# Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2024.2

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DOI https://doi.org/10.1200/JCO-24-02133

## ABSTRACT

*Living guidelines are developed for selected topic areas with rapidly evolving evidence that drives frequent change in recommended clinical practice. Living guidelines are updated on a regular schedule by a standing expert panel that systematically reviews the health literature on a continuous basis, as described in the ASCO Guidelines Methodology Manual. ASCO Living Guidelines follow the ASCO Conflict of Interest Policy Implementation for Clinical Practice Guidelines. Living Guidelines and updates are not intended to substitute for independent professional judgment of the treating clinician and do not account for individual variation among patients. See the Appendix for disclaimers and other important information (Appendix 1 and Appendix 2, online only). Updates are published regularly and can be found at https://ascopubs.org/nsclc-da-living-guideline.*

ACCOMPANYING CONTENT

Articles, April 10, 2024 issue on p. e1 and July 10, 2024 issue on p. e44

Appendix

Data Supplement

Accepted October 4, 2024

Published November 12, 2024

Evidence-Based Medicine Committee approval: September 17, 2024

J Clin Oncol 00:1-4



View Online Article



## BACKGROUND

In 2022, ASCO launched living clinical practice guidelines for systemic therapy for patients with stage IV non–small cell lung cancer (NSCLC) with[1] and without[2] driver alterations and both have been updated recently.[3-12] Based on routine literature searches (up to August 22, 2024), this version of the stage IV NSCLC with driver alterations living guideline reviews new evidence to assess if recommendations are up to date.

Refer to Appendix Table A2 for the full list of recommendations and Appendix Figure A1 for the updated algorithm. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) and Supplement provide additional information.

## RESULTS

The guideline Expert Panel (Appendix Table A1, online only) reviewed new evidence from four studies[13-16] that met the systematic review inclusion criteria (Appendix Tables A3-A6), and reviewed and approved the updated recommendations. Evidence supporting unchanged recommendations is reviewed in previous publications of this guideline.[3-6]

The committee is aware of and supports the recent US Food and Drug Administration approval of repotrectinib for patients with advanced neurotrophic tyrosine receptor kinase fusion-positive lung cancer and will update the recommendation when the peer-reviewed publication is available.

## UPDATED RECOMMENDATIONS

### *EGFR* Exon 19 Deletion, Exon 21 L858R Substitution

#### *First-Line Treatment Options Update*

**Recommendation 1.1.** Clinicians should offer osimertinib (Evidence quality: Moderate; Strength of recommendation: Strong).

**Recommendation 1.1.1.** Clinicians may offer osimertinib with platinum doublet chemotherapy or amivantamab plus

lazertinib (Evidence quality: Moderate; Strength of recommendation: Weak).

*Qualifying Statement:* Although Recommendation 1.1 addresses many patients in the target population, the guideline manuscript presents additional options that may be reasonable, based on the evidence reviewed. In addition, use of osimertinib in patients previously treated with adjuvant tyrosine kinase inhibitors is not reflected in this guideline.

The data supporting Recommendation 1.1.1 are derived from the phase III FLAURA 2 and MARIPOSA[14] trials. A detailed description of FLAURA 2[17] is available for review in the prior version of this guideline.[12] In the phase III MARIPOSA trial, patients with untreated advanced NSCLC harboring classical *EGFR* mutations were randomly assigned 2:2:1 to receive amivantamab plus lazertinib, osimertinib, or lazertinib alone. The primary endpoint was progression-free survival (PFS) with amivantamab plus lazertinib (n = 429) compared to osimertinib (n = 429). Median PFS was longer with amivantamab plus lazertinib versus osimertinib (23.7 *v* 16.6 months; hazard ratio [HR], 0.70; $P < .001$), albeit with higher toxicity (grade ≥3 treatment-related adverse events, 75% *v* 43%).[14] Subgroup analyses suggest that patients with a higher burden of disease, CNS metastases, and/or higher risk disease (eg, comutations, liver metastases) may benefit from intensified therapy. However, given the unknown impact on overall survival (OS) and of sequential therapies, the toxicity of therapeutic intensification may not be appropriate for or acceptable to many patients.[17,18]

In addition, recent findings from the phase III PALOMA 3 study[19] have established the non-inferiority of the subcutaneous (SC) formulation of amivantamab compared to the intravenous (IV) dosing in combination with lazertinib for *EGFR* mutation-positive NSCLC. In this study, 418 patients with *EGFR* mutation-positive NSCLC that had progressed on osimertinib, and chemotherapy were randomly assigned 1:1 to SC or IV amivantamab, both with lazertinib. The primary endpoint was pharmacokinetic noninferiority, with secondary endpoints including efficacy (objective response rate [ORR]), PFS, safety, administration times, and patient satisfaction). SC amivantamab plus lazertinib demonstrated noninferior pharmacokinetic properties and ORR, similar PFS, significantly fewer infusion-related reactions (13% *v* 66%), shorter administration time, and higher patient satisfaction at cycle 1 day 1 and the end of treatment. OS, an exploratory endpoint, was also improved in the SC arm (HR, 0.62; $P = .02$).

### *Second-Line Treatment Options Update*

**Recommendation 2.2.** For patients who have progressive disease on osimertinib or other EGFR tyrosine kinase inhibitors (TKIs) without emergent T790M or other targetable alterations, clinicians may offer platinum-based chemotherapy with or without amivantamab (Evidence quality: Moderate; Strength of recommendation: Strong).

*Qualifying Statement:* Patients that do not pursue amivantamab plus chemotherapy may also consider chemotherapy plus bevacizumab if they have adenocarcinoma and bevacizumab is deemed safe.

**Recommendation 2.2.2.** For patients who have progressive disease on EGFR TKI, anti-PD-(L)1 agents with or without platinum chemotherapy are not recommended (Evidence quality: High; Strength of recommendation: Strong).

The MARIPOSA-2 study[13] compared the added benefit of amivantamab to carboplatin-pemetrexed chemotherapy with and without lazertinib versus chemotherapy alone in patients with locally advanced or metastatic NSCLC with an *EGFR* mutation upon disease progression on osimertinib. The study enrolled 657 patients who were randomly assigned 2:2:1 to chemotherapy versus amivantamab plus lazertinib plus chemotherapy versus amivantamab plus chemotherapy. The dual primary endpoints of amivantamab plus chemotherapy and amivantamab plus lazertinib plus chemotherapy versus chemotherapy were reached with PFS of 6.3 months (HR, 0.48) and 8.3 months (HR, 0.44) versus 4.2 months, respectively. Similarly, ORR were higher in the experimental combinations versus chemotherapy alone (64% and 63% *v* 36%). OS results remain premature while adverse event (AE) profiles demonstrated excessive hematological toxicities in the amivantamab plus lazertinib plus chemotherapy arm necessitating a regimen change to start lazertinib upon completion of carboplatin. Anticipated additional *EGFR*- and *MET*-targeting–related AEs were seen in the amivantamab-containing regimens. While the quadruplet regimen will require longer follow-up to better understand risk-to-benefit profile, these results of the amivantamab plus chemotherapy regimen offer an evidence-based, potentially more effective approach versus doublet chemotherapy for the treatment of patients with advanced NSCLC and an *EGFR* mutation upon progression on front-line osimertinib. The added AE profile of amivantamab versus chemotherapy alone needs to be considered on an individual basis. There are no data available on the efficacy of this regimen following chemotherapy plus osimertinib or amivantamab plus lazertinib as initial therapy.

The phase III CheckMate 722[15] study randomly assigned patients with metastatic NSCLC and an *EGFR* mutation that progressed on EGFR TKIs to receive either nivolumab plus chemotherapy or chemotherapy alone. The primary endpoint was PFS, with secondary endpoints including OS, ORR, and duration of response (DOR). A total of 294 patients were enrolled. After a median follow-up of 38.1 months, the addition of nivolumab to chemotherapy

did not significantly improve PFS (5.6 *v* 5.4 months; HR, 0.75 [95% CI, 0.56 to 1.00]; *P* = .0528) or OS (19.4 *v* 15.9 months; HR, 0.82 [95% CI, 0.61 to 1.10]). Similarly, the KEYNOTE-789 study[16] randomly assigned patients who progressed on EGFR TKIs to receive either pembrolizumab or a placebo plus chemotherapy. The dual primary endpoints were PFS and OS, with secondary endpoints including ORR and DOR. A total of 492 patients were enrolled. After a median follow-up of 42 months, there was no significant difference in PFS (5.6 *v* 5.5 months; HR, 0.80 [95% CI, 0.65 to 0.97]; *P* = .0122) or OS (15.9 *v* 14.7 months; HR, 0.84 [95% CI, 0.69 to 1.02]; *P* = .0362) between the study arms.

**ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.**

## ADDITIONAL RESOURCES

Additional information including a supplement, clinical tools and resources can be found at www.asco.org/living-guidelines. Patient information is available at www.cancer.org.


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## EDITOR'S NOTE

This ASCO Living Clinical Practice Guideline provides recommendations, with review and analysis of the relevant literature for each recommendation. Additional information, including links to patient information at www.cancer.org, is available at www.asco.org/living-guidelines.

## EQUAL CONTRIBUTION

L.B. and N.B.L. were expert panel co-chairs.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-24-02133.

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**Collection and assembly of data:** All authors
**Data analysis and interpretation:** All authors
**Manuscript writing:** All authors
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## ACKNOWLEDGMENT

The authors wish to thank Drs Edgardo S. Santos Castillero and Latha Subramanian and the ASCO Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline update.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2024.2**

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No other potential conflicts of interest were reported.

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## APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

**TABLE A1.** Stage IV Non–Small Cell Lung Cancer Living Guideline Expert Panel Membership

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**TABLE A2.** All Recommendations

| Driver Alteration | Recommendation | Evidence Quality | Strength of Recommendation |
|---|---|---|---|
| NOTE:<br>For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored to each patient incorporating both efficacy and toxicity.<br>All biomarkers should be available at the time of decision making.<br>The following recommendations (strong or weak/conditional) and terminology (Data Supplement, online only) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible | | | |
| Clinical Question 1: What are the most effective first-line treatment options for patients' status based on the driver alterations: | | | |
| *EGFR* | Exon 19 deletion, exon 21 L858R substitution | | |
| | 1.1. Clinicians should offer osimertinib | Moderate | Strong |
| | 1.1.1. Clinicians may offer osimertinib with platinum doublet chemotherapy or amivantamab plus lazertinib | Moderate | Weak |
| | Qualifying Statement: Although Recommendation 1.1 addresses many patients in the target population, the guideline manuscript presents additional options that may be reasonable, based on the evidence reviewed. In addition, use of osimertinib in patients previously treated with adjuvant TKIs is not reflected in this guideline | | |
| | Others | | |
| | 1.2. For other activating *EGFR* alterations, (G719X, L861Q, S768I), clinicians may offer afatinib | Low | Strong |
| | 1.2.1. or osimertinib | Low | Weak |
| | 1.2.2. or standard treatment following the nondriver alteration guideline | Low | Weak |
| | Qualifying Statement: Recommendations 1.2, 1.2.1, and 1.2.2 exclude exon 20 insertion alterations, T790M | | |
| | 1.3. For any activating *EGFR* alteration, regardless of PD-L1 expression levels (including exon 20 insertions), single-agent immune checkpoint inhibitors should not be offered as first-line therapy | Moderate | Strong |
| | Exon 20 insertions | | |
| | 1.4. Clinicians may offer chemotherapy and amivantamab | Moderate | Strong |
| | 1.5. If amivantamab is not available, clinicians should offer standard treatment following the nondriver alteration guideline | Moderate | Strong |
| *ALK* | 1.6. Clinicians should offer alectinib or brigatinib or lorlatinib | High | Strong |
| | 1.7. If alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib | High | Strong |
| *ROS1* | 1.8. Clinicians may offer crizotinib, entrectinib, or repotrectinib | Moderate | Strong |
| | 1.9. If crizotinib, entrectinib, or repotrectinib are not available or not tolerated, clinicians may offer ceritinib or lorlatinib | Low | Weak |
| *BRAF*$^{V600E}$ | 1.10. Clinicians may offer dabrafenib and trametinib, or encorafenib and binimetinib | Low | Strong |
| | 1.11. If dabrafenib and trametinib, or encorafenib and binimetinib are not available, clinicians may offer standard first-line therapy following the nondriver alteration guideline | Low | Strong |
| *MET* exon 14 skipping mutation | 1.12. Clinicians may offer capmatinib or tepotinib | Low | Strong |
| | 1.13. If capmatinib or tepotinib is not available, clinicians may offer standard first-line therapy following the nondriver alteration guidelines | Low | Strong |

(continued on following page)

**TABLE A2.** All Recommendations (continued)

| Driver Alteration | Recommendation | Evidence Quality | Strength of Recommendation |
|---|---|---|---|
| *RET* rearrangement | 1.14. Clinicians should offer selpercatinib | High | Strong |
| | 1.15. If selpercatinib is not available, clinicians may offer pralsetinib | Moderate | Strong |
| | 1.16. If selpercatinib or pralsetinib are not available, clinicians may offer standard therapy following the nondriver alteration guideline | Low | Weak |
| *NTRK* rearrangement | 1.17. Clinicians may offer entrectinib or larotrectinib | Low | Strong |
| | 1.18. If entrectinib or larotrectinib are not available, clinicians may offer standard therapy following the nondriver alteration guideline | Low | Weak |
| 1.19. For patients with a poor PS, TKI may be offered based on drug access and toxicity profile | | Low | Weak |
| 1.20. Biomarker testing with a tissue- and blood-based broad multigene panel and an IHC assay for PD-L1 and HER2 should be universally accessible for all patients diagnosed with NSCLC | | High | Strong |
| Qualifying Statement: PD-L1 IHC alone should not be used to guide treatment decisions. Treatment decisions based on HER2 overexpression are restricted to second line and beyond | | | |
| 1.21. Patients with advanced lung cancer should be referred to interdisciplinary palliative care teams (consultation) that provide outpatient and inpatient care early in the course of disease, alongside active treatment of their cancer | | High | Strong |
| Clinical Question 2: What are the most effective second-line and subsequent treatment options for patients based on the driver alterations: | | | |
| NOTE:<br>Due to development of potentially targetable resistance mechanisms, every effort should be made to assess for presence of new mutation by tissue and/or blood NGS testing.<br>If patients have received all targeted options, or if no targeted options are available, clinicians may offer standard therapy following the nondriver alteration guideline | | | |
| *EGFR* | Exon 19 deletion, exon 21 L858R substitution | | |
| | 2.1. For patients that develop *EGFR* T790M resistance alterations in tumor after first- or second-generation *EGFR* TKIs, clinicians should offer osimertinib | High | Strong |
| | 2.2. For patients who have progressive disease on osimertinib or other EGFR TKIs without emergent T790M or other targetable alterations, clinicians may offer platinum-based chemotherapy with or without amivantamab | Moderate | Strong |
| | Qualifying Statement: Patients that do not pursue amivantamab plus chemotherapy may also consider chemotherapy plus bevacizumab if they have adenocarcinoma and bevacizumab is deemed safe | | |
| | 2.2.1. For patients who have progressive disease on osimertinib (or other third generation TKI), clinicians may offer platinum-based chemotherapy with or without amivantamab | Moderate | Strong |
| | 2.2.2. For patients who have progressive disease on *EGFR* TKI, anti-PD-(L)1 agents with or without platinum chemotherapy are not recommended | High | Strong |
| | *Others* | | |
| | 2.3. For patients with an exon 20 insertion alteration who have received prior treatment with platinum chemotherapy, clinicians may offer treatment with amivantamab | Low | Strong |
| *ALK* | 2.4. For patients who have previously received crizotinib, clinicians should offer alectinib, brigatinib, or ceritinib, and may offer lorlatinib | Moderate | Strong |
| | 2.5. For patients who have previously received other *ALK* inhibitors including alectinib or brigatinib, clinicians may offer lorlatinib | Low | Strong |

(continued on following page)

**TABLE A2.** All Recommendations (continued)

| Driver Alteration | Recommendation | Evidence Quality | Strength of Recommendation |
|---|---|---|---|
| *ROS1* | 2.6. For patients who have previously received crizotinib, entrectinib, lorlatinib, or ceritinib, clinicians may offer repotrectinib | Moderate | Strong |
| | 2.7. For patients who have received multiple *ROS-1* inhibitors, clinicians should offer platinum-based chemotherapy following the nondriver alteration guideline | Low | Strong |
| *BRAF*$^{V600E}$ | 2.8. For patients who have not received *BRAF* therapy, clinicians may offer dabrafenib and trametinib or encorafenib and binimetinib | Low | Strong |
| | 2.9. For patients who have previously received *BRAF*- or *MEK*-targeted therapy, clinicians should offer standard first-line therapy following the nondriver alteration guideline | Low | Strong |
| | 2.10. For *BRAF* alterations other than *BRAF* V600E alterations, clinicians should offer standard therapy following the nondriver alteration guideline | Low | Strong |
| *MET* exon 14 skipping mutation | 2.11. For patients who have not received *MET*-targeted therapy, clinicians may offer capmatinib or tepotinib | Low | Strong |
| | 2.12. For patients previously treated with *MET*-targeted therapy, clinicians should offer standard therapy following the nondriver alteration guideline | Low | Strong |
| *RET* rearrangement | 2.13. For patients who have not received a *RET* inhibitor, clinicians should offer selpercatinib or pralsetinib | Moderate | Strong |
| | 2.14. If selpercatinib or pralsetinib is not available, clinicians may offer treatment following the nondriver alteration guideline | Low | Strong |
| *NTRK* rearrangement | 2.15. For patients who have not received an *NTRK* inhibitor, clinicians should offer entrectinib or larotrectinib | Low | Strong |
| | 2.16. If entrectinib or larotrectinib is not available, clinicians may offer standard therapy following the nondriver alteration guideline | Low | Strong |
| *HER2 mutation* | 2.17. Clinicians may offer treatment with trastuzumab deruxtecan | Low | Strong |
| *KRAS* G12C | 2.18. Clinicians may offer treatment with sotorasib | Moderate | Strong |
| | 2.19. Clinicians may offer treatment with adagrasib | Low | Strong |
| | Qualifying Statement: Note that adagrasib and sotorasib are approved for patients who have received prior chemotherapy and/or anti-PD-(L)1 for patients with advanced *KRAS* G12C mutant NSCLC. In the first-line setting, these patients should be offered standard first-line treatment with immune checkpoint inhibitor therapy and/or chemotherapy following the nondriver alteration guideline | | |

NOTE. The strength of the recommendation is defined as follows: Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Weak/conditional: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; HER2, human epidermal receptor factor 2; NSCLC, non–small cell lung cancer; *NTRK*, neurotrophic tyrosine receptor kinase; PS, performance status; TKI, tyrosine kinase inhibitor.

**TABLE A3.** Patients With Stage IV NSCLC and an Untreated *EGFR*-Mutation (exon 19 deletion or L858R): Amivantamab-Lazertinib Versus Osimertinib[14]

| Outcome | Study Results and Measurements | Absolute Effect Estimates | | Quality of Evidence | Summary |
|---|---|---|---|---|---|
| | | Osimertinib | Amivantamab-Lazertinib | | |
| PFS | HR, 0.7 (95% CI, 0.58 to 0.85)<br>Based on data from 858 participants in 1 study<br>Follow-up 22 months | 587 per 1,000 | 462 per 1,000<br>Difference: 125 fewer per 1,000 (95% CI, 186 fewer to 59 fewer) | Moderate[a] | Amivantamab-lazertinib improves PFS |
| OS | HR, 0.8 (95% CI, 0.61 to 1.05)<br>Based on data from 858 participants in 1 study<br>Follow-up 22 months | 273 per 1,000 | 225 per 1,000<br>Difference: 48 fewer per 1,000 (95% CI, 96 fewer to 11 more) | Moderate[a] | Impact of amivantamab-lazertinib OS are premature |
| Safety | Based on data from 849 participants in 1 study<br>Follow-up 22 months | Grade 3 or higher AEs were reported in 75% of the patients treated with amivantamab-lazertinib, and in 43% of those treated with osimertinib, with paronychia and rash being the most common events. Serious AEs were reported in 49% of the patients treated with amivantamab-lazertinib and in 33% of those treated with osimertinib | | Moderate[a] | Predominant AEs were EGFR-related toxic effects. The incidence of discontinuation of all agents due to treatment-related AEs was 10% with amivantamab-lazertinib and 3% with osimertinib |

Abbreviations: AEs, adverse events; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a]Certainty of evidence is affected by interim nature of these results and data provided by one study.

**TABLE A4.** Patients With Stage IV NSCLC and an *EGFR*-Mutation (exon 19 deletion or L858R): Amivantamab-Lazertinib-Chemotherapy Versus Chemotherapy[13]

| Outcome | Study Results and Measurements | Absolute Effect Estimates | | Quality of Evidence | Summary |
|---|---|---|---|---|---|
| | | Chemotherapy | Amivantamab-Lazertinib-chemotherapy | | |
| PFS | HR, 0.44 (95% CI, 0.35 to 0.56)<br>Based on data from 526 participants in 1 study<br>Follow-up 8.7 months | 650 per 1,000 | 370 per 1,000<br>Difference: 280 fewer per 1,000 (95% CI, 343 fewer to 205 fewer) | Moderate[a] | Amivantamab-lazertinib-chemotherapy probably improves PFS |
| Intracranial PFS | HR, 0.58 (95% CI, 0.44 to 0.78)<br>Based on data from 526 participants in 1 study<br>Follow-up 8.7 months | 662 per 1,000 | 467 per 1,000<br>Difference: 195 fewer per 1,000 (95% CI, 282 fewer to 91 fewer) | Moderate[a] | Amivantamab-lazertinib-chemotherapy probably improves intracranial PFS |
| Safety | Based on data from 526 participants in 1 study<br>Follow-up 8.7 months | AEs of grade 3 or higher, mainly due to hematologic toxicities, were reported by 72% of patients treated with amivantamab + chemotherapy, 92% with amivantamab + lazertinib + chemotherapy, and 48% with chemotherapy | | Moderate[a] | The most common grade 3 or higher AEs (10% or higher in any arm) included neutropenia, thrombocytopenia, anemia, and leukopenia |

Abbreviations: AE, adverse event; HR, hazard ratio; PFS, progression-free survival.
[a]Certainty of evidence is affected by interim nature of these results and data provided by one study.

**TABLE A5.** Patients Who Have Progressive Disease on First- or Second-Generation EGFR Tyrosine Kinase Inhibitor Therapy (without EGFR T790M mutation) or Osimertinib (with/without T790M mutation): Nivolumab + Platinum-Doublet Chemotherapy Versus Platinum-Doublet Chemotherapy Alone[15]

| Outcome | Study Results and Measurements | Absolute Effect Estimates | | Quality of Evidence | Summary |
|---|---|---|---|---|---|
| | | Platinum-Doublet Chemotherapy Alone | Nivolumab + Platinum-Doublet Chemotherapy | | |
| PFS | HR, 0.75 (95% CI, 0.56 to 1.0)<br>Based on data from 294 participants in one study<br>Follow-up 38.1 months | 893 per 1,000 | 813 per 1,000<br>Difference: 80 fewer per 1,000 (95% CI, 179 fewer to 0 fewer) | Low[a] | Nivolumab + platinum-doublet chemotherapy may have little or no difference on PFS |
| OS | HR, 0.82 (95% CI, 0.61 to 1.1)<br>Based on data from 294 participants in one study<br>Follow-up 38.1 months | 693 per 1,000 | 620 per 1,000<br>Difference: 73 fewer per 1,000 (95% CI, 180 fewer to 34 more) | Low[a] | Nivolumab + platinum-doublet chemotherapy may have little or no difference on OS |
| Safety | Based on data from 294 participants in one study<br>Follow-up 38.1 months | Any-grade and grade 3/4 TRAEs were reported in 85.1% and 44.7% of patients in the nivolumab plus chemotherapy arm and 86.7% and 29.4% in the chemotherapy arm, respectively | | Low[a] | The most common any-grade TRAEs in both arms were anemia (39.7% with nivolumab plus chemotherapy and 35.0% with chemotherapy) and nausea (31.2% and 35.0%); the most frequent grade 3/4 events were anemia (15.6% and 9.1%) and decreased neutrophil count (11.3% and 11.2%). Any--grade TRAEs leading to treatment discontinuation occurred in 14.9% and 7.7% of patients, respectively |

Abbreviations: AE, adverse event; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TRAEs, treatment-related adverse events.
[a]Certainty of evidence is affected by low number of patients, which was due to slow accrual, and data provided by one study.

**TABLE A6.** Patients Who Have Progressive Disease EGFR TKI Therapy (DEL19 or L858R EGFR mutation): Pembrolizumab + Pemetrexed-Platinum Versus Placebo + Pemetrexed-Platinum[16]

| Outcome | Study Results and Measurements | Absolute Effect Estimates | | Quality of Evidence | Summary |
|---|---|---|---|---|---|
| | | Placebo + Pemetrexed-Platinum | Pembrolizumab + Pemetrexed-Platinum | | |
| OS | HR: 0.84 (95% CI, 0.69 to 1.02)<br>On the basis of data from 492 participants in one study<br>Follow-up, 28.6 months | 907 per 1,000 | 864 per 1,000 | Moderate[a] | Pembrolizumab + pemetrexed-platinum has little or no difference on OS |
| | | Difference: 43 fewer per 1,000 (95% CI, 101 fewer to 4 more) | | | |
| PFS | HR: 0.8 (95% CI, 0.65 to 0.97)<br>On the basis of data from 492 participants in one study<br>Follow-up, 28.6 months | 866 per 1,000 | 800 per 1,000 | Moderate[a] | Pembrolizumab + pemetrexed-platinum has little or no difference on PFS |
| | | Difference: 66 fewer per 1,000 (95% CI, 137 fewer to 8 fewer) | | | |
| Safety | On the basis of data from 492 participants in one study<br>Follow-up, 28.6 months | AEs of any grade occurred in 239 of 245 treated patients (97.6%) in the pembrolizumab-chemotherapy group and 241 of 246 patients (98.0%) in the placebo-chemotherapy group. Treatment-related AEs occurred in 220 patients (89.8%) and 212 patients (86.2%), respectively. These were grade ≥3 in 107 (43.7%) and 95 (38.6%) patients, respectively | | Moderate[a] | Immune-mediated AEs and infusion reactions occurred in 49 patients (20.0%) who received pembrolizumab-chemotherapy and 20 (8.1%) in the placebo–chemotherapy group<br>The only fatal immune-mediated event was myocarditis (0.4%) in the pembrolizumab-chemotherapy group |

Abbreviations: AEs, adverse events; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a]Imprecision: Serious. Only data from one study.

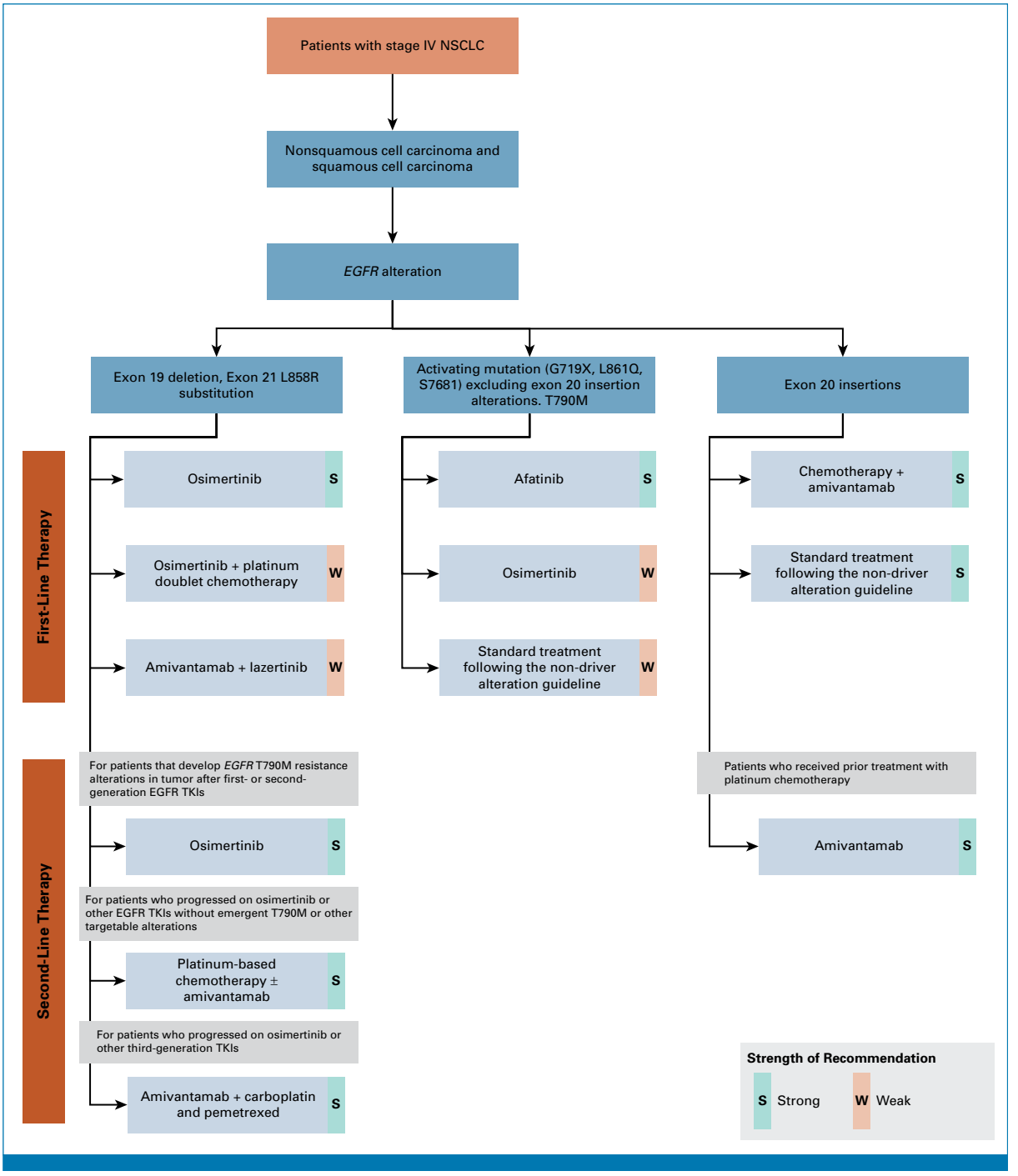


**FIG A1.** Algorithm for stage IV NSCLC with *EGFR* alterations. For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored to each patient incorporating both efficacy and toxicity. All biomarkers should be available at the time of decision making. For second-line and subsequent therapies, due to development of potentially targetable resistance mechanisms, every effort should be made to assess for presence of new mutation by tissue and/or blood NGS testing. If patients have received all targeted options, or if no targeted options are available, clinicians may offer standard therapy following the nondriver alteration guideline. For alterations without targeted therapy options, refer to the nondriver alteration guideline, Therapy for Stage IV Non–Small Cell Lung Cancer Without Driver Alterations: ASCO living Guideline. New active targeted therapies are anticipated soon. EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.