

Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, 2026.3.1

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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 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

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Appendix

Data Supplement

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BACKGROUND

In 2022, ASCO launched living clinical practice guidelines for systemic therapy for patients with stage IV non–small cell lung cancer (NSCLC) with and without driver alterations^{1,2} and both have been updated recently.^{3,4} Based on routine literature searches (up to January 21, 2026), this version ([Appendix 3](#)) of the stage IV NSCLC with driver alterations living guideline reviews evidence and provides updated recommendations on new therapeutics. Refer to [Appendix Table A1](#) (online only) for the full list of recommendations, and [Appendix Figure A1](#) for the updated algorithm. The ASCO Guidelines Methodology Manual (available at <https://www.asco.org/practice-patients/guidelines/guideline-methodology>) and the Data Supplement (online only) provide additional information.

RESULTS

The guideline Expert Panel ([Appendix Table A2](#)) reviewed new evidence from three studies^{5–7} that met the systematic review inclusion criteria ([Appendix Tables A3–A5](#)) and reviewed and approved the updated recommendations. Evidence supporting unchanged recommendations is reviewed in previous publications of this guideline.³

UPDATED RECOMMENDATIONS

First-Line Treatment Options, EGFR Exon 19 Deletion, Exon 21 L858R Substitution

Recommendation 1.2

Clinicians should offer osimertinib to patients not pursuing combination therapy (Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement for recommendation 1.2. For patients unable to access osimertinib, lazertinib monotherapy may be offered as an alternative treatment option if available.

Evidence review. Lazertinib is a highly selective third-generation EGFR tyrosine kinase inhibitor (TKI) that is used in combination with amivantamab in treatment of metastatic NSCLC with typical EGFR mutations. Its efficacy and safety as monotherapy were compared with osimertinib in an exploratory analysis of the phase III MARIPOSA trial.⁵ Results showed comparable efficacy between the two drugs with a median progression-free survival (PFS) of 18.5 months (95% CI, 14.8 to 20.1) in the lazertinib arm (n = 429) versus 16.6 months (95% CI, 14.8 to 18.5) in the

osimertinib arm (n = 216). Median overall survival (OS) was not reached in either arm. Similar efficacy was observed in patients with baseline brain metastases. Toxicity profile was also similar, with grade 3 or higher treatment-emergent adverse events (TEAEs) reported at 46% for lazertinib versus 43% in the osimertinib group. The most common any-grade TEAEs were diarrhea (lazertinib 32%, osimertinib 44%) and rash (lazertinib 45%, osimertinib 31%).

Clinical interpretation. Based on this analysis, lazertinib monotherapy is an acceptable alternative to osimertinib in patients who are not able to access osimertinib.

First-Line Treatment Options, Other Activating EGFR Alterations

Recommendation 1.4

For other activating EGFR alterations (G719X, L861Q, S768I), clinicians may offer amivantamab plus lazertinib (Evidence quality: Low; Strength of recommendation: Conditional).

Qualifying statement for recommendations 1.3, 1.4, and 1.5. Recommendations 1.3, 1.4, and 1.5 exclude exon 20 insertion alterations, T790M.

Evidence review. CHRYSALIS-2 Cohort C is a prospective, single-arm phase I/Ib study that evaluated amivantamab plus lazertinib in multiple unique cohorts.⁷ In Cohort C, patients with advanced NSCLC harboring both single and compound atypical EGFR mutations (eg, G719X [56%], L861Q [26%], S768I [23%], etc) were enrolled, excluding exon 19 deletions, L858R mutations, and exon 20 insertions. Patients were either treatment-naïve or had received ≤2 lines of treatment with chemotherapy and/or a first- or second-generation TKI. The primary endpoint of the study was overall response rate (ORR). A total of 105 patients received amivantamab plus lazertinib; 47% were treatment-naïve, and 53% were previously treated. At a median follow-up of 16.1 months, in the overall population, investigator-assessed ORR was 52% (95% CI, 42 to 62), median duration of response (DoR) 14.1 months (95% CI, 9.5 to 26.2), and median PFS 11.1 months (95% CI, 7.8 to 17.8); median OS was not estimable (NE). In treatment-naïve patients (n = 49), ORR was 57% (95% CI, 42 to 71) with median PFS 19.5 months (95% CI, 11.2 to NE) and median DoR 20.7 months (95% CI, 9.9 to NE), while in previously treated patients (n = 56), ORR was 48% (95% CI, 35 to 62) with median PFS 7.8 months (95% CI, 5.4 to 11.1). Adverse

events (AEs) were consistent with previous studies; the most common TEAEs included rash (67%), paronychia (67%), hypoalbuminemia (59%), infusion reactions (56%), and venous thromboembolism (30%); grade ≥3 treatment-related AEs (TRAEs) occurred in 48% of patients.

Clinical interpretation. Atypical EGFR mutations represent a biologically heterogeneous subgroup with modest responses to EGFR TKI monotherapy. CHRYSALIS-2 Cohort C evaluated a combination strategy of amivantamab plus lazertinib for the treatment of atypical EGFR mutations. Several key differences between the studies in this space warrant consideration. The ACHILLES study is the only randomized phase III trial providing evidence that afatinib is superior to chemotherapy. In contrast, both CHRYSALIS-2 Cohort C and UNICORN are single-arm studies that limit direct comparisons. Additionally, patient populations differed across the three trials: CHRYSALIS-2 Cohort C enrolled both treatment-naïve and previously treated patients, whereas ACHILLES and UNICORN enrolled only treatment-naïve patients.

The treatment naïve subgroup of the CHRYSALIS-2 Cohort C study demonstrated an encouraging PFS with the combination of amivantamab plus lazertinib (19.5 months), which was numerically higher than the reported PFS from the ACHILLES study (PFS 10.6 months with afatinib) and the UNICORN study (PFS 9.4 months with osimertinib), although the absence of randomization and cross-trial differences in patient selection preclude definitive comparisons. Based on these data, amivantamab plus lazertinib may be offered as a treatment option for patients with atypical EGFR mutations. Toxicity profile of amivantamab plus lazertinib in the CHRYSALIS-2 cohort C was consistent with prior experience with the combination with grade ≥3 TRAEs reported in 70% of patients. Grade ≥3 TRAEs were reported in 32.5% with osimertinib in UNICORN and 44% with afatinib in ACHILLES. Prophylactic anticoagulation to mitigate risk of venous thromboembolism, as well as preventative strategies for skin toxicities and infusion-related reactions, is recommended when prescribing amivantamab plus lazertinib.⁸

ADDITIONAL RESOURCES

Additional information including a supplement, clinical tools and resources can be found at <https://ascopubs.org/topics/asco-guidelines/thoracic-cancer>. Patient information is available at www.cancer.org.

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J.R. and S.P. were Expert Panel Co-Chairs.

EDITOR'S NOTE

This American Society of Clinical Oncology (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 <https://ascopubs.org/topics/asco-guidelines/thoracic-cancer>.

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-26-00843>.

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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.

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APPENDIX 1. GUIDELINE DISCLAIMER

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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 <https://www.asco.org/practice-patients/guidelines/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.

APPENDIX 3. VERSIONING AND NUMBERING STATEMENT

To ensure transparency and facilitate the tracking of evidence updates, ASCO has implemented a structured numbering system for living guidelines. This system reflects the status of the recommendations as follows: 1. Major Updates (eg, 2026.2.0): These represent full updates or significant revisions approved by the Expert Panel and the Evidence Based Medicine Committee (EBMC). They typically incorporate comprehensive literature reviews and involve resubmission of the entire guideline. 2. Rapid Updates (eg, 2026.2.1): These "mini updates" serve as timely notifications of revised recommendations or supporting evidence, ensuring the guideline remains current between full update cycles.

TABLE A1. All Recommendations

Driver Alteration	Recommendation
<i>General Note.</i> The following recommendations (strong or conditional/weak) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and individual patient preferences. Recommended care should be accessible to patients whenever possible. 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.	
Clinical Question 1: What are the most effective first-line treatment options for patients' status based on the driver alterations?	
Biomarker testing	1.0. Biomarker testing with a validated tissue and/or blood-based broad multi-gene panel and a validated tissue IHC assay for PD-L1, HER2, and MET protein expression should be universally accessible for all patients diagnosed with NSCLC. (Evidence quality: High; Strength of recommendation: Strong) <i>Qualifying Statement for Recommendation 1.0:</i> Combination of blood and tissue testing may maximize chance of detecting molecular alterations. Comprehensive NGS testing ideally incorporating RNA-based NGS for detecting genomic alterations is preferred. Tissue testing has the advantage of histologic assessment and should be attempted when feasible, and the false-negative rate of liquid biopsy should be considered. PD-L1 IHC alone should not be used to guide treatment decisions. Treatment decisions based on HER2 overexpression and MET IHC are discussed in the non-driver alteration guideline.
EGFR	<i>Exon 19 deletion, exon 21 L858R substitution</i> 1.1. Clinicians should offer osimertinib with platinum-pemetrexed chemotherapy or amivantamab plus lazertinib. (Evidence quality: Moderate; Strength of recommendation: Strong) 1.2. Clinicians should offer osimertinib to patients not pursuing combination therapy. (Evidence quality: Moderate; Strength of recommendation: Strong) <i>Qualifying Statement for Recommendation 1.2:</i> For patients unable to access osimertinib, lazertinib monotherapy may be offered as an alternative treatment option if available.^a <i>Others</i> 1.3. For other activating EGFR alterations (G719X, L861Q, S768I), clinicians may offer afatinib. (Evidence quality: Moderate; Strength of recommendation: Strong) 1.4. or amivantamab plus lazertinib. (Evidence quality: Low; Strength of recommendation: Conditional)^a 1.5. or osimertinib. (Evidence quality: Low; Strength of recommendation: Conditional) <i>Qualifying Statement for Recommendations 1.3, 1.4, and 1.5:</i> Recommendations 1.3, 1.4, and 1.5 exclude exon 20 insertion alterations, T790M. <i>Exon 20 insertions</i> 1.6. Clinicians should offer chemotherapy plus amivantamab. (Evidence quality: Moderate; Strength of recommendation: Strong) <i>All EGFR mutations</i> 1.7. For any activating EGFR alteration, regardless of PD-L1 expression levels, single-agent immune checkpoint inhibitors should not be offered as first-line therapy. (Evidence quality: Moderate; Strength of recommendation: Strong)
ALK	1.8. Clinicians should offer alectinib or brigatinib or lorlatinib. (Evidence quality: High; Strength of recommendation: Strong) 1.9. If alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib. (Evidence quality: High; Strength of recommendation: Strong)
ROS1	1.10. Clinicians may offer crizotinib, entrectinib, repotrectinib, or talretrectinib. (Evidence quality: Moderate; Strength of recommendation: Strong) 1.11. If crizotinib, entrectinib, repotrectinib, or talretrectinib are not available or tolerated, clinicians may offer ceritinib or lorlatinib. (Evidence quality: Low; Strength of recommendation: Conditional)
BRAF ^{V600E}	1.12. Clinicians may offer dabrafenib and trametinib, or encorafenib and binimetinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
MET exon 14 skipping mutation	1.13. Clinicians may offer capmatinib or tepotinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
RET rearrangement	1.14. Clinicians should offer selpercatinib. (Evidence quality: High; Strength of recommendation: Strong) 1.15. If selpercatinib is not available, clinicians may offer pralsetinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
NTRK rearrangement	1.16. Clinicians may offer entrectinib or larotrectinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
General approaches	1.17. For patients with a PS > 2, tyrosine kinase inhibitor may be offered based on drug access and toxicity profile and based on clinician evaluations that the benefit outweighs the risk. (Evidence quality: Low; Strength of recommendation: Conditional) 1.18. Patients with advanced lung cancer should be referred to interdisciplinary palliative care teams (consultation) that provide inpatient and outpatient care early in the course of disease, alongside active treatment of their cancer. (Evidence quality: High; Strength of recommendation: Strong)
Clinical Question 2: What are the most effective second-line and subsequent treatment options for patients based on the driver alterations?	
NOTE: Due to development of potentially targetable resistance mechanisms and histologic transformation, every effort should be made to assess for presence of histologic transformation by tissue biopsy. Acquired resistance mutations can be checked 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 non-driver alteration guideline.	

(continued on following page)

TABLE A1. All Recommendations (continued)

Driver Alteration	Recommendation
EGFR	<i>Exon 19 deletion, exon 21 L858R substitution</i> 2.1. For patients who have progressive disease on osimertinib (or other third-generation TKI), clinicians may offer platinum-based chemotherapy with amivantamab. (Evidence quality: Moderate; Strength of recommendation: Strong) <i>Qualifying Statement for Recommendation 2.1: For patients whose disease has progressed on EGFR TKIs who are not candidates for amivantamab and chemotherapy, chemotherapy alone ± anti-VEGF-targeting therapy combinations may be offered for those with adenocarcinoma histology and where anti-VEGF therapy is considered safe.</i> 2.2. For patients who are not candidates for Recommendation 2.1, platinum-based chemotherapy may be offered with or without osimertinib. (Evidence quality: Moderate; Strength of recommendation: Conditional) 2.3. For patients whose disease has progressed on osimertinib and platinum chemotherapy, clinicians may offer datopotamab deruxtecan. (Evidence quality: Low; Strength of recommendation: Conditional) 2.4. 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) <i>Qualifying Statement for Recommendation 2.4: Multiple phase III trials have shown no benefit to addition of PD-1 to platinum chemotherapy, however the role of additional immune combinations, including VEGF, are being explored in trials.</i> 2.5. For patients who have progressive disease on EGFR TKI with acquired MET amplification, clinicians may offer osimertinib in combination with tepotinib or savolitinib. (Evidence quality: Low; Strength of recommendation: Conditional) 2.6. For patients whose cancer develops EGFR T790M resistance alterations in tumor after first- or second-generation EGFR TKIs, clinicians should offer osimertinib. (Evidence quality: High; Strength of recommendation: Strong) <i>Exon 20 insertion</i> 2.7. For patients with an exon 20 insertion alteration who have received prior treatment with platinum chemotherapy, clinicians may offer treatment with amivantamab or sunvozertinib. (Evidence quality: Low; Strength of recommendation: Strong) 2.8. For patients with an exon 20 insertion alteration who have received prior treatment with platinum chemotherapy and amivantamab, clinicians may offer treatment with sunvozertinib. (Evidence quality: Low; Strength of recommendation: Strong)
ALK	2.9. For patients who have previously received crizotinib, clinicians should offer alectinib, brigatinib, lorlatinib, or ceritinib. (Evidence quality: Moderate; Strength of recommendation: Strong) 2.10. For patients who have previously received other ALK inhibitors including alectinib or brigatinib, clinicians may offer lorlatinib. (Evidence quality: Low; Strength of recommendation: Strong)
ROS1	2.11. For patients who have previously received crizotinib, entrectinib, lorlatinib, or ceritinib, clinicians may offer repotrectinib or taletrectinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
BRAF ^{V600E}	2.12. For patients who have not received BRAF therapy, clinicians may offer dabrafenib and trametinib, or encorafenib and binimetinib. (Evidence quality: Moderate; Strength of recommendation: Strong) 2.13. For BRAF alterations other than BRAF^{V600E} alterations, clinicians should offer standard therapy following the non-driver alteration guideline. (Evidence quality: Low; Strength of recommendation: Strong)
MET exon 14 skipping mutation	2.14. For patients who have not received MET-targeted therapy, clinicians may offer capmatinib or tepotinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
RET rearrangement	2.15. For patients who have not received a RET inhibitor, clinicians should offer selpercatinib or pralsetinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
NTRK rearrangement	2.16. For patients who have not received an NTRK inhibitor, clinicians should offer entrectinib or larotrectinib. (Evidence quality: Moderate; Strength of recommendation: Strong)
HER2 exon 20 mutations	2.17. Clinicians may offer treatment with trastuzumab deruxtecan or zongertinib or sevabertinib. (Evidence quality: Low; Strength of recommendation: Strong) 2.18. For patients who have previously received trastuzumab deruxtecan, clinicians may offer sevabertinib or zongertinib. (Evidence quality: Very Low, Strength of recommendation: Conditional)
KRAS G12C	2.19. Clinicians may offer treatment with sotorasib or adagrasib. (Evidence quality: Moderate; Strength of recommendation: Strong) <i>Qualifying Statement for Recommendation 2.19: 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 mutation-positive 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 non-driver alteration guideline.</i>
NRG1 fusion	2.20. Clinicians may offer treatment with zenocutuzumab. (Evidence quality: Low; Strength of recommendation: Strong)

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. Conditional/weak: 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 growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; NRG1, neuregulin 1; NTRK, neurotrophic tyrosine receptor kinase; PS, performance status; RET, rearranged during transfection; ROS1, c-ROS oncogene 1; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

^aDenotes updated recommendation.

