

Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2024.3

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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 [2](#)). Updates are published regularly and can be found at <https://ascopubs.org/nsclc-da-living-guideline>.

ACCOMPANYING CONTENT

 Listen to the podcast by Brittany Harvey and Dr Jyoti Patel at <http://sites.libsyn.com/115284/therapy-for-stage-iv-nsclc-with-driver-alterations-asco-living-guideline-update-20243-part-2>

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 Appendix

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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) with¹ and without² driver alterations and both have been updated recently.^{3–12} Based on routine literature searches (up to September 16, 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 A1](#) (online only) 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 the Data Supplement (online only) provide additional information.

RESULTS

The guideline Expert Panel (Appendix [Table A2](#)) reviewed new evidence from three studies^{13–15} 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.^{3–6,10,12}

UPDATED RECOMMENDATIONS

EGFR Exon 19 Deletion, Exon 21 L858R Substitution

First-Line Treatment Options Update

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 for this guideline, subgroup analyses indicate patients with select high-risk features appear to derive benefit from the combination therapies in recommendation 1.1.1. The full guideline manuscript presents additional options that may be reasonable, based on the evidence reviewed in subgroup analyses. In addition, this guideline does not reflect treatment of patients who were previously treated with adjuvant tyrosine kinase inhibitors (TKIs).

Evidence review and clinical interpretation.

When discussing first-line treatment with patients with EGFR exon 19 deletion or L858R-positive NSCLC, clinicians must balance efficacy with toxicity. This approach allows for the incorporation of patient goals, preferences, and co-morbidities when making shared treatment decisions. Combination therapies are associated with increased toxicity compared to osimertinib alone; 75% of patients treated with amivantamab plus lazertinib experienced grade ≥ 3 toxicities compared to 43% with osimertinib monotherapy; 64% of patients treated with osimertinib plus chemotherapy experienced grade ≥ 3 toxicities compared to 27% with osimertinib alone.¹⁶ In addition, patients receiving regular infusion therapy also experience additional treatment visit burden and financial toxicity.

Two studies evaluating high-risk cohorts including patients with CNS metastases (including leptomeningeal disease) at baseline and those patients with co-mutations in *TP53* were reviewed.^{14,17} In a subgroup analysis of FLAURA2, 118 of 279 patients in the combination arm and 104 of 278 patients in the osimertinib monotherapy arm had CNS disease. The hazard ratio (HR) for CNS progression or death was 0.58 (95% CI, 0.33 to 1.01) favoring osimertinib plus chemotherapy, whereas for patients without baseline CNS metastases, the HR was 0.67 (95% CI, 0.43 to 1.04). The reported median CNS progression-free survival (PFS) was 30.2 months (95% CI, 28.4 months to not calculable [NC]) versus 27.6 months (95% CI, 22.1 months to NC) in the osimertinib monotherapy arm.¹⁷

An exploratory analysis from the MARIPOSA study assessed efficacy in a subset of patients with detectable circulating tumor DNA, *TP53* co-mutations, and metastases to liver and/or brain. In patients with any of these features (amivantamab-lazertinib, $n = 280$; osimertinib,

$n = 288$), median PFS was 20.3 months (95% CI, 18.2 to 24.0) for patients receiving amivantamab-lazertinib versus 15.0 months (95% CI, 13.0 to 16.8) for patients receiving osimertinib with HR 0.72 (95% CI, 0.58 to 0.90; $P = .004$). Among those without high-risk features (amivantamab-lazertinib, $n = 40$; osimertinib, $n = 28$), no statistically significant difference in PFS was observed between treatments. In the subgroup of patients with co-mutations in *TP53*, amivantamab-lazertinib had a median PFS 18.2 versus 12.9 months with osimertinib (HR, 0.65 [95% CI, 0.48 to 0.87]; $P = .003$), while there was no significant improvement for patients with wild-type *TP53* (22.1 v 19.9 months; HR, 0.75 [95% CI, 0.52 to 1.07]).¹⁴

Incorporation of chemotherapy or amivantamab in the frontline setting will impact subsequent lines of therapy and potentially resistance mechanisms. At this juncture, the optimal sequence of therapies is unknown and overall survival data have yet to mature.

Second-Line Treatment Options Update

Recommendation 2.2. For patients whose disease has progressed on osimertinib or other EGFR 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. For patients whose disease has progressed on EGFR TKIs and not treated with amivantamab and chemotherapy, chemotherapy alone $\pm$ anti-vascular endothelial growth factor (VEGF)-targeting therapy combinations may be considered for those with adenocarcinoma histology and where anti-VEGF therapy is considered 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).

Qualifying statement. 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.

Evidence review and clinical interpretation. The HARMONi-A (AK112-301) trial was a randomized, double-blind, multicenter, phase III study conducted at 55 sites in China, involving 322 patients with EGFR mutation-positive lung adenocarcinoma whose disease had progressed on EGFR TKIs. Participants were randomly assigned to receive either ivonescimab, a bispecific antibody targeting PD-1 and VEGF, combined with chemotherapy, or placebo plus chemotherapy. The trial found a significant improvement in median PFS from 4.80 months to 7.06 months (HR, 0.46; $P < .001$). Median overall survival data were not mature. The objective response rate was also higher, at 50.6%

for ivonescimab versus 35.4% for placebo ($P = .006$). Immune-related adverse events (AEs) occurred more frequently in patients treated with ivonescimab, and 61.5% of patients receiving ivonescimab experienced grade ≥ 3 treatment-emergent AEs, compared to 49.1% in placebo-chemotherapy arm.¹⁵ Considerations for interpreting these results include (1) geographically homogeneous population, (2) inclusion of patients with a broad range of *EGFR* activating mutations (beyond only classical activating mutations of exon 19 deletions and exon 21 L858R point mutation), and (3) relatively short follow-up period of 7.89 months.

Several studies have evaluated the role of targeting the VEGF pathway in patients with *EGFR*-positive NSCLC in several settings. In patients with previously treated, T790M-positive NSCLC, combination osimertinib and bevacizumab did not improve PFS compared to osimertinib alone in two randomized phase II trials,^{18,19} as well as in a trial in patients with untreated NSCLC.²⁰ However, combination therapy with osimertinib and ramucirumab was studied in the frontline setting in the randomized phase II RAMOSE trial.¹³ In an interim analysis of 139 patients treated with either osimertinib + ramucirumab ($n = 93$) or osimertinib monotherapy ($n = 46$), the median investigator-assessed PFS was 24.8 (95% CI, 17.9 to not reported) months in ramucirumab with osimertinib arm

and 15.6 (95% CI, 11.7 to 22.8) months in the osimertinib monotherapy arm (HR, 0.55 [95% CI, 0.32 to 0.93]). Grade 3 AEs were observed in 53% in ramucirumab with osimertinib versus 41% in osimertinib alone. The ongoing, randomized, phase III, National Cancer Institute–sponsored trial EA5182 will add additional data in this space.

NTRK Rearrangement

On June 16, 2024, the US Food and Drug Administration granted accelerated approval to repotrectinib for the treatment of solid tumors harboring *NTRK* gene fusion. This approval was based on the multicenter, multicohort, TRI-DENT-1 study. The Expert Panel awaits the peer-reviewed publication of this study's findings to be considered in the evidence review for the guideline updates.

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.

EQUAL CONTRIBUTION

D.H.O and J.D.P. were Expert Panel Co-Chairs.

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Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO-24-02785>.

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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.

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

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TABLE A1. All Recommendations

Driver Alteration	Recommendation	Evidence Quality	Strength of Recommendation
NOTE: 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. The following recommendations (strong or weak/conditional) and terminology (Data Supplement) 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	<i>Exon 19 deletion, Exon 21 L858R substitution</i>		
	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
	<i>Qualifying Statement:</i> Although recommendation 1.1 addresses many patients in the target population for this guideline, subgroup analyses indicate patients with select high-risk features appear to derive benefit from the combination therapies in recommendation 1.1.1. The full guideline manuscript presents additional options that may be reasonable, based on the evidence reviewed in subgroup analyses. In addition, this guideline does not reflect treatment of patients who were previously treated with adjuvant TKIs.		
	<i>Others</i>		
	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 non-driver alteration guideline	Low	Weak
	<i>Qualifying Statement:</i> Recommendations 1.2, 1.2.1, and 1.2.2 excludes 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
ALK	<i>Exon 20 insertions</i>		
	1.4. Clinicians may offer chemotherapy and amivantamab	Moderate	Strong
	1.5. If amivantamab is not available, clinicians should offer standard treatment following the non-driver alteration guideline	Moderate	Strong
ROS1	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
BRAF ^{V600E}	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
MET exon 14 skipping mutation	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 non-driver alteration guideline	Low	Strong
	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 non-driver alteration guidelines	Low	Strong

(continued on following page)

TABLE A1. 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 non-driver 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 non-driver 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/or blood-based broad multi-gene panel and an IHC assay for PD-L1 and HER2 should be universally accessible for all patients diagnosed with NSCLC		High	Strong
<i>Qualifying Statement:</i> Combination of blood and tissue testing may maximize chance of detecting molecular alterations. Tissue testing has 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 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: 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 to inform subsequent treatment. 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.			
EGFR	<i>Exon 19 deletion, Exon 21 L858R substitution</i>		
	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 whose disease has progressed 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
	<i>Qualifying Statement:</i> For patients whose disease has progressed on EGFR TKIs and not treated with amivantamab and chemotherapy, chemotherapy alone ± anti-VEGF-targeting therapy combinations may be considered for those with adenocarcinoma histology and where anti-VEGF therapy is considered safe.		
	2.2.1. For patients who have progressive disease on osimertinib (or other 3rd-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
	<i>Qualifying Statement:</i> 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>Exon 20 insertions</i>		
	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

(continued on following page)

TABLE A1. All Recommendations (continued)

Driver Alteration	Recommendation	Evidence Quality	Strength of Recommendation
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
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 non-driver 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 non-driver alteration guideline	Low	Strong
	2.10. For BRAF alterations other than BRAF V600E alterations, clinicians should offer standard therapy following the non-driver 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 non-driver 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 non-driver 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 non-driver 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 non-driver 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 growth factor receptor 2; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; PS, performance status; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

TABLE A2. Stage IV Non–Small Cell Lung Cancer Living Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Co-chairs		
Lyudmila Bazhenova, MD	University of California, San Diego, San Diego, CA	Medical oncology
Natasha B. Leighl, MD	Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada	Medical oncology
Dwight H. Owen, MD, MS	Ohio State University, Columbus, OH	Medical oncology
Jyoti D. Patel, MD	Northwestern University, Chicago, IL	Medical oncology
Panel members		
Fawzi Abu Rous, MD	Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI	Medical oncology
Amith Ahluwalia, MD	Confluence Health Wenatchee Valley Hospital and Clinics, Wenatchee, WA	Medical oncology
Krishna Alluri, MD	Texas Oncology, San Antonio, TX	Medical oncology
Ibrahim Hanna Azar, MD	IHA Hematology Oncology Consultants, Ypsilanti, MI	Medical oncology
Greg Durm, MD	Indiana University Health, Indianapolis, IN	Medical oncology
Jill Feldman, MA	EGFR Resisters patient advocacy group, Deerfield, IL	Patient research advocate
Narjust Florez, MD	Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	Medical oncology
Janet Freeman-Daily, MSc, Engr	The ROS1ders, Seattle, WA	Patient Research Advocate
Naoki Furuya, MD, PhD	St Marianna University School of Medicine, Kawasaki, Japan	Medical oncology
Shirish Gadgeel, MD	Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI	Medical oncology
Balazs Halmos, MD	Montefiore Einstein Comprehensive Center for Cancer Care, Bronx, NY	Medical oncology
Sara Kuruvilla, MD (Ontario Health representative)	London Health Sciences Center, London, ON, Canada	Medical oncology
Narinder Malhotra, MD	Medicus Healthcare Solutions, Windham, NH	Medical oncology
Kristen Ashley Marrone, MD	John Hopkins Medical Center, Baltimore, MD	Medical oncology
Deebye Raj Mishra, MD	BP Koirala Institute of Health Sciences, Kathmandu, Nepal	Pulmonology
Michael Mullane, MD	Aurora Cancer Care, Mount Pleasant, WI	Medical oncology
Jarushka Naidoo, MBBCh	Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD	Medical oncology
Bruna Pellini, MD	Moffitt Cancer Center, Tampa, FL	Medical oncology
Carolyn J. Presley, MD MHS	Ohio State University, Comprehensive Cancer Center and The James Cancer Hospital/Solove Research Institute, Columbus, OH	Medical oncology Geriatric oncology
Sonam Puri, MD	Moffitt Cancer Center, Tampa, FL	Medical oncology
Angel Qin, MD	University of Michigan Health System, Ann Arbor, MI	Medical oncology
Joshua Reuss, MD	Georgetown University, Washington, DC	Medical oncology
Logan Roof, MD	Ohio State University, Columbus, OH	Medical oncology
Erin L. Schenk, MD, PhD	University of Colorado Anschutz Medical Center, Aurora, CO	Medical oncology
Lecia Sequist, MD, MPH	Massachusetts General Hospital, Boston, MA	Medical oncology
Navneet Singh, MD, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Medical oncology
Eric K. Singhi, MD	University of Texas MD Anderson Cancer Center, Houston, TX	Medical oncology
Ana I. Velazquez, MD, MSc	University of California, San Francisco, CA	Medical oncology
Yubao Wang, MD, PhD	Lovelace Cancer Care, Albuquerque, NM	Medical oncology
Paul Wheatley Price, MD, MBChB	The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada	Medical oncology
Nofisat Ismaila, MD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO practice guidelines staff (health research methods)

TABLE A3. Characteristics of Studies Identified in the Literature Search Since Last Update

Author Year Reference	Interventions and Comparisons	Patients, No.	Patient Characteristics					Disease Characteristics		
			Median Age, Years	Sex, %		% Smokers	Race or Ethnicity, %	History of Brain Metastasis, %	ECOG PS, %	EGFR Mutation, %
				Male	Female					
Phase III RCTs										
Cho et al ¹⁶ 2024	Amivantamab-lazertinib v	429	64	36	64	30	Asian: 58 White: 38	41	0: 33 1: 67	Ex19del: 60 L858R: 40
Felip et al ¹⁴ 2024 MARIPOSA	Osimertinib	429	63	41	59	31	American Indian or Alaska Native: 2 Black:1 Others: 1 Asian: 59 White: 38 American Indian or Alaska Native: 2 Black: 1 Others: 1	40	0: 35 1: 65	Ex19del: 60 L858R: 40
Fang et al ¹⁵ 2024 HARMONi-A	Ivonescimab + chemotherapy v	161	59.6	48	52	NR	NR	22	0: 15 1: 85	Ex19del: 57 L858R: 37
	Placebo + chemotherapy	161	59.4	49	51			23	0: 21 1: 79	Other: 22 T790M: 16 Ex19del: 48 L858R: 48 Other: 16 T790M: 11
Le et al ¹³ 2024 RAMOSE	Ramucirumab + osimertinib v	93	65	29	71	31	White: 64 Asian: 26 Black: 3	43	0: 33 1: 67	Ex19del: 69 L858R: 31
	Osimertinib	46	65	28	72	35	Others: 6 White: 56 Asian: 22 Black: 4 Others: 17	52	0: 39 1: 61	Ex19del: 70 L858R: 30

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NR, not reported.

TABLE A4. Untreated *EGFR*-Mutated (exon 19 deletion or L858R): Amivantamab-Lazertinib Versus Osimertinib Subgroup Analysis

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Osimertinib	Amivantamab-Lazertinib		
PFS—ctDNA	HR 0.68 (95% CI, 0.53 to 0.86) Based on data from 540 participants in one study Follow-up 22 months	569 per 1,000 Difference: 133 fewer per 1,000 (95% CI, 209 fewer to 54 fewer)	436 per 1,000	Moderate Due to serious imprecision ^a	Amivantamab-lazertinib probably improves PFS in patients with detectable baseline ctDNA
PFS-TP53	HR: 0.65 (95% CI, 0.48 to 0.87) Based on data from 293 participants in one study Follow-up 22 months	472 per 1,000 Difference: 132 fewer per 1,000 (95% CI, 208 fewer to 46 fewer)	340 per 1,000	Low Due to serious imprecision, due to serious indirectness ^b	Amivantamab-lazertinib may improve PFS in patients with TP53 comutations
PFS wild-type TP53	HR: 0.75 (95% CI, 0.52 to 1.07) Based on data from 247 participants in one study Follow-up 22 months	731 per 1,000 Difference: 105 fewer per 1,000 (95% CI, 236 fewer to 24 more)	626 per 1,000	Low Due to serious imprecision, due to serious indirectness ^b	Amivantamab-lazertinib may improve PFS in patients with wild-type TP53

Abbreviations: AE, adverse event; ctDNA, circulating tumor DNA; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.

^aImprecision: serious. Only data from one study.

^bIndirectness: serious. Due to smaller sample size for subgroup analysis. Imprecision: serious. Only data from one study.

TABLE A5. Patients Who Have Progressive Disease on First- or Second-Generation EGFR Tyrosine Kinase Inhibitor Therapy: Ivonescimab + Chemotherapy Versus Placebo + Chemotherapy

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Placebo + Chemotherapy	Ivonescimab + Chemotherapy		
PFS	HR: 0.46 (95% CI, 0.34 to 0.62) Based on data from 322 participants in one study Follow-up 7.89 months	671 per 1,000 Difference: 271 fewer per 1,000 (95% CI, 356 fewer to 173 fewer)	400 per 1,000	Moderate Due to serious imprecision ^a	Ivonescimab + chemotherapy probably improves PFS
PFS Patients with brain metastases	HR: 0.4 (95% CI, 0.22 to 0.73) Based on data from 72 participants in one study Follow-up 7.89 months	757 per 1,000 Difference: 325 fewer per 1,000 (95% CI, 490 fewer to 113 fewer)	432 per 1,000	Low Due to serious imprecision, due to serious indirectness ^b	Ivonescimab + chemotherapy probably improves PFS in patients with brain metastasis
PFS Patients without brain metastases	HR: 0.48 (95% CI, 0.34 to 0.69) Based on data from 250 participants in one study Follow-up 7.89 months	645 per 1,000 Difference: 253 fewer per 1,000 (95% CI, 348 fewer to 134 fewer)	392 per 1,000	Low Due to serious imprecision, due to serious indirectness ^b	Ivonescimab + chemotherapy probably improves PFS in patients without brain metastasis
Safety	Based on data from 322 participants in one study Follow-up 7.89 months	Grade 3 or higher treatment-emergent AEs occurred in 99 patients (61.5%) in the ivonescimab group v 79 patients (49.1%) in the placebo group, the most common of which were chemotherapy-related		Moderate Due to serious imprecision ^a	Grade 3 or higher immune-related AEs occurred in 10 patients (6.2%) in the ivonescimab group v four (2.5%) in the placebo group. Grade 3 or higher VEGF-related AEs occurred in five patients (3.1%) in the ivonescimab group v four (2.5%) in the placebo group
Objective response	Based on data from 322 participants in one study Follow-up 7.89 months	ORR was 50.6% (95% CI, 42.6% to 58.6%) with ivonescimab and 35.4% (95% CI, 28.0% to 43.3%) with placebo (difference, 15.6% [95% CI, 5.3% to 26.0%]; <i>P</i> = .006)		Moderate Due to serious imprecision ^a	Ivonescimab + chemotherapy probably improves objective response

Abbreviations: AEs, adverse events; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

^aImprecision: serious. Only data from one study.

^bIndirectness: serious. Due to smaller sample size for subgroup analysis. Imprecision: serious. Only data from one study.

TABLE A6. Patients With Tyrosine Kinase Inhibitor–Naïve Metastatic EGFR-Mutant Non–Small Cell Lung Cancer: Ramucirumab + Osimertinib Versus Osimertinib

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Osimertinib	Ramucirumab + Osimertinib		
PFS	HR 0.55 (95% CI, 0.32 to 0.93) Based on data from 139 participants in one study Follow-up 16.6 months	421 per 1,000 Difference: 161 fewer per 1,000 (95% CI, 261 fewer to 23 fewer)	260 per 1,000	Low Due to serious risk of bias, due to serious imprecision ^a	Ramucirumab + osimertinib may improve PFS
Safety	Based on data from 139 participants in one study Follow-up 16.6 months	Grade 3 AEs were observed in 53% in ramucirumab with osimertinib in arm A v 41% in osimertinib alone in arm B. Diarrhea, fatigue, headache, and cough were the most common AEs in arm A, whereas diarrhea, fatigue, and rash were the most common AEs in arm B		Low Due to serious risk of bias, due to serious imprecision ^a	There was no grade 5 AE, and one grade 4 AE, of hyponatremia in arm A (not attributed to ramucirumab)

Abbreviations: AE, adverse event; HR, hazard ratio; PFS, progression-free survival.

^aRisk of bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Imprecision: serious. Only data from one study, low number of patients.

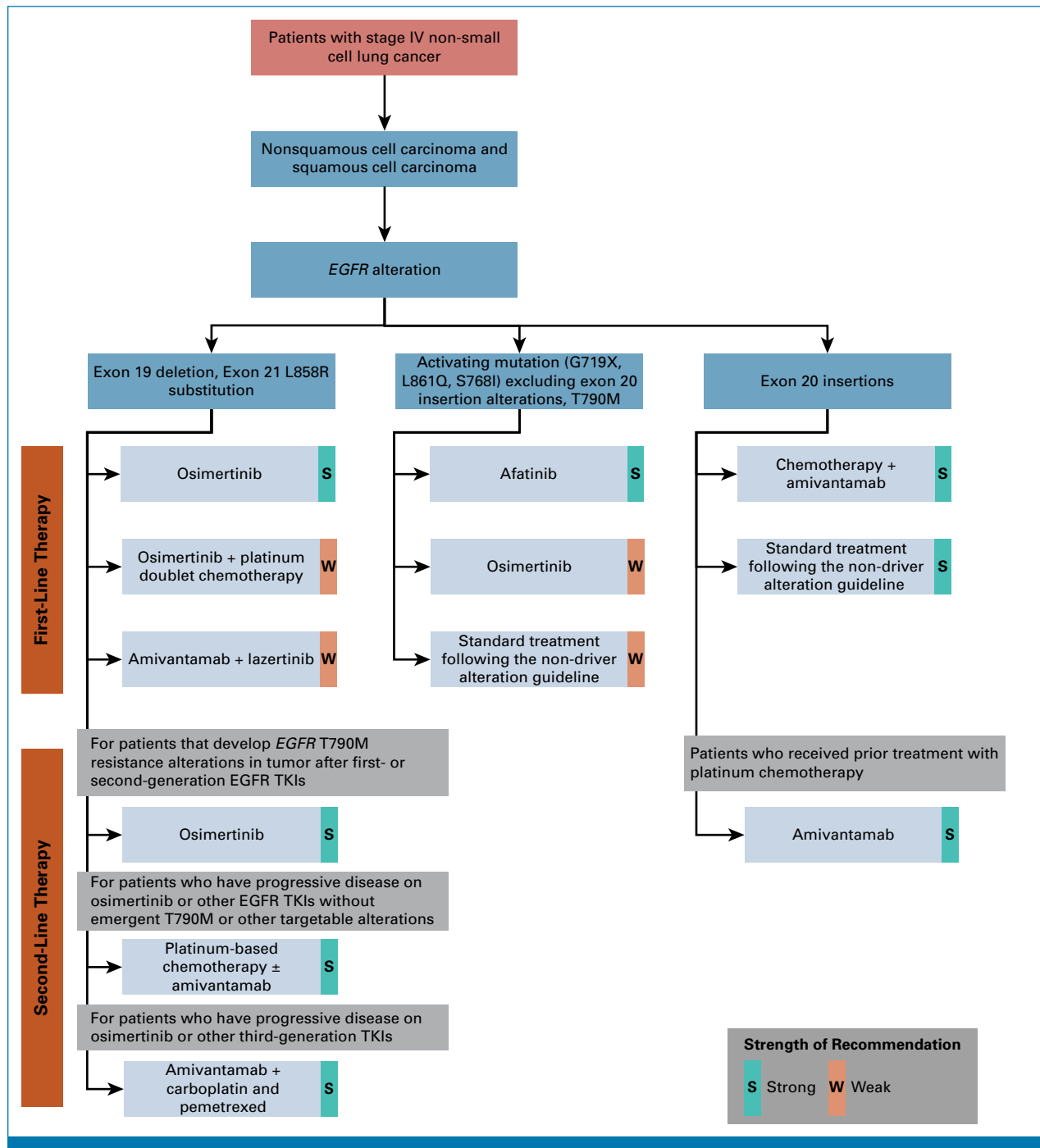


FIG A1. Treatment options for patients with stage IV non-small cell lung cancer with EGFR alterations. For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored to each patient incorporating 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 non-driver alteration guideline. For alterations without targeted therapy options, refer to the non-driver alteration guideline, "Therapy for Stage IV Non-Small Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline."^{2,7,8,9,11} New active targeted therapies are anticipated soon. EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitor.