Therapy for Stage IV Non–Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2024.1

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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 provider and do not account for individual variation among patients. See appendix for disclaimers and other important information (Appendix 1 and Appendix 2). 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[1] and without driver alterations[2] and both have been updated recently.[3-11] Based on routine literature searches (up to January 19, 2024), this version of the stage IV NSCLC with driver alterations living guideline reviews new evidence to assess if recommendations are up to date.

The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) and Data Supplement (online only) provide additional information.

RESULTS

The guideline Expert Panel (Appendix Table A1; online only) reviewed new evidence from seven studies that met the systematic review inclusion criteria[12-18] (Appendix Tables A3-A9) and reviewed and approved the updated recommendations. Evidence supporting unchanged recommendations is reviewed in previous publications of this guideline.[3-6]

UPDATED RECOMMENDATIONS

EGFR Exon 19 Deletion, Exon 21 L858R Substitution

First-Line Treatment Options Update

Recommendation 1.1.1. Clinicians may offer osimertinib with chemotherapy. (Evidence quality: Moderate; Strength of recommendation: Weak)

Second-Line and Subsequent Treatment Options Update

Recommendation 2.2.1. For patients who progressed on osimertinib (or other third-generation tyrosine kinase inhibitor [TKI]), clinicians may offer amivantamab plus carboplatin and pemetrexed. (Evidence quality: Moderate; Strength of recommendation: Strong)

In the FLAURA-2 trial, 557 patients with *EGFR*-mutated (exon 19 deletion or L858R exon 21 mutation) advanced NSCLC were randomly assigned 1:1 to receive osimertinib alone or with platinum doublet chemotherapy. Progression-free survival (PFS) was longer with osimertinib plus chemotherapy (hazard ratio [HR], 0.62 [95% CI, 0.49 to 0.79];

$P < .0001$). In patients with CNS metastases at baseline, median PFS was longer with osimertinib plus chemotherapy (24.9 months *v* 13.8 months and in patients with L858R exon 21 mutations (24.7 months *v* 13.9 months). Toxicity was higher with osimertinib plus chemotherapy (grade ≥3 adverse events [AEs] 64% *v* 27%).[13]

In the MARIPOSA trial, to our knowledge, to date only published as a conference abstract,[19] treatment-naïve patients with advanced NSCLC and classic *EGFR* mutations were allocated 1:1 to receive amivantamab plus lazertinib (n = 429) or osimertinib monotherapy (n = 429). Median PFS was longer with amivantamab plus lazertinib versus osimertinib (27.5 months *v* 18.5 months; HR, 0.68; $P < .001$) with more toxicity (grade ≥3 treatment-related AEs 73% *v* 43%). Given multiple treatment options with differences in toxicity profiles and no reported difference in overall survival (OS), the panel recommends most patients receive osimertinib monotherapy and tailoring frontline treatment after discussing benefits and toxicities with each patient. Some patients (eg, CNS metastases at baseline) may benefit from combination strategies, as observed in FLAURA-2.[13]

In the MARIPOSA-2 trial, 657 patients who experienced disease progression on osimertinib[16] were randomly assigned 2:2:1 to amivantamab plus lazertinib plus chemotherapy, chemotherapy, or amivantamab plus chemotherapy. The median PFS was 6.3 months with amivantamab plus chemotherapy, 8.3 months with amivantamab plus lazertinib plus chemotherapy, and 4.2 months with chemotherapy (amivantamab plus chemotherapy *v* chemotherapy arm PFS HR, 0.48 [95% CI, 0.36 to 0.64]; $P < .001$). There was no difference in OS between arms. Serious treatment-emergent AEs were observed in 32% of patients treated with amivantamab plus chemotherapy, 52% with amivantamab plus lazertinib plus chemotherapy, and 20% with chemotherapy.

In the ATTLAS trial, 228 patients (*EGFR* n = 215, *ALK* n = 13) who experienced disease progression or intolerance to one or more EGFR or ALK TKIs were randomly assigned 2:1 to either atezolizumab plus bevacizumab, paclitaxel, and carboplatin (ABCP) or to pemetrexed plus platinum.[15] Median PFS was longer in the patients treated with ABCP versus chemotherapy (8.48 *v* 5.62 months; HR, 0.62 [95% CI, 0.45 to 0.86]; $P = .004$). There was no difference in OS. In subgroup analysis of patients with *EGFR* exon 19 deletion, there was no significant difference in PFS (HR, 0.69 [95% CI, 0.44 to 1.08]; $P = .101$), whereas there was for patients with *EGFR* exon 21 L858R mutation (HR, 0.52 [95% CI, 0.31 to 0.88]; $P = .012$). Grade 3 or higher treatment-related AEs were 35.1% in the ABCP arm and 14.9% in the chemotherapy-alone arm.

Both MARIPOSA-2 and ATTLAS demonstrated improvement in PFS but not OS compared with platinum chemotherapy alone with significantly increased toxicity including serious AEs. The panel recommends that platinum-doublet chemotherapy be offered for most patients who experience progression after osimertinib, given the lack of OS difference and increased toxicity profiles seen, although the above regimens offer additional treatment options.

ROS1

First-line treatment options update.

Recommendation 1.8. Clinicians may offer repotrectinib, entrectinib, or crizotinib (Evidence quality: Moderate; Strength of recommendation: Strong).

Recommendation 1.9. If crizotinib, entrectinib, or repotrectinib are not available or not tolerated, clinicians may offer ceritinib or lorlatinib (Evidence quality: Low; Strength of recommendation: Weak).

Second-Line and Subsequent Treatment Options Update

Recommendation 2.6. For patients who have previously received crizotinib, entrectinib, lorlatinib, or ceritinib, clinicians may offer repotrectinib (Evidence quality: Moderate; Strength of recommendation: Strong).

In the single-arm TRIDENT-1 trial of repotrectinib, 426 patients received the recommended phase II dose of 160 mg by mouth once daily for 14 days, followed by 160 mg twice daily.[18] Its results support repotrectinib use for TKI-naïve patients, previously treated patients who have acquired resistance to TKIs and patients who have brain metastases. In 71 patients who were treatment-naïve, the response rate (RR) was 79%, the median duration of response (DOR) was 34.1 months, and the median PFS was 35.7 months. In 56 patients who received one prior ROS1 TKI but no prior chemotherapy, the RR was 38%, the median DOR was 14.8 months, and the median PFS was 9.0 months. Of note, 10 of 17 patients who had the *ROS1* G2032R resistance mutation (most common on-target ROS1 resistance mechanism) responded to repotrectinib. In patients with baseline CNS metastases, intracranial responses occurred in eight of nine TKI-naïve patients and 5 of 13 patients who received one prior ROS1 TKI and no chemotherapy. Most AEs were low grade and manageable with dose reductions or interruptions.

Refer to Appendix Table A2 for the full list of recommendations and Appendix Figures A1 and A2 for the updated algorithms.

ASCO believes cancer clinical trials are vital to inform medical decisions and improve cancer care, and 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.net.

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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.net, is available at www.asco.org/living-guidelines.

EQUAL CONTRIBUTION

D.H.O. and N.B.L. were Expert Panel co-chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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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 NSCLC Living Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Co-chairs		
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TABLE A2. All Recommendations

Driver Alteration	Recommendation	Evidence Quality	Strength of Rec
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			
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	High	Strong
	1.1.1. or may offer osimertinib with chemotherapy	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 tyrosine kinase inhibitors 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 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
	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 repotrectinib, entrectinib, or crizotinib	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
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

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TABLE A2. All Recommendations (continued)

Driver Alteration	Recommendation	Evidence Quality	Strength of Rec
	1.19. For patients with a poor PS, tyrosine kinase inhibitor may be offered based on drug access and toxicity profile	Low	Weak
	1.20. Comprehensive genomic biomarker test results should be available and used to guide treatment	High	Strong
	Qualifying statement: PD-L1 IHC alone should not be used to guide treatment decisions		
	1.21. 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	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 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 progressed on osimertinib (or other EGFR TKIs without emergent T790M or other targetable alterations), clinicians should offer platinum-based chemotherapy following the nondriver alteration guideline	Moderate	Strong
	2.2.1. For patients who progressed on osimertinib (or other third-generation TKI), clinicians may offer amivantamab plus carboplatin and pemetrexed	Moderate	Strong
	Qualifying statement: Anti–PD-(L)1 agents with platinum chemotherapy are not recommended although other emerging combination strategies may be considered and are discussed in manuscript		
	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
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

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TABLE A2. All Recommendations (continued)

Driver Alteration	Recommendation	Evidence Quality	Strength of Rec
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	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		

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. *EGFR* Mutations (exon 19 deletions or L858R)—Amivantamab-Chemotherapy Versus Chemotherapy[16]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Chemotherapy	Amivantamab-Chemotherapy		
PFS	HR: 0.48 (95% CI, 0.36 to 0.64) Based on data from 394 participants in one study Follow-up, 8.7 months	650 per 1,000	396 per 1,000	High	Amivantamab-chemotherapy improves PFS
		Difference: 254 fewer per 1,000 (95% CI, 335 fewer to 161 fewer)			
OS	HR: 0.77 (95% CI, 0.49 to 1.21) Based on data from 394 participants in one study Follow-up, 8.7 months	650 per 1,000	554 per 1,000	Moderate[a]	Amivantamab-chemotherapy has little or no effect on OS
		Difference: 96 fewer per 1,000 (95% CI, 248 fewer to 69 more)			
Intracranial PFS	HR: 0.55 (95% CI, 0.38 to 0.79) Based on data from 394 participants in one study Follow-up, 8.7 months	658 per 1,000	446 per 1,000	High	Amivantamab-chemotherapy improves intracranial PFS
		Difference: 212 fewer per 1,000 (95% CI, 323 fewer to 86 fewer)			
ORR	OR: 3.1 (95% CI, 2.0 to 4.8) Based on data from 394 participants in one study Follow-up, 8.7 months	402 per 1,000	676 per 1,000	High	Amivantamab-chemotherapy improves ORR
		Difference: 274 more per 1,000 (95% CI, 171 more to 361 more)			

Abbreviations: HR, hazard ratio; NGS, next-generation sequencing; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
[a]Certainty of evidence is impacted by relatively short follow-up and interim nature of these results.

TABLE A4. *EGFR* Mutations (exon 19 deletions or L858R)—Amivantamab-Lazertinib-Chemotherapy Versus Chemotherapy[16]

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) Based on data from 526 participants in one study Follow-up, 8.7 months	650 per 1,000	370 per 1,000	High	Amivantamab-lazertinib-chemotherapy improves PFS
		Difference: 280 fewer per 1,000 (95% CI, 343 fewer to 205 fewer)			
OS	HR: 0.96 (95% CI, 0.67 to 1.35) Based on data from 526 participants in one study Follow-up, 8.7 months	650 per 1,000	635 per 1,000	High	Amivantamab-lazertinib-chemotherapy has little or no difference on OS
		Difference: 15 fewer per 1,000 (95% CI, 145 fewer to 108 more)			
Intracranial PFS	HR: 0.58 (95% CI, 0.44 to 0.78) Based on data from 526 participants in one study Follow-up, 8.7 months	659 per 1,000	464 per 1,000	High	Amivantamab-lazertinib-chemotherapy improves intracranial PFS
		Difference: 195 fewer per 1,000 (95% CI, 282 fewer to 91 fewer)			
ORR	OR: 2.97 (95% CI, 2.08 to 4.24) Based on data from 526 participants in one study Follow-up, 8.7 months	361 per 1,000	627 per 1,000	High	Amivantamab-lazertinib-chemotherapy improves ORR
		Difference: 266 more per 1,000 (95% CI, 179 more to 344 more)			

Abbreviations: HR, hazard ratio; OR, odds ratio; ORR, objective response rate; OS, overall survival PFS, progression-free survival.

TABLE A5. *EGFR* Exon 19 Deletions or Exon 21 Leu858Arg—Befotertinib Versus Oral Icotinib[14]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Oral Icotinib	Befotertinib		
PFS	HR: 0.49 (95% CI, 0.36 to 0.68) Based on data from 362 participants in one study Follow-up, 20.7 months	567 per 1,000	336 per 1,000	Moderate Due to serious indirectness[a]	Befotertinib probably improves PFS
		Difference: 231 fewer per 1,000 (95% CI, 307 fewer to 133 fewer)			
Grade ≥3 AEs	Based on data from 362 participants in one study Follow-up, 20.7 months	Grade 3 or higher treatment-related AEs occurred in 55 (30%) of 182 patients in the befotertinib group and in 14 (8%) of 180 patients in the icotinib group. Treatment-related serious AEs were reported in 37 (20%) patients in the befotertinib group and in five (3%) patients in the icotinib group. Two (1%) patients in the befotertinib group and one (1%) patient in the icotinib group died due to treatment-related AEs		Moderate Due to serious indirectness[b]	Befotertinib probably worsens grade ≥3 AEs

Abbreviations: AEs, adverse events; HR, hazard ratio; PFS, progression-free survival.
[a]Primary study. Baseline/comparator primary study.
[b]Indirectness: serious. The outcome time frames in studies were insufficient.

TABLE A6. *EGFR*-Mutated Advanced NSCLC—Osimertinib Plus Platinum-Pemetrexed Versus Osimertinib Monotherapy[13,17]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Osimertinib Monotherapy	Osimertinib Plus Platinum-Pemetrexed		
PFS	HR: 0.62 (95% CI, 0.48 to 0.8) Based on data from 557 participants in one study Follow-up, 22.2 months	597 per 1,000	431 per 1,000 Difference: 166 fewer per 1,000 (95% CI, 243 fewer to 80 fewer)	High	Osimertinib plus platinum-pemetrexed improves PFS
CNS PFS (CNS full analysis set)	HR: 0.58 (95% CI, 0.33 to 1.01) Based on data from 222 participants in one study Follow-up, 20.1 months	298 per 1,000	186 per 1,000 Difference: 112 fewer per 1,000 (95% CI, 188 fewer to 2 more)	Moderate[a]	Osimertinib plus platinum-pemetrexed probably improves CNS PFS (CNS full analysis set) slightly
CNS PFS (CNS evaluable for response set)[3]	HR: 0.4 (95% CI, 0.19 to 0.84) Based on data from 78 participants in one study Follow-up, 20.1 months	474 per 1,000	227 per 1,000 Difference: 247 fewer per 1,000 (95% CI, 359 fewer to 57 fewer)	Moderate[a]	Osimertinib plus platinum-pemetrexed probably improves CNS PFS (CNS evaluable for response set)
CNS ORR (CNS full analysis set)	OR: 1.19 (95% CI, 0.67 to 2.14) Based on data from 222 participants in one study Follow-up, 20.1 months	692 per 1,000	728 per 1,000 Difference: 36 more per 1,000 (95% CI, 91 fewer to 136 more)	High	Osimertinib plus platinum-pemetrexed probably improves CNS ORR (CNS full analysis set)
CNS ORR (CNS evaluable-for-response set)	OR: 1.06 (95% CI, 0.28 to 4.0) Based on data from 78 participants in one study Follow-up, 20.1 months	868 per 1,000	875 per 1,000 Difference: 7 more per 1,000 (95% CI, 220 fewer to 95 more)	High	Osimertinib plus platinum-pemetrexed has little or no difference on CNS ORR (CNS evaluable for response set)
ORR	Based on data from 557 participants in one study Follow-up, 22.2 months	An objective response as assessed by the investigator was observed in 83% of the patients (95% CI, 78 to 87) in the osimertinib–chemotherapy group and in 76% of those (95% CI, 70 to 80) in the osimertinib group. An objective response as assessed according to blinded independent central review occurred in 92% (95% CI, 88 to 95) and 83% (95% CI, 78 to 87), respectively		High	Osimertinib plus platinum-pemetrexed improves ORR
Grade ≥3 AEs	Based on data from 557 participants in one study[5] Follow-up, 22.2 months	AEs were reported in 276 patients (100%) in the osimertinib–chemotherapy group and in 268 (97%) in the osimertinib group. Grade ≥3 AEs were reported in 176 patients (64%) in the osimertinib–chemotherapy group and in 75 (27%) in the osimertinib group		High	Osimertinib plus platinum-pemetrexed increases grade ≥3 AEs

Abbreviations: AEs, adverse events; HR, hazard ratio; OR, odds ratio; ORR, objective RR; PFS, progression-free survival.
[a]Indirectness: serious. The outcome time frames in studies were insufficient.

TABLE A7. *EGFR* Mutation or *ALK* Translocation-Atezolizumab Plus ABCP Versus Pemetrexed Plus Carboplatin or Cisplatin[15]

Outcome Timeframe	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		PC Arm	ABCP		
PFS	HR: 0.62 (95% CI, 0.45 to 0.86) Based on data from 228 participants in one study Follow-up, 26.1 months	851 per 1,000	693 per 1,000 Difference: 158 fewer per 1,000 (95% CI, 276 fewer to 46 fewer)	High	ABCP improves PFS
OS	HR: 1.01 (95% CI, 0.69 to 1.46) Based on data from 228 participants in one study Follow-up, 26.1 months	568 per 1,000	572 per 1,000 Difference: 4 more per 1,000 (95% CI, 128 fewer to 138 more)	High	ABCP has little or no difference on OS
TRAEs	Based on data from 228 participants in one study Follow-up, 26.1 months	Any TRAEs were observed in 96.7% of the ABCP arm and 75.7% of the PC arm. Incidences of grade 3 or higher TRAEs were 35.1% in the ABCP arm and 14.9% in the PC arm		High	ABCP increases TRAEs
ORR	Based on data from 228 participants in one study Follow-up, 26.1 months	ORRs (69.5% *v* 41.9%, $P < .001$) were significantly better in the ABCP than PC arm		High	ABCP slightly improves ORR

Abbreviations: ABCP, atezolizumab plus bevacizumab, paclitaxel, and carboplatin; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PC, pemetrexed plus carboplatin; TRAEs, treatment-related adverse events.

TABLE A8. Previously Treated *HER2*-Mutant Metastatic Non–Small Cell Lung Cancer—Trastuzumab Deruxtecan 5.4 mg/kg IV Once Every 3 Weeks Versus Trastuzumab Deruxtecan 6.4 mg/kg IV Once Every 3 Weeks[12]

		Absolute Effect Estimates			
Outcome	Study Results and Measurements	T-DXd 6.4 mg/kg IV once every 3 weeks	T-DXd 5.4 mg/kg IV once every 3 weeks	Quality of Evidence	Summary
ORR	Based on data from 152 participants in one study Follow-up, 11.5 months (range, 1.1-20.6) with 5.4 mg/kg IV once every 3 weeks and 11.8 months (range, 0.6-21.0) with 6.4 mg/kg IV once every 3 weeks	Confirmed ORR was 49.0% (95% CI, 39.0 to 59.1) and 56.0% (95% CI, 41.3 to 70.0) and median duration of response was 16.8 months (95% CI, 6.4 to NE) and NE (95% CI, 8.3 to NE) with 5.4 and 6.4 mg/kg IV once every 3 weeks, respectively. Median treatment duration was 7.7 months (range, 0.7-20.8) with 5.4 mg/kg IV once every 3 weeks and 8.3 months (range, 0.7-20.3) with 6.4 mg/kg IV once every 3 weeks		Moderate Due to serious indirectness[a]	T-DXd 5.4 mg/kg IV once every 3 weeks probably improves ORR
Grade ≥3 AEs	Based on data from 152 participants in one study Follow-up, 11.5 months (range, 1.1-20.6) with 5.4 mg/kg IV once every 3 weeks and 11.8 months (range, 0.6-21.0) with 6.4 mg/kg IV once every 3 weeks	Grade ≥ 3 drug-related treatment-emergent AEs occurred in 39 of 101 (38.6%) and 29 of 50 (58.0%) patients with 5.4 and 6.4 mg/kg IV once every 3 weeks, respectively. 13 of 101 (12.9%) and 14 of 50 (28.0%) patients had adjudicated drug-related interstitial lung disease (2.0% grade ≥ 3 in each arm) with 5.4 and 6.4 mg/kg IV once every 3 weeks, respectively		Moderate Due to serious indirectness[b]	T-DXd 5.4 mg/kg IV once every 3 weeks probably decreases grade ≥3 AEs

Abbreviations: AEs, adverse events; NE, not estimable; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.
[a]Indirectness: serious. Direct comparisons with other therapies not available.
[b]Indirectness: serious. Direct comparisons not available.

TABLE A9. *ROS1*, *NTRK1–3*, or *ALK* Gene Fusions—Repotrectinib[18]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		None	Repotrectinib		
ORR	Based on data from 127 participants in one study[1] Follow-up, 24 months		Response occurred in 56 of the 71 patients (79%; 95% CI, 68 to 88) with *ROS1* fusion–positive NSCLC who had not previously received a ROS1 TKI; the median duration of response was 34.1 months (95% CI, 25.6 to could not be estimated). Response occurred in 21 of the 56 patients (38%; 95% CI, 25 to 52) with *ROS1* fusion–positive NSCLC who had previously received one ROS1 TKI and had never received chemotherapy; the median duration of response was 14.8 months (95% CI, 7.6 to could not be estimated). Ten of the 17 patients (59%; 95% CI, 33 to 82) with the ROS1 G2032R mutation had a response	Moderate This is a study in a rare disease population that has not had a randomized trial completed yet	Repotrectinib probably improves ORR based on historical data for chemotherapy
PFS	Based on data from 127 participants in one study Follow-up, 24 months		In patients who had not previously received a ROS1 TKI; the median PFS was 35.7 months (95% CI, 27.4 to could not be estimated). In patients who had previously received one ROS1 TKI and had never received chemotherapy; the median PFS was 9.0 months (95% CI, 6.8 to 19.6)	Moderate	Repotrectinib probably improves PFS based on historical data for chemotherapy
AEs	Based on data from 127 participants in one study Follow-up, 24 months		The most common treatment-related AEs were dizziness (in 58% of the patients), dysgeusia (in 50%), and paresthesia (in 30%), and 3% discontinued repotrectinib owing to treatment-related adverse events	Moderate	NA (no comparator arm)

Abbreviations: AE, adverse event; NA, not available; NSCLC, non–small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

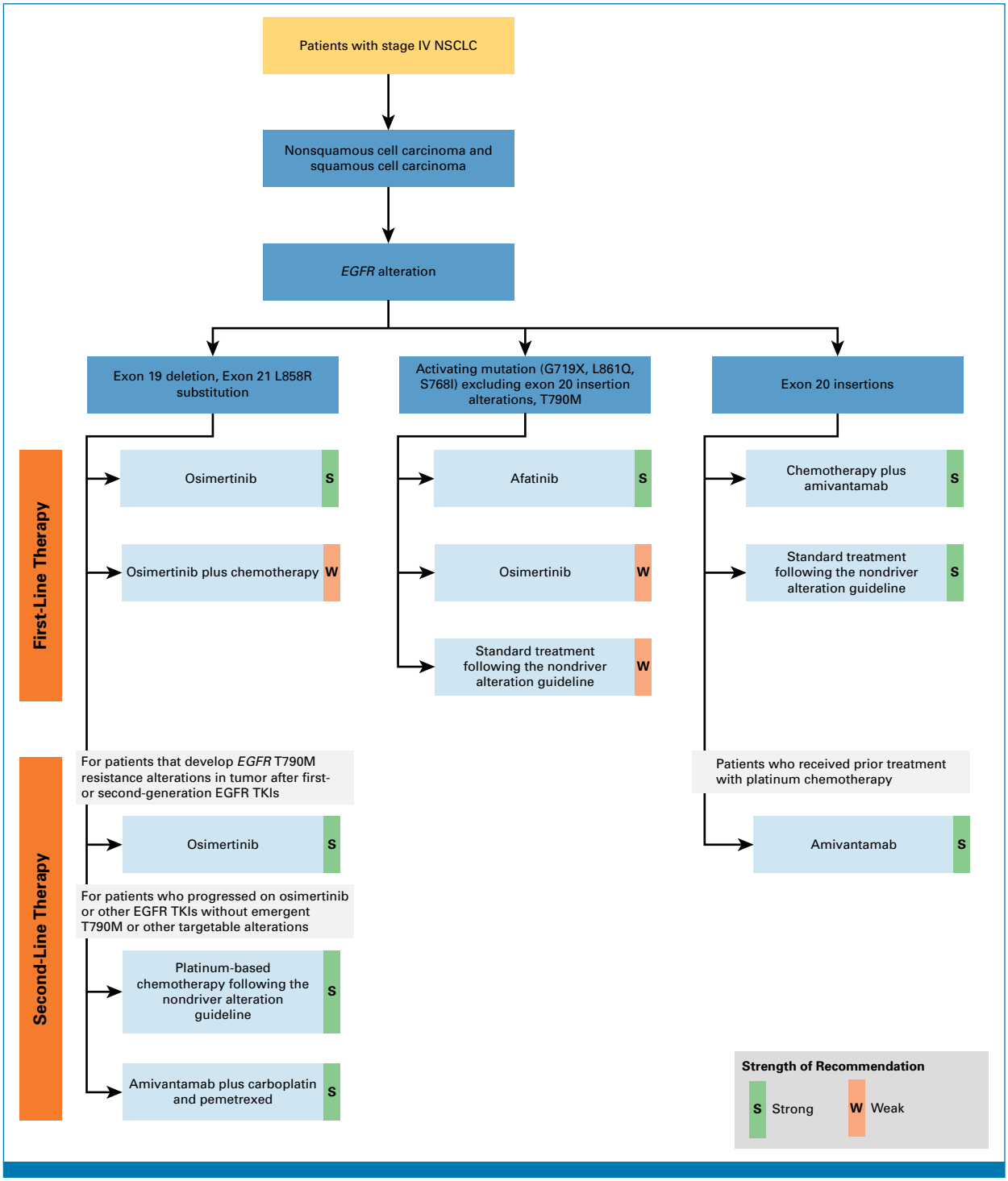

FIG A1. Algorithm for treatment options for patients with stage IV NSCLC with *EGFR* alterations. For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored to each patient incorporating both 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 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.

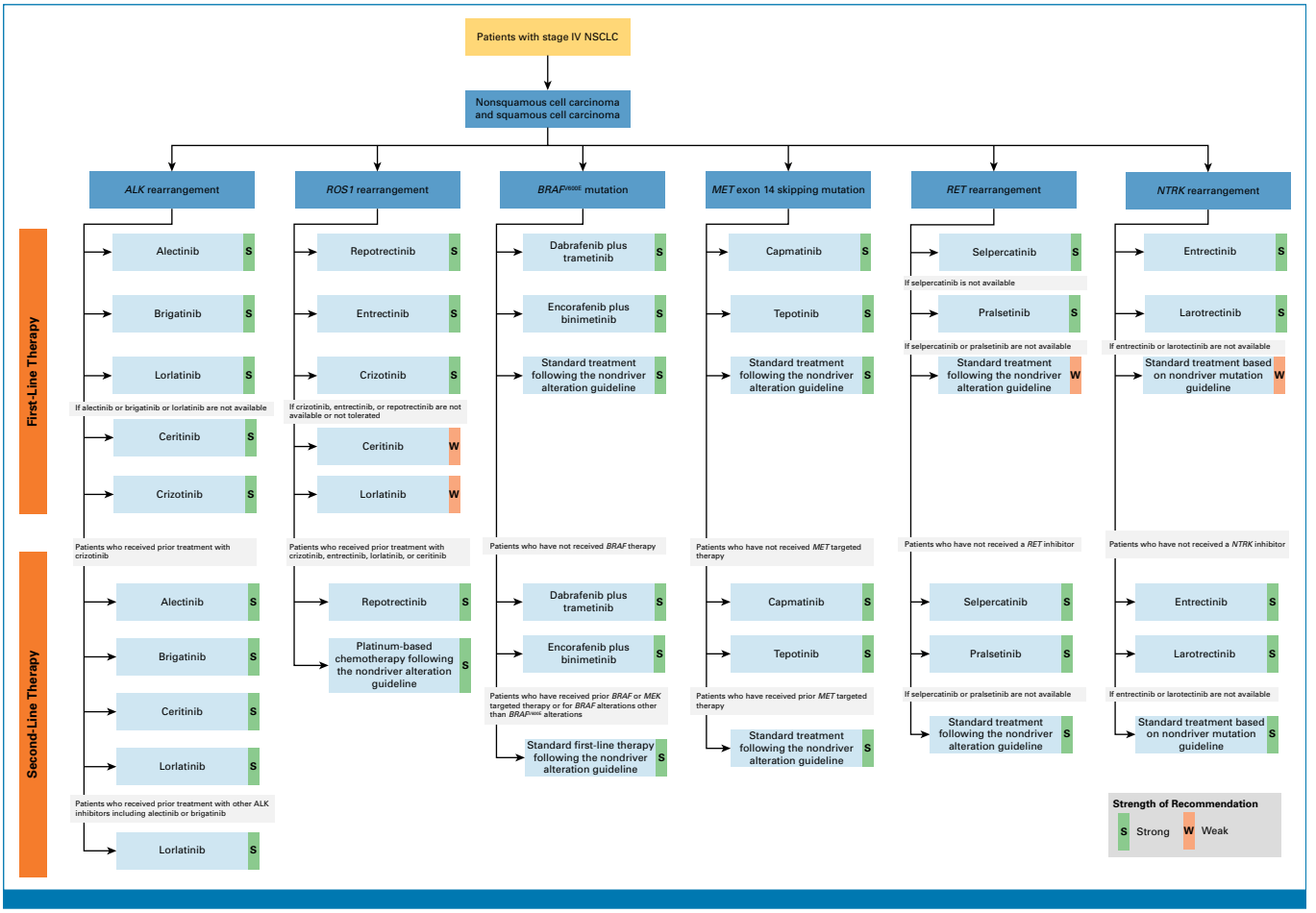

FIG A2. Algorithm for treatment options for patients with stage IV NSCLC with *ALK* rearrangements, *ROS1* rearrangements, *BRAFV600E* mutations, *MET* exon skipping mutations, *RET* rearrangements, or *NTRK* rearrangements. For recommendations with multiple treatment options of the same evidence quality 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. ALK, anaplastic lymphoma kinase; NGS, next-generation sequencing; NSCLC, non–small cell lung cancer; NTRK, neurotrophic tropomyosin receptor kinase.