TABLE A2. Stage IV NSCLC Living Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
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Kristen Ashley Marrone, MD	John Hopkins Medical Center, Baltimore, MD	Medical Oncology
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TABLE A3. Characteristics of Studies Identified in the Literature Search Since Last Update

Author Reference	Interventions and Comparisons	Patients, No.	Patient Characteristic					Disease Characteristic		
			Median Age, Years	Sex, %		% Smokers	Race or Ethnicity: %	History of Brain Metastasis, %	ECOG PS: %	EGFR Mutation: %
				Male	Female					
Phase II RCTs										
Lee et al ⁵ MARIPOSA	Osimertinib	429	63	41	59	31	Asian: 59	40	0: 35	Exon 19 del: 60
	Lazertinib	216	63	37	63	34	White: 38 Black: 1 Other: 2 Asian: 59 White: 37 Black: 2 Other: 2	40	1: 65 0: 35 1: 65	Exon 21 (L858R): 40 Exon 19 del: 61 Exon 21 (L858R): 39
Tomasini et al ⁷ CHRYSLIS-2 Single-arm phase I/Ib	Amivantamab + lazertinib Treatment-naïve subgroup	49	60	55	45	NR	Asian: 57 White: 39 Black: 2 Other: 2	27	0: 37 1: 63	Exon 19 del: 61 Exon 21 (L858R): 39

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NA, not available; NR, not reported; PS, performance status; RCT, randomized controlled trial.

TABLE A4. Lee et al⁵

Population: Patients with Previously Untreated *EGFR*-Mutated (exon 19 deletion or L858R) NSCLC—Subgroup Analysis
 Intervention: Osimertinib
 Comparator: Lazertinib

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Lazertinib	Osimertinib		
PFS	HR, 0.98 (95% CI, 0.79 to 1.22) Based on data from 645 participants in one study. Follow-up 22 months.	560 per 1,000 Difference: 7 fewer per 1,000 (95% CI, 83 fewer to 73 more)	553 per 1,000	Moderate Due to serious imprecision. ^a	Osimertinib probably has little or no difference on PFS.
OS	HR, 1.0 (95% CI, 0.73 to 1.38) Based on data from 645 participants in one study. Follow-up 22 months.	292 per 1,000 Difference: 0 fewer per 1,000 (95% CI, 69 fewer to 87 more)	292 per 1,000	Low Due to serious imprecision and serious indirectness. ^b	Osimertinib may have little or no difference on OS.
Adverse events	Based on data from 645 participants in one study. Follow-up 22 months.	The most common TEAEs for lazertinib and osimertinib were rash (45% v 31%), diarrhea (32% v 44%), and paronychia (29% v 28%), respectively. Grade 3 or higher AEs were reported in 46% of the participants treated with lazertinib and 43% of the participants treated with osimertinib. Serious AEs were reported in 35% of the participants treated with lazertinib and 33% of the participants treated with osimertinib.		Moderate Due to serious imprecision. ^c	Adverse events for both arms were mostly grade 1 to 2 and frequently related to <i>EGFR</i> inhibition. Lazertinib was associated with lower rates of QT interval prolongation versus osimertinib.

Abbreviations: AEs, adverse events; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TEAEs, treatment-emergent adverse events.

^aImprecision: serious. Wide CIs, only data from one study.

^bIndirectness: serious due to interim analysis and median OS not reached for both arms. Imprecision: serious. Wide CIs, only data from one study.

^cImprecision: serious. Only data from one study.

TABLE A5. Tomasini et al⁷

Population: Patients With Atypical *EGFR*-Mutated Advanced NSCLC
 Intervention: Amivantamab + Lazertinib
 Comparator: Not Applicable

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Not Applicable	Amivantamab + Lazertinib		
Response	Based on data from 49 participants in one study. Follow-up 17.3 months.	The investigator-assessed ORR was 57% (95% CI, 42 to 71). The median DoR was 20.7 months (95% CI, 9.9 to NE), and the CBR was 84% (95% CI, 70 to 93).		Very low Due to serious imprecision. ^a	Amivantamab + lazertinib may improve response.
Adverse events	Based on data from 49 participants in one study. Follow-up 17.3 months.	Individual TEAEs most commonly reported by participants were rash (67%), paronychia (67%), hypoalbuminemia (59%), and IRRs (56%), and were mostly grade 1 and 2. The majority (95%) of IRRs occurred during the first infusion and were grade 1 and 2. Overall, grade ≥ 3 TEAEs were reported in 73 (70%) participants. Fifty (48%) participants experienced grade ≥ 3 treatment-related AEs. VTE was reported in 31 (30%) participants.		Very low Due to serious imprecision. ^b	Adverse events were consistent with previous studies and primarily grade 1 and 2.

Abbreviations: AEs, adverse events; CBR, clinical benefit rate; DoR, duration of response; IRRs, infusion-related reactions; NE, not estimable; ORR, overall response rate; TEAEs, treatment-emergent adverse events; VTE, venous thromboembolism.

^aImprecision: serious. Only data from one study, and low number of patients.

^bImprecision: serious. Only data from one study.

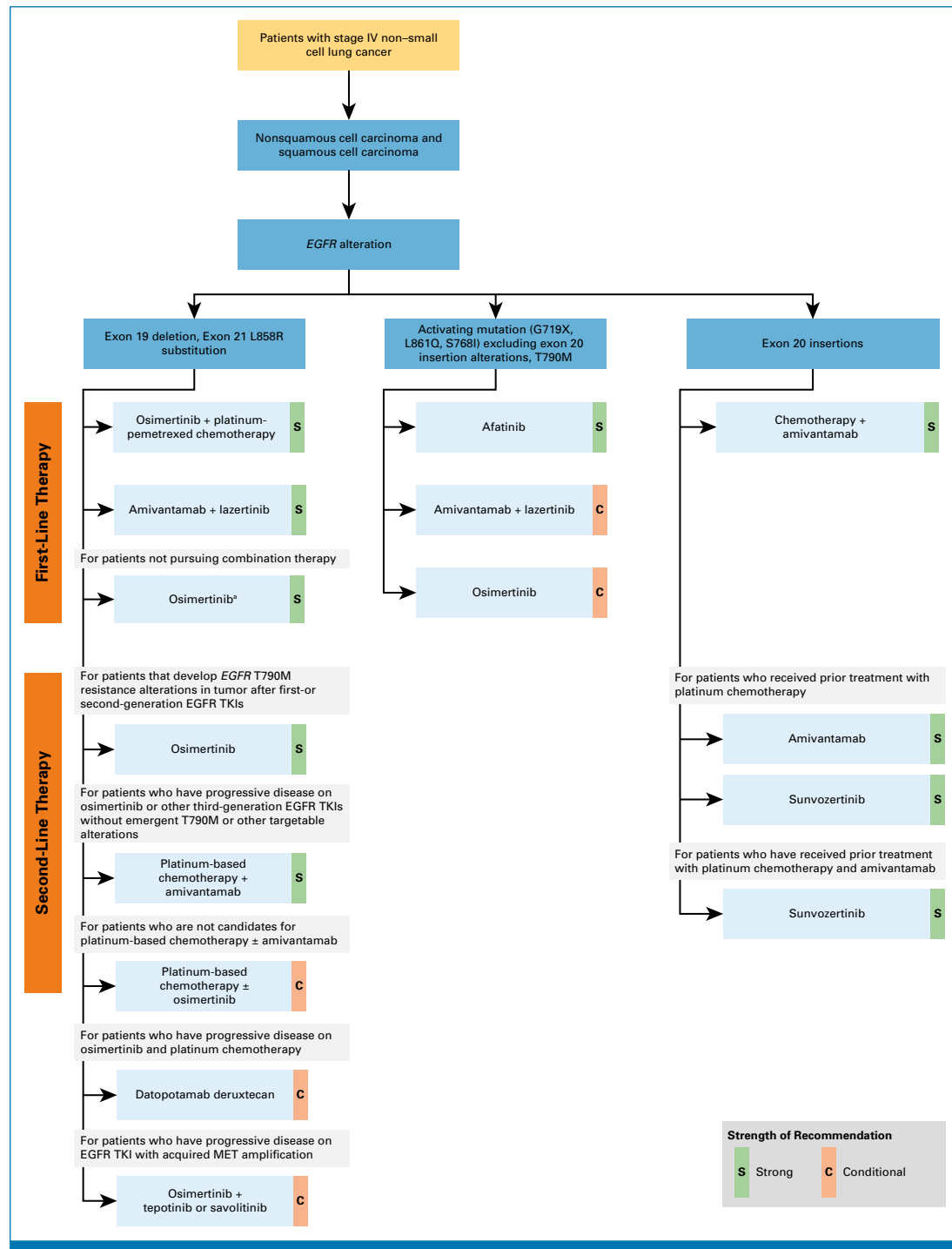


FIG A1. Treatment options for patients with stage IV NSCLC with *EGFR* alterations. For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored to each patient incorporating both efficacy and 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 patients unable to access osimertinib, lazertinib monotherapy may be offered as an alternative treatment option. EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitor.