included hypercholesterolemia and hypertriglyceridemia. Serious treatment-related AEs occurred in 7% of patients including cognitive effects in 1%; the cognitive effects resulted in permanent discontinuation of lorlatinib.

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 such as brigatinib, alectinib, or ceritinib.¹⁵⁰ The objective response rate with lorlatinib was 62% when using plasma ctDNA (and 69% when using tissue) for patients with ALK resistance mutations and disease progression on second-generation ALK TKIs compared with 32% (plasma) and 27% (tissue) in patients without ALK mutations. 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).^{150–152}

NCCN Recommendations

The NCCN NSCLC Panel recommends alectinib, brigatinib, or lorlatinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC and ALK rearrangements. Ceritinib is an “other recommended” first-line option, whereas crizotinib is considered useful in certain circumstances (see Figures 8–10). All these options are appropriate for patients with performance status 0–4 and are category 1 recommendations if an ALK rearrangement is discovered before first-line systemic therapy.

On disease progression, the NCCN panel recommends considering plasma and/or tissue-based testing using broad molecular profiling to determine genomic resistance mechanisms and to guide use of subsequent therapy options.¹⁵⁰

After progression on alectinib, brigatinib, or ceritinib, 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.

Systemic therapy options such as chemotherapy (see NSCL-K 1 of 5 or NSCL-K 2 of 5 in these guidelines at NCCN.org) are recommended as additional subsequent therapy options for patients with symptomatic systemic progression and multiple lesions. Data suggest that PD-1/PD-L1 inhibitor monotherapy is less effective in *ALK*-positive NSCLC, irrespective of PD-L1 expression.^{38,46,113}

Definitive local therapy has a role in the treatment of metastatic *ALK*-positive NSCLC. For patients with a limited number of initial sites of metastasis (oligometastasis; limited number is not universally defined, but clinical trials have included 3–5 metastases), definitive local therapy (eg, SABR or surgery) should be considered as consolidation after initiating *ALK* TKI therapy (local consolidative therapy) if not given before *ALK* TKI therapy (see “Principles of Radiation Therapy,” [NSCL-C] and NSCL-15,

in the guidelines at NCCN.org). Local therapy may also be an appropriate subsequent therapy option for certain patients 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 guidelines at NCCN.org). For patients with CNS progression, definitive local therapy (eg, SRS with or without surgical resection) 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.

NSCLC With *ROS1* Rearrangement

It is estimated that *ROS1* gene rearrangements occur in about 1% to 2% of patients with NSCLC.^{153–156} *ROS1* rearrangements can result in *ROS1* kinase dysregulation and inappropriate signaling.¹⁵⁷ Although *ROS1* is a distinct receptor tyrosine kinase, it is similar to *ALK* and members of the insulin receptor family.^{155,158} Several (but not all) targeted therapies recommended for the treatment of *ALK*-positive metastatic NSCLC are also recommended for the treatment of *ROS1*-positive metastatic disease (ie, ceritinib, crizotinib, lorlatinib).

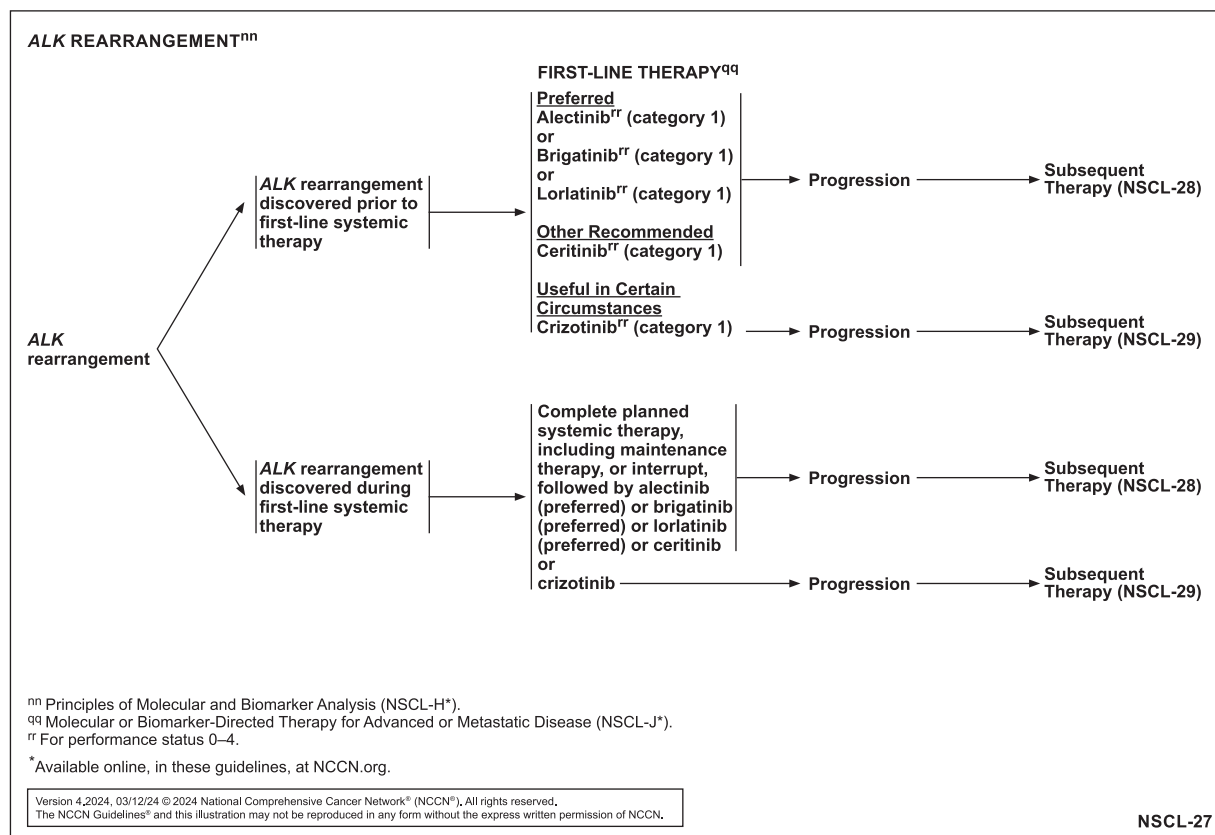


Figure 8. NSCL-27. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

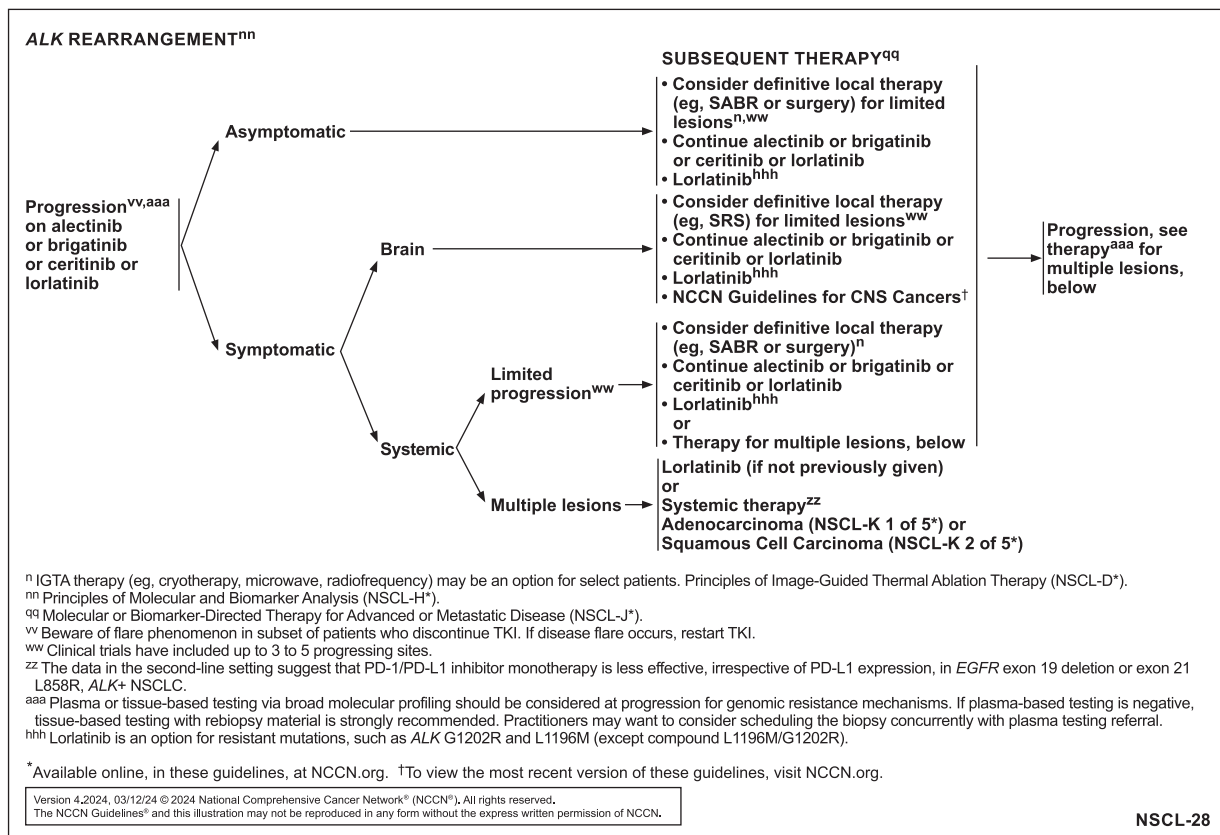


Figure 9. NSCL-28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

Clinical Data

Crizotinib is a first-generation oral TKI that inhibits ALK, ROS1, and MET.^{132,159–165} Crizotinib is approved for the treatment of adults with *ROS1*-positive and *ALK*-positive metastatic NSCLC.¹³⁴ Crizotinib is effective for patients with *ROS1* rearrangements with response rates of about 70%–80% including complete responses.^{155,161,166–168}

A phase II single-arm trial assessed crizotinib in 127 East Asian patients with *ROS1*-positive advanced NSCLC who had received 3 or fewer lines of systemic therapy. The objective response rate was 71.7% with 17 complete responses; the median duration of response was 19.7 months. The median PFS was 15.9 months.¹⁶⁷

PROFILE 1001, a phase I study, assessed crizotinib in 50 patients with advanced NSCLC and *ROS1* rearrangements.¹⁵⁵ Crizotinib yielded an objective response rate of 72%; there were 3 complete responses and 33 partial responses.¹⁵⁵ The median duration of response was 17.6 months, and the median PFS was 19.2 months. Updated results from PROFILE 1001 reported an objective response rate of 72% with crizotinib including 6 confirmed complete responses in 53 patients with *ROS1*-positive advanced NSCLC.²² The median OS was 51.4 months. No grade 4 or higher treatment-related AEs were reported.

The phase II single-arm EUCROSS study reported that crizotinib yielded an objective response rate of 70% and a median PFS of 20 months in 30 patients with *ROS1*-positive advanced NSCLC.¹⁶⁶ AEs related to treatment occurred in 97% of patients. A retrospective study based on data from Europe in patients (n=30 evaluable) with stage IV lung adenocarcinoma and *ROS1* rearrangements also assessed crizotinib.¹⁶¹ There were 5 complete

responses (overall response rate, 80%; disease control rate, 86.7%). The median PFS was 9.1 months. Many patients (n=26) received pemetrexed (either alone or in combination with platinum and either before or after crizotinib) and had a response rate of 57.7%; the median PFS was 7.2 months.

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.^{169–171} Entrectinib has been assessed in several phase I and II trials in patients with *ROS1*-positive metastatic NSCLC (ie, phase II STARTRK-2 trial, phase I STARTRK-1 trial, phase I ALKA-372-001 trial).^{172,173} Pooled data from these 3 trials in 53 patients with *ROS1*-positive metastatic NSCLC receiving first-line entrectinib showed an objective response rate of 77% (3 complete responses).^{172,174} The intracranial overall response rate was 55% (4 complete responses, 7 partial responses) among the 20 patients with baseline CNS metastases.^{172,173} In the larger *ROS1* population (n=134), grade 3 to 4 AEs were seen in 34% of patients. Fifteen patients had serious AEs such as nervous system disorders and cardiac disorders. Although entrectinib has better CNS penetration than crizotinib, it is more toxic.¹⁷⁴

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.^{175,176} 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,

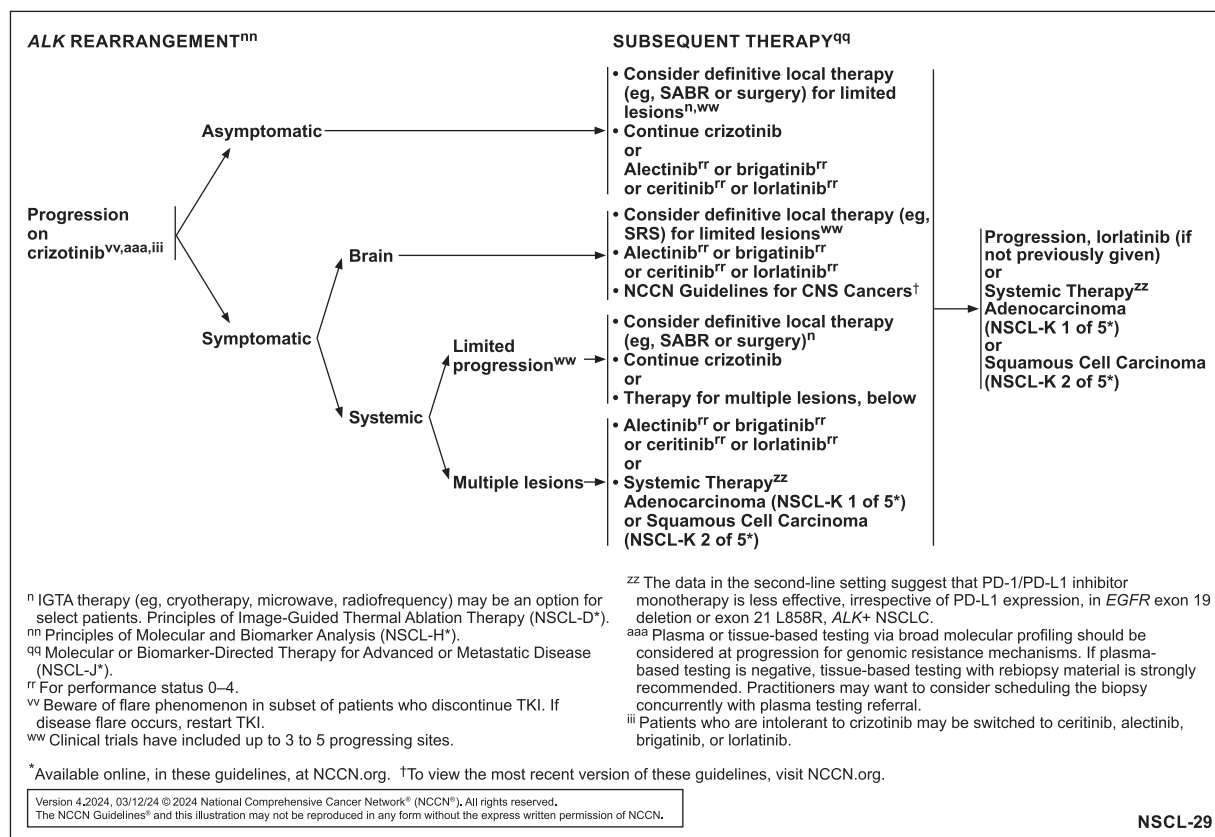


Figure 10. NSCL-29. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

entrectinib, or ceritinib) and never received chemotherapy.¹⁷⁷ The confirmed objective response with repotrectinib was 79% among those who had not received a ROS1 TKI and 38% among those who had received one ROS1 TKI. Patients who had not received a ROS1 TKI had a median duration of response of 34.1 months and median PFS of 35.7 months. Patients who previously received one ROS1 TKI and no chemotherapy had a median duration of response of 14.8 months and a median PFS of 9 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 TKI and no chemotherapy. The most common treatment-related AEs were dizziness, dysgeusia, and paresthesia.

Lorlatinib is an oral TKI that is active against both ALK and ROS1 and can penetrate the blood-brain barrier.^{144,178} A phase I–II trial assessed lorlatinib in 69 patients with ROS1-positive metastatic NSCLC.¹⁷⁹ Many patients (58%) had previously received crizotinib; some patients were TKI naïve (30%). Objective responses were achieved in 35% (14/40) of patients who previously received crizotinib and 62% (13/21) of those who were TKI-naïve. An intracranial response was observed in 50% (12/24) of patients who previously received crizotinib and 64% (7/11) of those who were TKI-naïve. Serious treatment-related AEs occurred in 7% of patients.

Data suggest that ceritinib, an oral TKI that has activity against both ALK and ROS1, can also be considered as a treatment option for patients with NSCLC and ROS1 rearrangements.^{135,178,180}

NCCN Recommendations

The NCCN NSCLC Panel recommends entrectinib, crizotinib, or repotrectinib as preferred first-line treatment options for patients with ROS1-positive advanced or metastatic NSCLC, while ceritinib is considered an “other recommended” first-line treatment option. All are appropriate for patients with performance status 0–4; however, entrectinib or repotrectinib may be better for patients with brain metastases. (These recommendations are shown in Figures 11 and 12.)

On disease progression, plasma or tissue-based testing via broad molecular profiling should be considered to identify genomic resistance mechanisms. If plasma-based testing is negative, the panel strongly recommends tissue-based testing with rebiopsy material.

For asymptomatic progression on entrectinib, crizotinib, repotrectinib, or ceritinib, the NCCN NSCLC Panel recommends repotrectinib (if not previously given) or lorlatinib as subsequent therapy options. For patients with CNS progression, entrectinib (if previously treated with crizotinib or ceritinib), repotrectinib (if previously treated with crizotinib, ceritinib, or entrectinib), or lorlatinib are recommended options. See also the NCCN Guidelines for CNS Cancers (available at NCCN.org) for additional recommendations. For symptomatic systemic progression with multiple systemic lesions, repotrectinib (if not previously given) or lorlatinib are recommended targeted therapy options. Systemic therapies (such as chemotherapy with or without immunotherapy) can be considered in this setting as well (see NSCL-K 1 of 5 and NSCL-K 2 of 5, available in these guidelines,

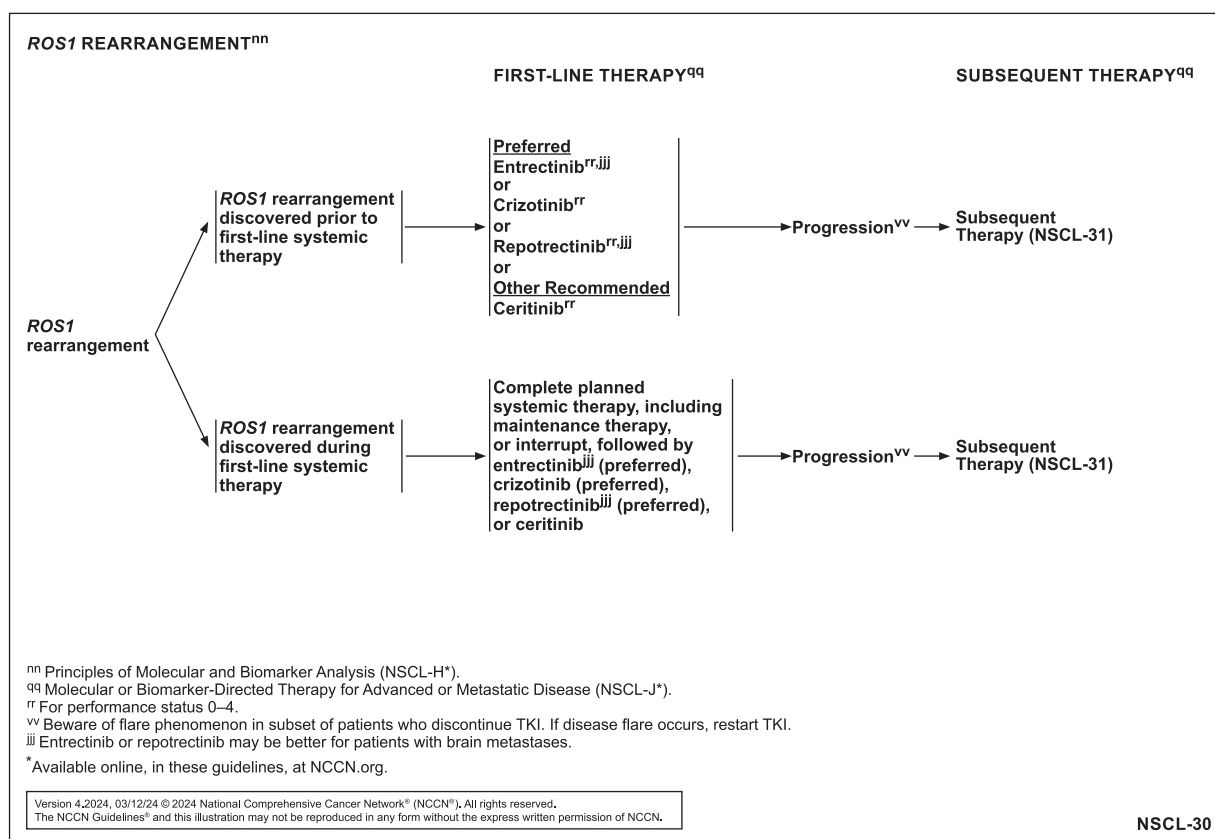


Figure 11. NSCL-30. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

at NCCN.org). Data indicate that ICI monotherapy is less effective in NSCLC with *ROS1* alterations.^{38,113}

Continuation of entrectinib, crizotinib, repotrectinib, or ceritinib 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*-positive NSCLC. For patients with a limited number of initial sites of metastasis (oligometastasis; “limited number” is not universally defined, but clinical trials have included 3–5 metastases), definitive local therapy (eg, SABR or surgery) should be considered as consolidation after initiating *ROS1* TKI therapy (local consolidative therapy) if not given prior to *ROS1* TKI therapy (see “Principles of Radiation Therapy” [NSCL-C] and NSCL-15, available in these guidelines, at NCCN.org). Local therapy may also be an appropriate subsequent therapy option for certain patients who have progressed after initial therapy 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 these guidelines at NCCN.org for additional information. For those with CNS progression, definitive local therapy (eg, SRS with or without surgical resection) 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.

NSCLC With *BRAF* V600E Mutation

The *BRAF* V600E mutation occurs in 1% to 2% of patients with lung adenocarcinoma; it is the most common of the *BRAF* point mutations when considered across all tumor types.^{181,182} Rare *BRAF* mutations include V600K and V600D. The *BRAF* gene encodes for BRAF, a serine/threonine kinase; activating mutations in *BRAF* result in unregulated signaling through the MAP/ERK pathway.¹⁸³

Clinical Data

Dabrafenib and encorafenib are both oral BRAF kinase inhibitors.^{181,184–186} Dabrafenib, in combination with MEK1/2 inhibitor trametinib, is approved by the FDA for the treatment of metastatic NSCLC with *BRAF* V600E mutation.¹⁸⁷ Encorafenib, in combination with MEK1/2 inhibitor binimetinib, is FDA-approved for the treatment of metastatic NSCLC with a *BRAF* V600E mutation.¹⁸⁸

A phase II trial assessed dabrafenib in combination with trametinib as first-line therapy in 36 patients with metastatic NSCLC and *BRAF* V600E mutations.^{15,189} The overall response rate was 63.9%; there were 2 complete responses.¹⁵ The median PFS was 10.8 months.¹⁵ Many patients (69%) had one or more grade 3 or 4 AEs.¹⁸⁹ Serious AEs included increased ALT, increased

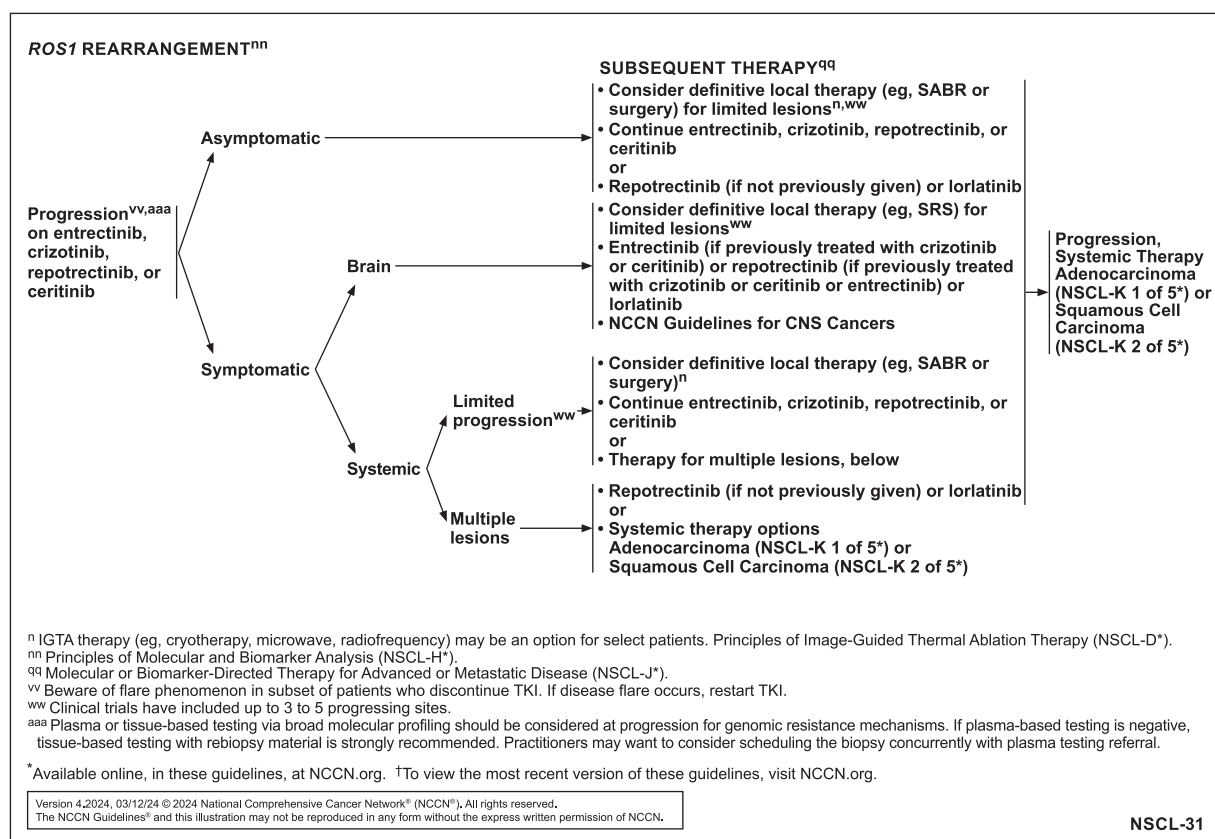


Figure 12. NSCL-31. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

AST, pyrexia, and decreased ejection fraction.¹⁸⁹ An updated analysis reported that patients receiving dabrafenib plus trametinib had a median OS of 17.3 months.¹⁵ After 5 years, the OS rate was 22%.

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.^{15,181} The overall response rate was 68.4% and the median PFS was 10.2 months.¹⁵ Serious AEs occurred in 56% of patients, including pyrexia, anemia, confused state, hemoptysis, hypercalcemia, and cutaneous squamous cell carcinoma.¹⁸¹ Grade 3 to 4 AEs included neutropenia, hyponatremia, and anemia.¹⁸¹ An updated analysis reported that the median OS was 18.2 months.¹⁵ After 5 years, the OS rate was 19%.

A phase II, open-label, single-arm study evaluated encorafenib in combination with binimetinib in patients with *BRAF* V600E-positive metastatic NSCLC in both the first-line and subsequent therapy settings.¹⁸⁶ The objective response rate was 75% in treatment-naïve patients and 46% in previously treated patients. The median PFS was not estimable for the treatment-naïve patients and 9.3 months in those who were previously treated. 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.¹⁹⁰ Results from retrospective studies indicate that patients with advanced NSCLC and

BRAF mutations may also derive benefit from PD-1/PD-L1 inhibitors.^{38,191} 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 NCCN NSCLC Panel recommends dabrafenib plus trametinib or encorafenib plus binimetinib as preferred first-line therapy options for patients with *BRAF* V600E mutation-positive advanced or metastatic NSCLC (Figure 13). The panel also recommends dabrafenib plus trametinib or encorafenib plus binimetinib as subsequent therapy options if the patient with *BRAF* V600E mutation did not previously receive a *BRAF* inhibitor. Single-agent therapy with dabrafenib or vemurafenib can be considered for those who do not tolerate dabrafenib plus trametinib. These options are all appropriate for patients with performance status 0–4.

Other first-line therapy options include systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed on NSCL-K 1 of 5 and NSCL-K 2 of 5 in the guidelines (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.

NSCLC With *NTRK* Gene Fusion

NTRK1/2/3 gene fusions encode TRK fusion proteins that act as oncogenic drivers for various solid tumors, including lung, salivary gland, thyroid, and sarcoma.^{192,193} It is estimated that *NTRK1/2/3*

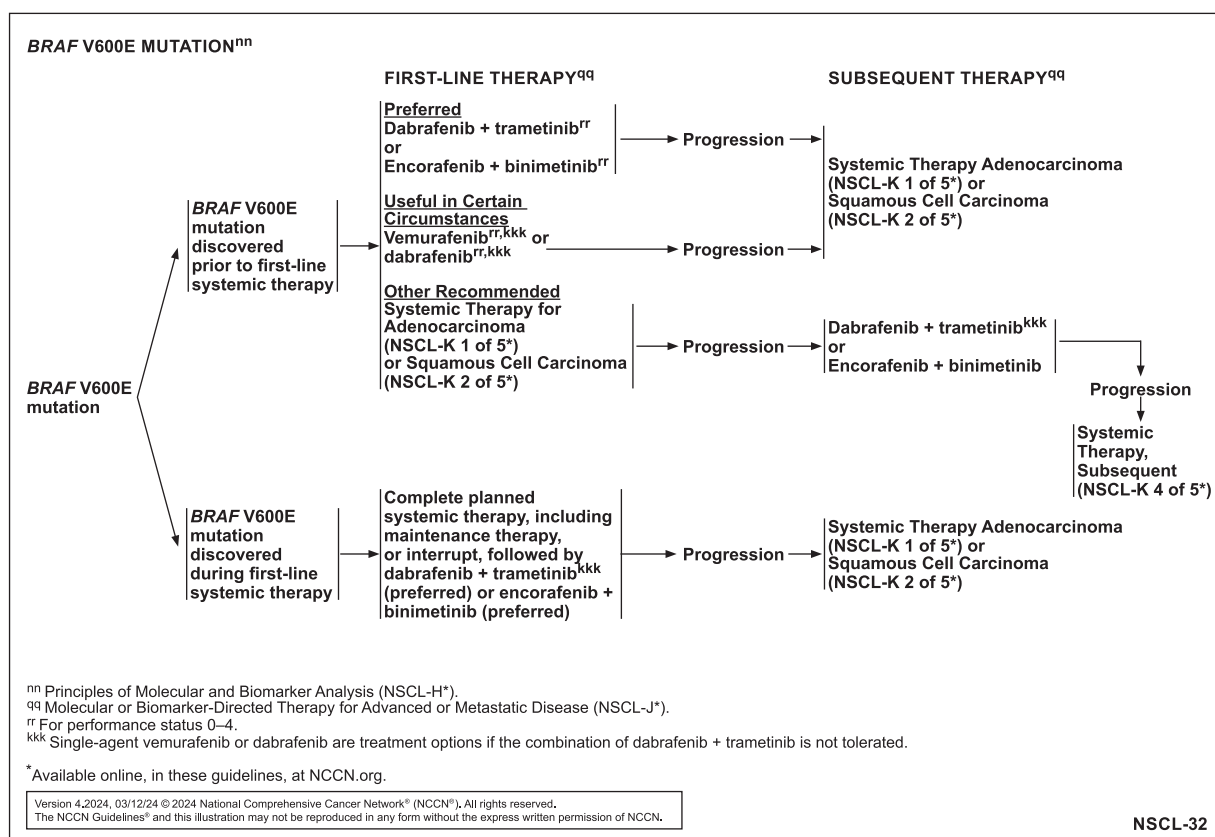


Figure 13. NSCL-32. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

fusions occur in 0.2% of patients with NSCLC and do not typically overlap with other oncogenic drivers such as *EGFR*, *ALK*, or *ROS1*.¹⁹⁴

Clinical Data

Entrectinib and larotrectinib are oral TRK inhibitors and both were granted accelerated approval by the FDA for the treatment of patients with solid tumors that have an *NTRK* gene fusion.^{171,193,195} Entrectinib is also approved for the treatment of *ROS1*-positive metastatic NSCLC (see previous sections for more information).¹⁷¹

Entrectinib has been assessed in several phase I and II trials in patients with *NTRK* gene fusion-positive metastatic NSCLC (phase II STARTRK-2 trial, phase I STARTRK-1 trial, and phase I ALKA-372-001 trial).¹⁹⁶ Pooled data from these 3 trials in 10 patients with *NTRK* gene fusion-positive NSCLC showed that entrectinib yielded an overall response rate of 70% (7/10).¹⁹⁶ Updated data in 22 patients with *NTRK*-positive locally advanced or metastatic NSCLC found that the objective response rate was 64.5%; a complete response was observed in 16.1% of patients.¹⁹⁷ Among the 15 patients with CNS metastases at baseline, the intracranial objective response rate was 60%. 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%.¹⁹² In an analysis of 15 patients with *NTRK* fusion-positive lung cancer, the objective response rate by investigator assessment was 73%; 1 patient had a complete response and 10 had a partial response.¹⁹⁸ 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 reported AEs were grade 1 or 2.

NCCN Recommendations

The NCCN NSCLC Panel recommends larotrectinib or entrectinib as preferred first-line therapy options for patients with *NTRK1/2/3* gene fusion-positive advanced or metastatic NSCLC (performance status 0–4) (Figure 14). Either may be used as a subsequent therapy option for *NTRK1/2/3* gene fusion-positive metastatic NSCLC if larotrectinib or entrectinib was not previously given as first-line therapy.

Other systemic therapies (such as chemotherapy with or without immunotherapy) on NSCL-K 1 of 5 and NSCL-K 2 of 5 in the guidelines (at NCCN.org) are categorized as first-line treatment options that may be useful in certain circumstances for *NTRK*-positive advanced or metastatic NSCLC; these are also recommended as subsequent therapy options for patients whose disease progressed after treatment with larotrectinib or entrectinib. Data indicate that ICI monotherapy may be less effective in NSCLC with *NTRK* mutations.^{38,113}

NSCLC With *MET* Exon 14 Skipping Mutation

*MET*ex14 skipping mutations occur in 3% to 4% of patients with adenocarcinoma NSCLC and 1% to 2% of patients with other NSCLC histologies.^{199,200} *MET*ex14 skipping mutations lead to dysregulation of the *MET* receptor tyrosine kinase and inappropriate signaling. The presence of this type of mutation is associated with

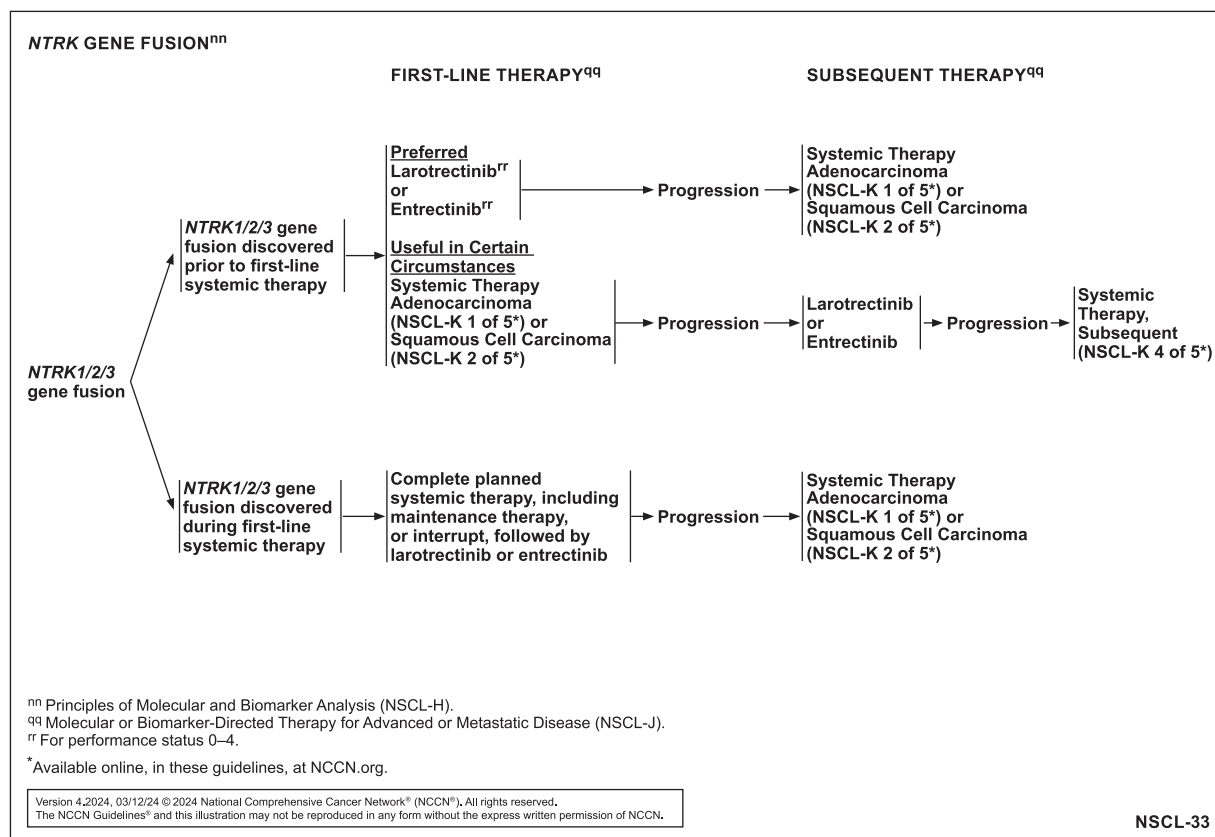


Figure 14. NSCL-33. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

responsiveness to oral MET TKIs. The NCCN Guidelines recommend testing for *MET*ex14 skipping mutations as part of broad molecular profiling, due to the availability of FDA-approved targeted therapies for this biomarker.

In contrast, high-level *MET* amplification is designated as an emerging biomarker in the NCCN Guidelines because there is less evidence for using targeted agents for this biomarker. In addition, no therapies have been approved by the FDA for the treatment of metastatic NSCLC with *MET* amplification.

Clinical Data

Capmatinib and tepotinib are oral TKIs that selectively inhibit MET kinase and are both approved by the FDA for the treatment of adults with metastatic NSCLC whose tumors have a *MET* ex14 skipping mutation.^{201–203}

GEOMETRY, a phase II study, assessed capmatinib in different cohorts of patients with *MET* genomic alterations, including those with *MET*ex14 skipping mutations; patients had stage IIIB or IV NSCLC and were wild-type for *EGFR* and *ALK* genomic alterations.^{204,205} Updated data from GEOMETRY showed that first-line therapy with capmatinib resulted in an overall response rate of 68% in 28 patients with *MET*ex14 skipping mutations; the median PFS was 12.4 months for first-line therapy.²⁰⁴ Subsequent therapy with capmatinib yielded an overall response rate of 41% in 69 patients with *MET*ex14 skipping mutations; the median PFS was 5.4 months for subsequent therapy.²⁰⁴ The data from GEOMETRY also suggest that capmatinib is effective for patients with brain metastases.^{204,206} Among patients with brain metastases, a

response to capmatinib was reported in 54%; 4 patients had a complete response in the brain. However, 43% of patients whose disease responded had previously received RT.²⁰⁴ Common AEs for patients with *MET*ex14 skipping mutations across all cohorts included peripheral edema, nausea, and vomiting, but most of these events were grades 1 to 2.²⁰⁴ One treatment-related death occurred.

VISION, a phase II study, assessed tepotinib in patients with *MET*ex14 skipping mutations; patients mainly had stage IV NSCLC and were wild-type (negative) for *EGFR* and *ALK* genomic alteration.^{207–209} The response rate to tepotinib was 46%; PFS was 8.5 months in the combined biopsy group (tissue biopsy plus plasma ctDNA).²⁰⁹ Grade 3 or higher AEs occurred in 28% of patients receiving tepotinib, such as peripheral edema; 11% of patients had to permanently discontinue tepotinib because of peripheral edema, pleural effusion, or dyspnea.²⁰⁹ One treatment-related death occurred.²⁰⁹ The 18-month follow-up analysis of VISION confirmed the efficacy of tepotinib in patients with *MET*ex14-positive advanced/metastatic NSCLC.²¹⁰ Among treatment-naïve patients, the objective response rate with tepotinib was 57.3% and the median duration of response was 46.6 months. Among previously treated patients, the objective response rate was 45% and the median duration of response was 12.6 months.

Data suggest that crizotinib, an oral TKI that inhibits multiple kinases, including ALK, ROS1, and MET, is also a viable option for patients with advanced NSCLC and *MET*ex14 skipping mutations.²¹¹

NCCN Recommendations

The NCCN NSCLC Panel recommends capmatinib, tepotinib, or crizotinib as first-line treatment options for patients with advanced or metastatic NSCLC and *MET*ex14 skipping mutation (Figure 15). 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.

Other systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed on NSCL-K 1 of 5 and NSCL-K 2 of 5 in the guidelines 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.^{38,113}

NSCLC With *RET* Rearrangement

RET rearrangements occur in about 1%–2% of patients with NSCLC and are more frequent in patients with adenocarcinoma histology.^{212–216} Rearrangements may occur between *RET* and other genes, including *KIF5B* and *CCDC6*, which can lead to overexpression and dysregulation of *RET* kinase and inappropriate signaling.^{212,213}

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.^{217–219}

Libretto-001, a phase I–II study, assessed selpercatinib in patients with NSCLC and *RET* rearrangements.^{220,221} Updated results from the trial showed that first-line therapy with selpercatinib yielded an objective response rate of 85%.²²⁰ Second-line therapy with selpercatinib yielded an objective response rate of 64%; the median PFS was 18.4 months. Of patients with brain metastases, a response to selpercatinib was reported in 91% (10/11). Common grade 3 or more AEs with selpercatinib included hypertension, increased liver enzyme levels, hyponatremia, and lymphopenia.

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.²²² Based on the interim analysis, the median PFS was longer with selpercatinib than with the control treatment (24.8 vs 11.2 months; HR, 0.46; *P* < .001). The HR for time to CNS progression was 0.28. 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%).

ARROW, a phase I–II study, assessed pralsetinib in 233 patients with metastatic NSCLC and *RET* rearrangements.²²³ First-line therapy with pralsetinib resulted in an overall response rate of 70%; 3 patients (11%) had a complete response. Second-line

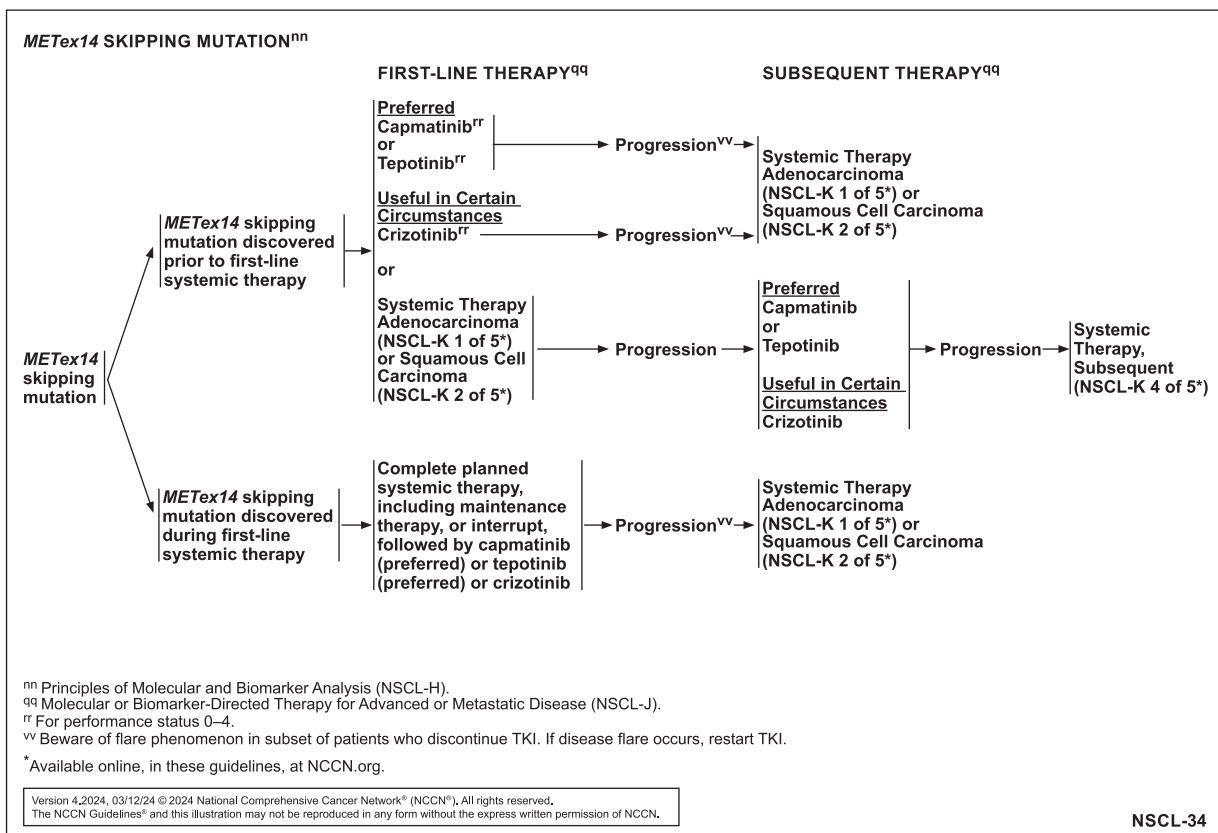


Figure 15. NSCL-34. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

therapy with pralsetinib resulted in an overall response rate of 61% (53/87); 5 patients (6%) had a complete response. Among the nine patients with measurable brain metastases, a response to pralsetinib was reported in 56%; 3 patients had an intracranial complete response. Grade 3 or more AEs with pralsetinib include anemia, neutropenia, and hypertension. Common AEs with pralsetinib included increased aspartate transferase levels, increased alanine transaminase 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.²²⁴ 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, MET, VEGFR2, and others,²¹⁷ is another viable treatment option for patients with *RET*-positive metastatic NSCLC.^{225–227}

NCCN Recommendations

The NCCN NSCLC Panel recommends selpercatinib or pralsetinib as preferred first-line therapy options for patients with advanced or metastatic NSCLC and *RET* rearrangements. Cabozantinib is recommended by the panel as a first-line therapy option that may be useful in certain circumstances (Figure 16). All are appropriate for performance status 0–4. These agents are also recommended as subsequent therapy options for patients with *RET* rearrangement–positive metastatic NSCLC if selpercatinib, pralsetinib, or cabozantinib were not previously given as first-line therapy. The

panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended.

Other systemic therapies (such as chemotherapy with or without immunotherapy) on NSCLC-K 1 of 5 and NSCLC-K 2 of 5 in the guidelines (at NCCN.org) are categorized as “other recommended” first-line treatment options for *RET*-positive advanced or metastatic NSCLC; these are also recommended as subsequent therapy options in patients whose disease progressed after treatment with selpercatinib, pralsetinib, or cabozantinib. Data indicate that ICI monotherapy may be less effective in NSCLC with *RET* rearrangements.^{38,113}

NSCLC With *ERBB2* (*HER2*) Mutation

ERBB2 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.²²⁸ Approximately 3% of advanced NSCLC (adenocarcinoma) have a mutation in *ERBB2* (*HER2*).²²⁹ Resources are available to assess whether a specific *ERBB2* (*HER2*) mutation is oncogenic or likely to be oncogenic (such as oncoKB.org).

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.²³⁰ Fam-trastuzumab deruxtecan-nxki is a humanized monoclonal antibody–drug conjugate consisting of trastuzumab, an antibody targeting

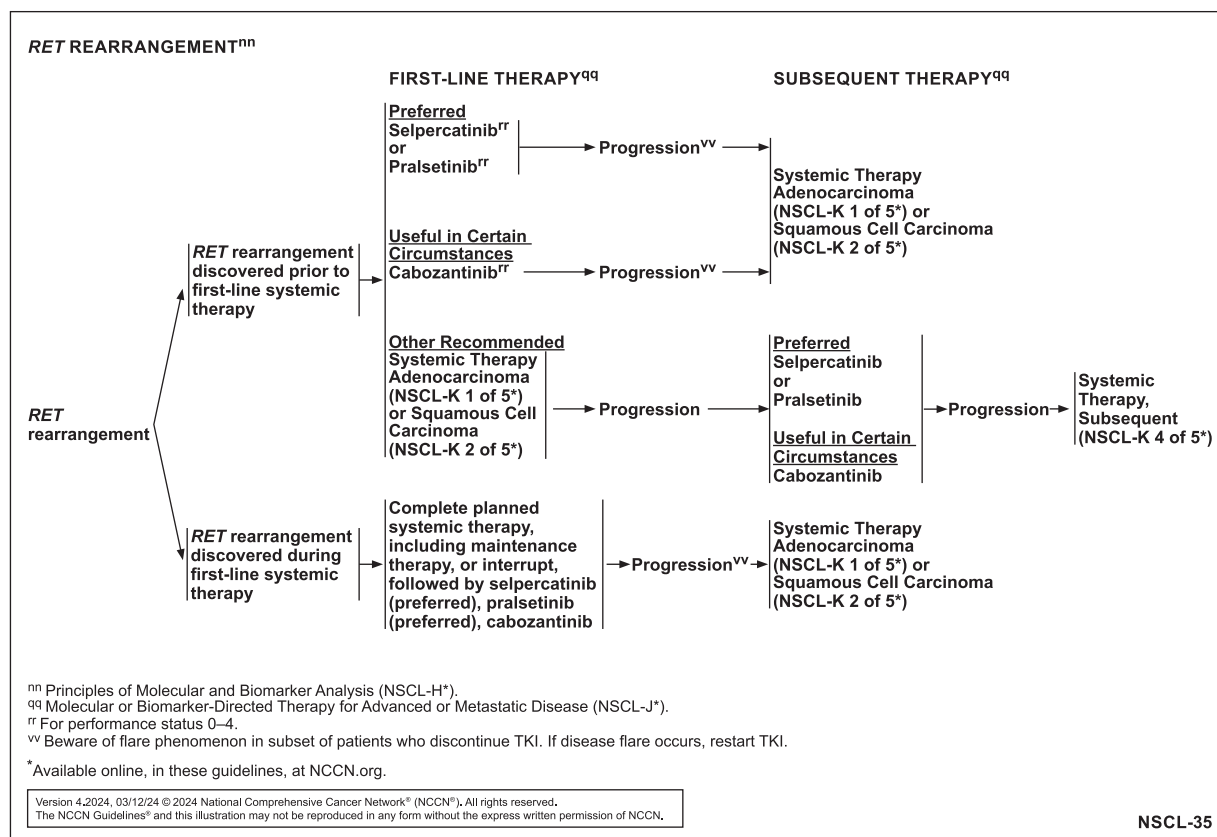


Figure 16. NSCL-35. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

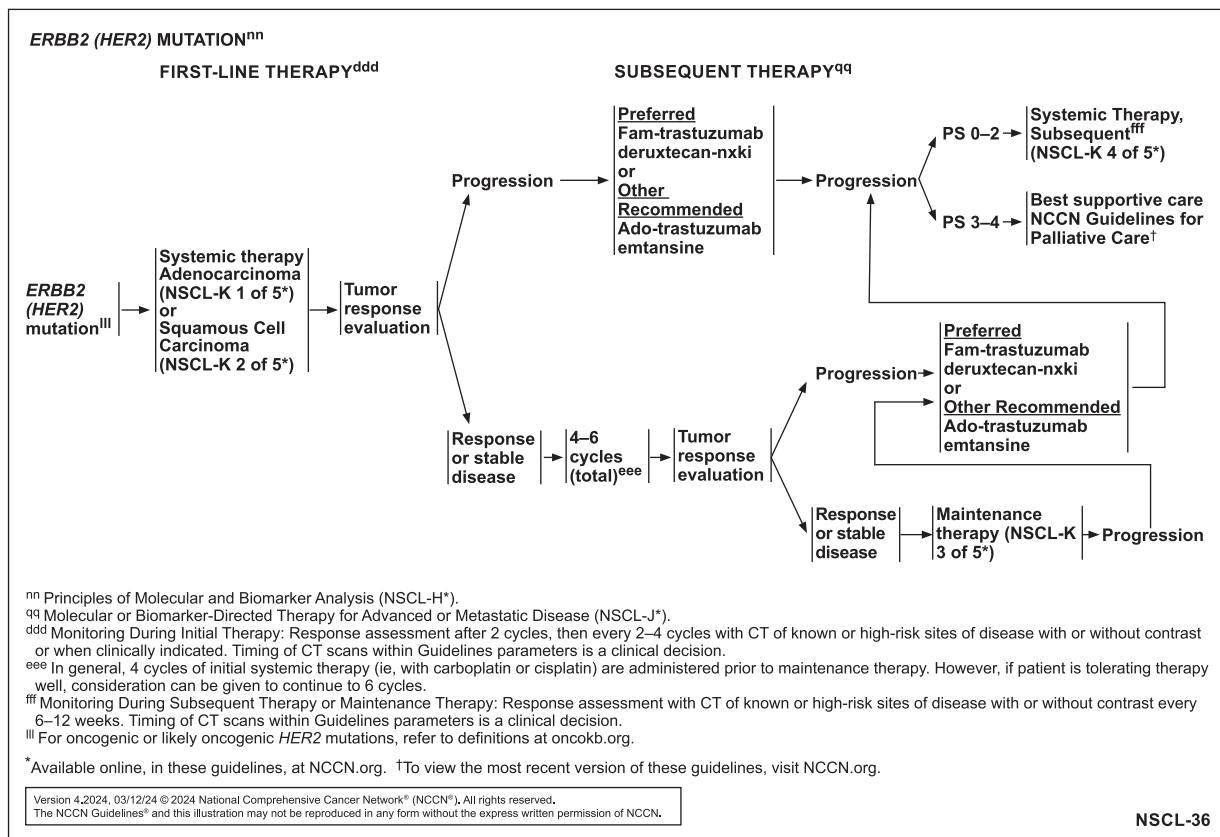


Figure 17. NSCL-36. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non-Small Cell Lung Cancer, Version 4.2024.

HER2, linked to deruxtecan, a topoisomerase I inhibitor; the agent remains stable until it is cleaved by peptides in cancer cells.²²⁹

DESTINY-Lung01, a phase II study, assessed fam-trastuzumab deruxtecan-nxki in 91 patients with metastatic nonsquamous NSCLC and *ERBB2* mutations (not *ERBB2* amplification).^{229,231,232} Most patients had *ERBB2* (*HER2*) exon 20 insertion mutations (86%); 66% were female, 57% had never smoked cigarettes, 36% had CNS metastases at baseline, and all had nonsquamous NSCLC.²²⁹ The objective response rate with fam-trastuzumab deruxtecan-nxki was 55%; most patients had received prior treatment.²²⁹ Median OS was 17.8 months.²²⁹ Grade 3 or higher AEs occurred in 46% of patients including neutropenia (19%). Two patients died of drug-related interstitial lung disease.

Data have shown that ado-trastuzumab emtansine (also known as T-DM1), a humanized antibody–drug conjugate consisting of trastuzumab and microtubule inhibitor emtansine, also has efficacy in patients with metastatic or recurrent NSCLC and *ERBB2* (*HER2*) mutations.^{233,234}

NCCN Recommendations

The NCCN NSCLC Panel recommends the systemic therapy regimens (such as chemotherapy with or without immunotherapy) listed on NSCL-K 1 of 5 or NSCL-K 2 of 5 in the guidelines (at

NCCN.org) for the first-line treatment of advanced or metastatic NSCLC with *ERBB2* (*HER2*) mutations. Data indicate that ICI monotherapy may be less effective in NSCLC with *ERBB2* (*HER2*) mutations (Figure 17).^{38,113}

After disease progression, fam-trastuzumab deruxtecan-nxki is recommended as a preferred subsequent therapy option, while ado-trastuzumab emtansine is categorized as an “other recommended” option. The panel notes that switching between agents with a similar mechanism of action at the time of progression is not recommended.

Summary

Management of NSCLC is described in the NCCN Guidelines for NSCLC; recommendations for SCLC are provided in a different guideline (see the NCCN Guidelines for Small Cell Lung Cancer, available at NCCN.org). Molecular testing to guide use of appropriate targeted therapies is a key component of care for patients with advanced or metastatic NSCLC. In the absence of actionable molecular biomarkers listed in the guidelines, refer to the full list of NCCN Guidelines on NCCN.org for further guidance. The NCCN Guidelines for NSCLC will continue to be updated at least once a year by the NCCN NSCLC Panel based on consensus and clinical evidence.

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