

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

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abstract

Living guidelines are routinely updated guidelines that are developed for selected topic areas with rapidly evolving evidence that drives frequent change in clinical practice. These guidelines are updated on a regular schedule, based on the work of a standing panel that reviews the literature on a continuous basis. Updates will be made regularly and can be found at <https://ascopubs.org/nsclc-da-living-guideline>.

PURPOSE To provide evidence-based recommendations updating the 2021 ASCO and Ontario Health (Cancer Care Ontario) guideline on systemic therapy for patients with stage IV non–small-cell lung cancer (NSCLC) with driver alterations.

METHODS ASCO updated recommendations on the basis of an ongoing systematic review of randomized control trials from 2020 to 2021.

RESULTS This guideline update reflects changes in evidence since the previous update. Two studies provide the evidence base. Outcomes of interest include efficacy and safety.

RECOMMENDATIONS For patients with an anaplastic lymphoma kinase rearrangement, a performance status (PS) of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib or lorlatinib. For patients with an anaplastic lymphoma kinase rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib. For patients with a *RET* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib or pralsetinib. In second line, for patients with a *RET* rearrangement who have not received RET-targeted therapy, clinicians may offer selpercatinib or pralsetinib.

Additional information is available at www.asco.org/thoracic-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The purpose of this guideline update is to rapidly update the ASCO and Ontario Health (Cancer Care Ontario) guidelines on the systemic treatment of patients with stage IV non–small-cell lung cancer (NSCLC) last published in February 2021. The update is a result of potentially practice-changing evidence published since the last update. ASCO published the last full clinical practice guideline update on systemic therapy for patients with stage IV NSCLC that included patients whose cancer have driver alterations, in February 2021.

This update is based on two trials that directly affected clinical questions 3 and 11.

GUIDELINE QUESTIONS

This clinical practice guideline addresses one overarching clinical question with three subquestions: What systemic therapy treatment options should be offered to patients with stage IV NSCLC with driver alterations, depending on the subtype of the patient's cancer?

Subquestions

1. What is the most effective first-line therapy?
2. What is the most effective second-line therapy?
3. Is there a role for a third-line therapy or beyond?

The update does not apply to patients with stage IV NSCLC without known driver alterations. The guideline also does not apply to patients with stage IV NSCLC with rarer histologies, eg, large cell, neuroendocrine, etc.

THE BOTTOM LINE

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

Guideline Question

What systemic therapy treatment options should be offered to patients with stage IV non–small-cell lung cancer (NSCLC) with driver alterations, depending on the specific alteration of the patient's cancer?

Target Population

Patients with stage IV NSCLC with driver alterations

Target Audience

Oncology care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team), patients, and their caregivers in North America and beyond.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Recommendations (Fig 1)

Recommendation 3.1. For patients with an anaplastic lymphoma kinase (*ALK*) rearrangement, a performance status (PS) of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib (Type: Evidence based; benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong) or lorlatinib (Type: Evidence based; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 3.2. For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib (Type: Evidence based; benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Updated recommendation 11.1 (combination of recommendations 11.1 and 11.3). For patients with a *RET* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib or pralsetinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Updated recommendation 12.2 (combination of recommendations 12.2 and 12.3). For patients with *RET* rearrangement who have not received RET targeted therapy, clinicians may offer selpercatinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate) or pralsetinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A1 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

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.

METHODS

Guideline Development Process

This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included two patient representatives and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A2, online only). ASCO reconvened the original guideline Expert Panel, with some new members. The Expert Panel met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and

finalize the guideline recommendations (Table 1). The guideline recommendations were sent for an open comment period of two weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* (JCO) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee

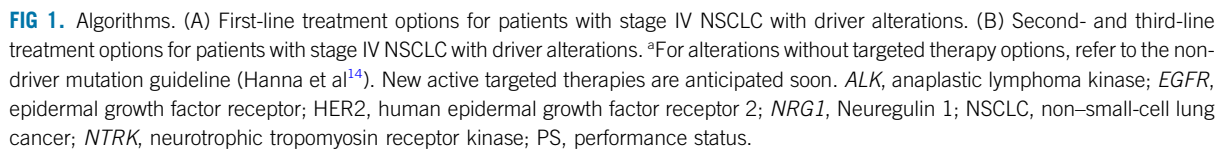


TABLE 1. Comparison of 2021 and 2022 Recommendations

Clinical Question (CQ)	2021 Recommendation	2022 Recommendation
<p>A1. CLINICAL QUESTION – General (note: CQ from 2015)</p> <p>What is the most effective first-line therapy for patients with stage IV NSCLC with a tumor <i>EGFR</i>-sensitizing mutation and PS 0-2?</p>	<p>Recommendation 1.1: For patients with a sensitizing (L858R/Exon19 deletion, with or without a concomitant T790M mutation) <i>EGFR</i> mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy, clinicians should use osimertinib monotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)</p> <p>Qualifying statement: Although Recommendation 1.1 addresses many patients in the target population, the guideline manuscript presents additional options that may be reasonable, on the basis of the evidence reviewed. This statement applies to all recommendations with the word should. In addition, use of osimertinib in patients previously treated with adjuvant or consolidation tyrosine kinase inhibitors is not part of this guideline</p> <p>Recommendation 1.2: For patients with a sensitizing (L858R/Exon19deletion) <i>EGFR</i> mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy and for whom osimertinib is not available, clinicians may use combination gefitinib with doublet chemotherapy (platinum/pemetrexed with maintenance pemetrexed; Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate)</p> <p>Recommendation 1.3: For patients with a sensitizing (L858R/Ex19del) <i>EGFR</i> mutation with stage IV NSCLC and a PS of 0-2 previously untreated with systemic therapy and for whom osimertinib is not available, clinicians may use dacomitinib monotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate)</p> <p>Recommendation 1.4: For patients with a sensitizing (L858R/Ex19del) <i>EGFR</i> mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy, and do not have access to osimertinib, clinicians may use monotherapy with afatinib or erlotinib/bevacizumab or erlotinib/ramucirumab (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)</p> <p>Recommendation 1.5: For patients with a sensitizing (L858R/Ex19del) <i>EGFR</i> mutation with stage IV NSCLC and a PS of 0-2 who have not had previous systemic therapy, and do not have access to other regimens, clinicians may use monotherapy with gefitinib, erlotinib, or icotinib (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)</p> <p>Recommendation 1.6: For patients with a sensitizing (L858R/Ex19del) <i>EGFR</i> mutation with stage IV NSCLC and a PS of 3, who have not had previous systemic therapy, monotherapy with an <i>EGFR</i> tyrosine kinase inhibitor may be given, with the choice dependent on access and toxicity profile of each agent (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak)</p> <p>Recommendation 1.7: For patients with an activating <i>EGFR</i> mutation other than exon 20 insertion mutations, T790M, L858R, or Ex19Del, (eg, G719X, L861Q, and S768I), and a PS of 0-2 who have not had previous systemic therapy, clinicians may offer afatinib monotherapy (Type: informal consensus; Evidence Quality: low; Strength of Recommendation: moderate) or osimertinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak) or standard treatment on the basis of non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 1.8: For patients with any activating <i>EGFR</i> mutation, regardless of PD-L1 expression levels (including exon 20 insertion mutations), single-agent immunotherapy should not be used as first-line therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 1.9: For patients with an exon 20 insertion mutation causing resistance to first- and second-generation <i>EGFR</i> tyrosine kinase inhibitors, clinicians may offer platinum doublet chemotherapy with or without bevacizumab (Type: informal consensus; Evidence quality low; Strength of recommendation: moderate) or standard treatment on the basis of the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p>	No change

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TABLE 1. Comparison of 2021 and 2022 Recommendations (continued)

Clinical Question (CQ)	2021 Recommendation	2022 Recommendation
What is the most effective first-line therapy for patients with stage IV NSCLC with <i>ALK</i> gene rearrangement and PS 0 to 1 or possibly PS 2?	<p>Recommendation 3.1: For patients with an <i>ALK</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians should offer brigatinib or alectinib (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)</p> <p>If brigatinib and alectinib are not available, clinicians should offer ceritinib or crizotinib (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)</p>	<p>Recommendation 3.1 For patients with an <i>ALK</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) or lorlatinib (Type: evidence based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak)</p> <p>Recommendation 3.2 For patients with an <i>ALK</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)</p>
CLINICAL QUESTION A2.a. What is the most effective first-line therapy for patients with stage IV NSCLC with <i>ROS1</i> rearrangement?	<p>Recommendation 5.1: For patients with <i>ROS1</i> rearrangement, a PS of 0-2, and previously untreated lung cancer, clinicians may offer crizotinib or entrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 5.2: For patients with <i>ROS1</i> rearrangement, a PS of 0-2, and previously untreated lung cancer, clinicians may offer standard therapy on the basis of the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 5.3: For patients with <i>ROS1</i> rearrangement, a PS of 0-2, and previously untreated lung cancer, clinicians may offer ceritinib or lorlatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak)</p>	No change
For patients with a <i>BRAF</i> V600E mutation, what is the optimal first-line therapy?	<p>Recommendation 7.1: For patients with a <i>BRAF</i> V600E mutation, clinicians may offer dabrafenib/trametinib as first-line treatment (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 7.2: For patients with a <i>BRAF</i> V600E mutation, clinicians may offer standard first-line therapy following the non-driver alterations guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p>	No change
What is the optimal first-line therapy for patients with a <i>MET</i> exon 14 skipping mutation?	<p>Recommendation 9.1: For patients with a <i>MET</i> exon 14 skipping mutation, a PS of 0-2, previously untreated NSCLC, clinicians may offer MET-targeted therapy with capmatinib or tepotinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 9.2: For patients with a <i>MET</i> exon 14 skipping mutation, a PS of 0-2, previously untreated NSCLC, clinicians may offer standard first-line therapy following the non-driver mutations guidelines (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p>	No change
What is the most effective first-line therapy for patients with stage IV NSCLC with <i>RET</i> rearrangement and PS 0-2?	<p>Recommendation 11.1: For patients with a <i>RET</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 11.2: For patients with a <i>RET</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer standard therapy following the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of Recommendation: moderate)</p> <p>Recommendation 11.3: For patients with an <i>RET</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer pralsetinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak)</p>	<p>Recommendation 11.1: For patients with a <i>RET</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib or pralsetinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak; combination of 11.1 and 11.3)</p> <p>Recommendation 11.2: For patients with a <i>RET</i> rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer standard therapy following the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of Recommendation: moderate)</p> <p>No change</p>
What is the most effective first-line therapy for patients with stage IV NSCLC with a <i>NTRK</i> rearrangement and PS 0-2?	<p>Recommendation 13.1: For patients with a <i>NTRK</i> fusion, a PS of 0-2, previously untreated lung cancer, clinicians may offer entrectinib or larotrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p> <p>Recommendation 13.2: For patients with <i>NTRK</i> fusion, a PS of 0-2, previously untreated lung cancer, clinicians may offer standard therapy following the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)</p>	No change

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TABLE 1. Comparison of 2021 and 2022 Recommendations (continued)

Clinical Question (CQ)	2021 Recommendation	2022 Recommendation
CLINICAL QUESTION A2.a.1. What is the most effective second-line therapy for patients with stage IV NSCLC with a sensitizing <i>EGFR</i> mutation who received a first-line <i>EGFR</i> TKI and experienced disease progression?	Recommendation 2.1: For patients with a sensitizing (L858R/Ex19del) <i>EGFR</i> mutation with stage IV NSCLC and a PS of 0-2 who have had previous <i>EGFR</i> -targeted therapy (except osimertinib) and subsequently have an <i>EGFR</i> T790M resistance mutation, clinicians should recommend osimertinib (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) Recommendation 2.2: For patients with any <i>EGFR</i> mutation who have progressed on <i>EGFR</i> TKIs with no T790M mutation OR whose disease has progressed on osimertinib, clinicians may treat on the basis of the non-driver mutation guidelines (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)	No change
What is the most effective second-line therapy for patients with stage IV NSCLC with <i>ALK</i> rearrangement with progression after first-line crizotinib?	Recommendation 4.2: For patients with an <i>ALK</i> rearrangement, a PS of 0-2, and have previously received crizotinib in the first-line setting, clinicians should offer alectinib, brigatinib, or ceritinib in the second-line setting (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong)	No change
What is the most effective second- or third-line therapy for patients with stage IV NSCLC with <i>ALK</i> gene rearrangement and PS 0-2?	Recommendation 4.1: For patients with an <i>ALK</i> rearrangement, a PS of 0-2, and have previously received alectinib or brigatinib, clinicians may offer lorlatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 4.3: For patients with an <i>ALK</i> rearrangement, a PS of 0-2, and have received prior crizotinib in the first-line setting and either alectinib, brigatinib, or ceritinib in the second-line setting, clinicians may offer lorlatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) or clinicians may offer standard therapy following the non-driver mutation guideline in the third-line setting (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak)	No change
<i>ROS1</i> rearrangement – What is the most effective second-line therapy for patients with <i>ROS1</i> rearrangement?	Recommendation 6.1: For patients with <i>ROS1</i> rearrangement, a PS of 0-2, and previously treated with <i>ROS1</i> targeted therapy, clinicians should offer standard therapy following the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 6.2: For patients with <i>ROS1</i> rearrangement, a PS of 0-2, and previously treated with nontargeted therapy first-line, clinicians may offer crizotinib or entrectinib or ceritinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)	No change
What is the most effective therapy for patients with stage IV NSCLC and <i>BRAF</i> mutations who have received prior chemotherapy? <i>CQ changed in 2020.</i> What is appropriate second-line therapy and above for patients with a <i>BRAF</i> V600E mutation?	Recommendation 8.1: For patients with a <i>BRAF</i> V600E mutation who have had previous B-RAF/MEK-targeted therapy, clinicians should offer standard first-line therapy following the non-driver alteration guideline (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate) Recommendation 8.2: For patients with a <i>BRAF</i> V600E mutation who have had previous chemotherapy or chemotherapy/immunotherapy, clinicians may offer dabrafenib/trametinib (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate) or dabrafenib alone (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak) or vemurafenib (Type: informal consensus; benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak) Recommendation 8.3: For patients with a <i>BRAF</i> V600E mutation who have had previous chemotherapy, immunotherapy, and <i>BRAF</i> -targeted therapy, clinicians should offer treatment following the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 8.4: For patients with <i>BRAF</i> mutations other than <i>BRAF</i> V600E mutations, clinicians should offer standard therapy following the non-driver mutation guidelines (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)	No change

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TABLE 1. Comparison of 2021 and 2022 Recommendations (continued)

Clinical Question (CQ)	2021 Recommendation	2022 Recommendation
What is the optimal second-line therapy for patients with a <i>MET</i> exon 14 skipping mutation?	Recommendation 10.1: Patients with <i>MET</i> abnormalities other than exon 14 skipping mutations, a PS of 0-2, or those previously treated with <i>MET</i> targeted therapy, clinicians should offer standard therapy following the non-driver mutations guidelines (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 10.2: For patients with a <i>MET</i> exon 14 skipping mutation, a PS of 0-2, and who have previously received or been ineligible for first-line chemotherapy with or without immunotherapy therapy, clinicians may offer <i>MET</i> targeted therapy with capmatinib or tepotinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)	No change
What is the most effective second-line therapy for patients with stage IV NSCLC with <i>RET</i> rearrangement with a PS 0-2?	Recommendation 12.1: For patients with <i>RET</i> rearrangement who have had previous <i>RET</i> -targeted therapy, clinicians may offer treatment per the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 12.2: For patients with <i>RET</i> rearrangement who have not received <i>RET</i> -targeted therapy, clinicians may offer selpercatinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 12.3: For patients with <i>RET</i> rearrangement, if <i>RET</i> -targeted therapy was not given in the first-line setting, clinicians may offer pralsetinib ^a (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak)	Recommendation 12.1: For patients with <i>RET</i> rearrangement who have had previous <i>RET</i> targeted therapy, clinicians may offer treatment per the non-driver mutation guideline (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate; no change) Recommendation 12.2: For patients with <i>RET</i> rearrangement who have not received <i>RET</i> targeted therapy, clinicians may offer selpercatinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate) or pralsetinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak; combination of recommendations 12.2 and 12.3)
What is the most effective second-line therapy for patients with stage IV NSCLC with a <i>NTRK</i> rearrangement and PS 0-2?	Recommendation 14.1: For patients with <i>NTRK</i> fusion previously treated with a <i>NTRK</i> inhibitor, clinicians may offer standard therapy following the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 14.2: For patients with <i>NTRK</i> fusion previously treated lung cancer who have not received an <i>NTRK</i> inhibitor, clinicians may offer entrectinib or larotrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)	No change
What is the most effective third-line therapy for patients with tumor <i>EGFR</i> -sensitizing mutation–positive status who have had prior platinum-based chemotherapy and <i>EGFR</i> TKI?	See second line above	No change

NOTE. If patients have previously received a *MET* exon 14 TKI and experienced disease progression, there is insufficient evidence to recommend changing to another *MET* exon 14 TKI.

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; PD-L1, programmed death-ligand 1; PS, performance status.

^aProvisionally included pending confirmatory data.

(EBMC) before publication. All funding for the administration of the project was provided by ASCO.

In 2021, ASCO published an update of its guideline on systemic therapy for patients with stage IV NSCLC with driver alterations. The current recommendations were developed by using a systematic review of evidence identified through a targeted electronic literature search of PubMed from June 2018 through December 2021 to identify any trials meeting the inclusion criteria of the 2021 update, published since then, and clinical experience. Articles were selected for inclusion in the systematic review on the basis of the following criteria:

- Population: Patients with stage IV NSCLC whose test results show cancer is:
 - With driver alterations in epidermal growth factor receptor (*EGFR*), *ALK*, *ROS1* fusions, *BRAF* V600e mutations, *RET* fusions, *MET* exon 14 skipping mutations, human epidermal growth factor receptor 2 alterations, and *NTRK* fusions (with known marker status test results available to the clinician).
- Interventions: Chemotherapy, monoclonal antibodies, targeted therapy, palliative care, and no treatment
- Comparisons: Chemotherapy, monoclonal antibodies, targeted therapy, palliative care, and no treatment

- Outcomes: Included progression-free survival (PFS), overall survival (OS), treatment toxicity (adverse events [AEs]; usually grade 3-4 AEs), overall response rates, and quality of life (if reported).
- Sample size:
 - With driver alterations: Minimum sample size of 20 or 1% of target population required to have the actionable driver alteration of total participants

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology and accompanying BRIDGE-Wiz software.¹ In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for type and strength of the recommendation, and evidence quality are provided with each recommendation. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.^{2,3} GRADE quality assessment labels (ie, high, moderate, low, and very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO’s Conflict of Interest Policy Implementation for

TABLE 2. Characteristics of Studies Identified in the Literature Search

Author Year Reference	Comparisons	No. of Patients	Median Age	Patient Characteristics			Disease Characteristics
				Sex, %		% Never Smokers	Adenocarcinoma, %
				Male	Female		
Phase III RCTs							
CROWN	Lorlatinib	149	61	44	56	54	94
Shaw et al 2020 ⁴	Crizotinib	147	56	38	62	64 ^a	95
Observational studies							
Gainor et al 2021 ^{5,6} ARROW NCT03037385	Noncomparative	92	60 (63-68)	50	50	65	96

Abbreviation: RCTs, randomized control trials.

^aStudy did not report smoking status for one patient in crizotinib arm.

Clinical Practice Guidelines (“Policy,” found at <https://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.

RESULTS

Characteristics of Studies Identified in the Literature Search

After applying the eligibility criteria, one randomized control trial (RCT) and one single-arm study remained, forming the evidentiary basis for the guideline recommendations.^{4,5}

The identified trials were published between 2020 and 2021. The primary outcome for the RCT was therapeutic efficacy⁴; morbidities was a coprimary outcome for one of the studies,⁵ although they were framed in a variety of ways such as PFS and OS. The cohort study⁵ reported a mix of efficacy and AE-related outcomes. Tables 2-6 present the included articles from the literature search pertinent to the development of the recommendations. Evidence supporting unchanged recommendations is reviewed in the previous guideline publications.^{7,8}

Study Quality Assessment

Study design aspects related to individual study quality, quality of evidence, strength of recommendations, and risk of bias were assessed. Refer to the Methodology Manual for more information and for definitions of ratings for overall potential risk of bias.

As seen in Tables 4 and 6, study quality was formally assessed for the one RCT and one cohort study identified. Evidence quality (ie, certainty of the evidence) for each outcome was assessed using elements of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) quality assessment and recommendations development process. To facilitate the quality assessment ratings, MAGIC App guideline development software was used; within this framework, outcomes from randomized controlled trials are rated high quality and can subsequently be downgraded as factors that affect quality are identified. Observational nonrandomized studies are rated as low quality and can be upgraded for factors such as large

magnitude of effect. GRADE quality assessment labels of high, moderate, low, or very low and a recommendation strength of strong or weak were assigned by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. Definitions for these ratings are provided in Appendix Table A1.

Key Outcomes of Interest

Additional data on key outcomes of interest and key AEs are reported in Tables 3-6.

RECOMMENDATIONS

Clinical Question 3 (from parent guideline)

What is the most effective therapy for patients with *ALK* rearrangement and previously untreated NSCLC?

Recommendation 3.1. For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib (Type: Evidence based; benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong) or lorlatinib (Type: Evidence based; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 3.2. For patients with an *ALK* rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib (Type: Evidence based; benefits outweigh harms; Evidence quality: High; Strength of recommendation: Strong).

Literature review update and analysis. The CROWN trial included 296 patients who received either lorlatinib or crizotinib⁴ (crizotinib data were reviewed in prior guideline updates). A difference in OS was not observed, but the survival data were immature at the time of the analysis. There was an improvement in PFS compared with crizotinib. The PFS difference result was hazard ratio = 0.28 (95% CI, 0.19 to 0.41). There was an increase in grade 3-4 AEs with lorlatinib, with an absolute increase of 167 more per 1,000. With the GRADE assessment, certainty of the evidence was low for OS and grade 3-4 AEs, and moderate for PFS.

Clinical interpretation. Although lorlatinib is effective in patients with *ALK*-rearranged stage IV NSCLC and may be considered as another option for first-line treatment in this patient population, clinicians need awareness of its AE profile. Notably, neurocognitive and mood disorders (both any grade), grade 3-4 hypercholesterolemia, and hypertriglyceridemia were increased. Weight gain and hypertension were also increased in the lorlatinib arm. Because of immature OS results, a wide CI for PFS, methodologic risk of bias, and toxicity, the strength of the recommendation is weak. Although no head-to-head comparison of alectinib and lorlatinib has occurred, longer follow-up data with alectinib and its more favorable safety profile still make it the preferred first-line treatment for patients with *ALK*-

TABLE 3. Studies Informing the Anaplastic Lymphoma Kinase Evidence Review

Trial Author Year	No. of Patients Randomly Assigned	Comparison	Significance <i>P</i> < .05		Grade 3 or Worse AEs
			OS	PFS	
CROWN	149	Lorlatinib	—	↑	72%
Shaw et al 2020 ⁴	147	Crizotinib			56%

NOTE. No crossover allowed per protocol.

Abbreviations: AE, adverse event; OS, overall survival; PFS, progression-free survival.

↑ Favors intervention *P* < .05.

↓ Favors control *P* < .05.

— No significant differences.

rearranged stage IV NSCLC. Brigatinib was discussed in the previous version of the guideline; there was no new evidence to add in this update.

Clinical Question 11 (from parent guideline)

What is the most effective therapy for patients with *RET* rearrangement?

Recommendation 11.1. Combination of Recommendations

11.1 and 11.3. For patients with a *RET* rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib or pralsetinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

2021 additional option: For patients with a *RET* rearrangement, a performance status of 0-2, and previously untreated NSCLC, clinicians may offer standard therapy following the non-driver mutation guideline (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).

TABLE 4. Lorlatinib Versus Crizotinib Outcomes (Shaw et al 2020⁴)

Population: Stage IV NSCLC With *ALK* Rearrangements

Intervention: Lorlatinib

Comparator: Crizotinib

Outcome Time Frame	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Crizotinib	Lorlatinib		
OS at 12 months	HR: 0.72 (95% CI, 0.41 to 1.25) On the basis of data from 296 patients in one study ^a Follow-up 18.3 months for lorlatinib, 14.8 months for crizotinib	130 per 1,000 Difference: 35 fewer per 1,000 (95% CI, 75 fewer to 30 more)	95 per 1,000	Low Due to serious risk of bias Due to serious imprecision ^b	Lorlatinib may have little or no difference in OS compared with crizotinib
PFS (primary outcome) at 12 months	HR: 0.28 (95% CI, 0.19 to 0.41) On the basis of data from 296 patients in one study ^c Follow-up 18.3 months for lorlatinib, 14.8 months for crizotinib	610 per 1,000 Difference: 378 fewer per 1,000 (95% CI, 446 fewer to 290 fewer)	232 per 1,000	Moderate Due to serious risk of bias ^d	Lorlatinib probably improves PFS compared with crizotinib
Grade 3-4 AEs	Relative risk: 1.3 (95% CI, 1.09 to 1.56) On the basis of data from 291 patients in one study	556 per 1,000 Difference: 167 more per 1,000 (95% CI, 50 more to 311 more)	723 per 1,000	Low Due to serious risk of bias Due to serious imprecision ^e	Lorlatinib may cause more grade 3-4 AEs than crizotinib

Abbreviations: AE, adverse event; *ALK*, anaplastic lymphoma kinase; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival.

^aPrimary study: OS HR data from Shaw et al 2020.⁴ Baseline/comparator control arm of reference used for intervention. Twelve-month survival rate of 87% for crizotinib estimated visually from Kaplan-Meier OS curve in Shaw et al 2020, eg, 130 events per 1,000.

^bRisk of bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; because of interim analysis, no reported concealment of allocation during random assignment process, resulting in potential for selection bias; imprecision: serious. Only data from one study (not considered serious), wide CIs (include possibility of no clinically meaningful difference); publication bias: no serious. Mostly commercially funded studies (not considered serious).

^cPrimary study: PFS HR from Shaw et al 2020.⁴ Baseline/comparator control arm of reference used for intervention. Comparison event rate at 12 months from Camidge et al 2020.⁹ Thirty-nine percent PFS at 12 months is 610 events per 1,000.

^dRisk of bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; no reported concealment of allocation during random assignment process, resulting in potential for selection bias; imprecision: no serious. Only data from one study (not considered serious); publication bias: no serious. Mostly commercially funded studies (not considered serious).

^eRisk of bias: serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; no reported concealment of allocation during random assignment process, resulting in potential for selection bias; imprecision: serious. Only data from one study (not considered serious), wide CIs; publication bias: no serious. Mostly commercially funded studies (not considered serious).

TABLE 5. Pralsetinib Study Informing the Evidence Review

Author Trial Year Reference	No. of Patients	Comparison	Significance <i>P</i> < .05		Grade 3-5 AEs
			ORR, % (95% CI)	Response Duration, months	
Gainor et al 2021 ⁶ ARROW NCT03037385	87	Previous platinum chemotherapy	61 (50 to 71)	≥ 6	45% ^a
	27	Previously untreated	70 (50 to 86)	9	

Abbreviations: AE, adverse event; CR, complete response; ORR, objective response rate; PR, partial response.

^aSafety population: 233, most commonly reported: pneumonia, pneumonitis, sepsis, urinary tract infection, and pyrexia.

Clinical Question 12 (from parent guideline)

What is the most effective second-line therapy for patients with stage IV NSCLC with *RET* rearrangement with a PS 0-2?

Recommendation 12.2. Combination of Recommendations 12.2 and 12.3. For patients with *RET* rearrangement who have not received RET targeted therapy, clinicians may offer selpercatinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate) or pralsetinib (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

2021 additional option: For patients with *RET* rearrangement who have had previous RET targeted therapy, clinicians may offer treatment per the non-driver mutation guideline (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).

Literature review update and analysis. The ARROW trial was a single-arm study in the first line and the second line.^{5,6} One open-label phase I-II trial reporting on pralsetinib

in this setting was obtained, comprising all the available evidence. In this trial, patients were consecutively enrolled in the phase I portion of the trial and retained in the phase II portion. The primary end point was objective response, and the secondary end point was duration of response. Study outcomes of interest are presented in [Tables 5 and 6](#).

One hundred fourteen patients whose cancer had a *RET* alteration, in the second-line setting, received pralsetinib. The primary outcome was response rate. The response rate was 70% for patients who had not received prior treatment and 61% for those with prior treatment. The certainty of the evidence was low due to factors such as single-arm trial design, small sample size, and more. The sample size for those in the first line did not meet the criteria for inclusion in this guideline.

Clinical interpretation The only change is combining the two recommendations and downgrading the recommendation strength to weak. *RET* rearrangements are seen in approximately 1-2 percent of patients with NSCLC.⁷ Two selective RET antagonists selpercatinib and pralsetinib have now been shown to produce high response rates in patients whose cancer is treatment-naïve as well as those who have been previously treated. Given the tolerable toxicity, these are now approved for patients with *RET* rearranged stage IV NSCLC first- or subsequent-line therapy following chemotherapy and/or immunotherapy on the basis of the results of the respective phase I-II studies. This recommendation does not apply to patients with large cell or neuroendocrine tumors. The Expert Panel understands the limitations of these studies and encourages patient participation in ongoing phase III studies comparing selpercatinib or pralsetinib to standard first-line treatments to help confirm the efficacy of these novel targeted therapies.

TABLE 6. Pralsetinib Outcomes (Gainor et al 2021⁶)

Population: Stage IV NSCLC With *RET* Rearrangement
Intervention: Pralsetinib
Comparator: No Comparator

Outcome Time Frame	Study Results and Measurements	Certainty of the Evidence (quality of evidence)	Plain Text Summary
Objective response rate	On the basis of data from 114 patients in one study	Very low Due to serious risk of bias, due to serious inconsistency, due to serious indirectness, due to serious imprecision, due to serious publication bias ^a	Previous platinum chemotherapy, ORR, 61% (6% CR, 55% PR) and previously untreated, ORR, 70% (11% CR, 59% PR)
Response duration	On the basis of data from 114 patients in one study	Very low Due to serious risk of bias, due to serious inconsistency, due to serious indirectness, due to serious imprecision, due to serious publication bias ^a	Previous platinum chemotherapy, ≥ 6 months, previously untreated, 9 months

Abbreviations: CR, complete responses; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PR, partial response.

^aRisk of bias: serious. Inadequate sequence generation/generation of comparable groups, resulting in potential for selection bias; inadequate concealment of allocation during random assignment process, resulting in potential for selection bias; inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, missing intention-to-treat analysis, carryover effects in crossover trial; inconsistency: serious. Due to single-arm trial; indirectness: serious. Direct comparisons not available; imprecision: serious. Only data from one study, low number of patients; publication bias: serious. Mostly commercially funded studies.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from January 10, 2022, through January 24, 2022. Response categories of “Agree as written,” “Agree with suggested modifications” and “Disagree. See comments” were captured for every proposed recommendation with 22 written comments received. A total of 91% of the 22 respondents’ responses either agreed or agreed with slight modifications to the recommendations and 9% of the responses disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before EBMC review and approval.

The draft was submitted to one external reviewer with content expertise. It was rated as high quality, and it was agreed it would be useful in practice. Review comments regarding lorlatinib were reviewed by the Expert Panel and integrated into the final manuscript before approval by the EBMC.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO’s Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

LIMITATIONS OF THE RESEARCH AND FUTURE RESEARCH

Limitations of the research include that there was a single RCT on lorlatinib and that the pralsetinib study was a single-arm study. After the closing date parameter of the systematic review, the US Food and Drug Administration (FDA)

approved two agents via breakthrough designation: telisotuzumab vedotin (ABBV-399; teliso-V)¹⁰ and patritumab deruxtecan.¹¹

In addition, the Expert Panel is following ongoing trials on sotorasib, pyrotinib, adagrasib, and others, listed in the Data Supplement (online only). The Expert Panel suggests more research on both US Food and Drug Administration breakthrough designation-awarded agents and ongoing trials and will review in future 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

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/thoracic-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Care¹² (<http://ascopubs.org/doi/10.1200/JCO.2016.70.1474>)
- Patient-Clinician Communication¹³ (<http://ascopubs.org/doi/10.1200/JCO.2017.75.2311>)
- 2020 Update for Stage IV NSCLC Without Driver Alterations¹⁴ (<https://ascopubs.org/full/doi/10.1200/JCO.19.03022>)
- 2021 Update for Stage IV NSCLC With Driver Alterations⁷ (<https://ascopubs.org/doi/full/10.1200/JCO.20.03570>)
- Molecular Testing for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors¹⁵ (<http://ascopubs.org/doi/10.1200/JCO.2017.76.7293>)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/thoracic-cancer-guidelines.

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

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
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	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

TABLE A2. Therapy for Stage IV Non–Small-Cell Lung Cancer Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Navneet Singh, MD, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Medical oncology
Ishmael A. Jaiyesimi, MD, MS	Beaumont Health Royal Oak and Oakland University William Beaumont School of Medicine, Royal Oak, MI	Medical oncology/hematology PGIN rep
Sherman Baker Jr, MD	Virginia Commonwealth University, Richmond, VA	Medical oncology
Elizabeth Blanchard, MD	Southcoast Centers for Cancer Care, New Bedford, MA	Medical oncology
Julie R. Brahmer, MD	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD	Medical oncology
Paul Celano, MD, FASCO	The Cancer Center at GBMC, Towson, MD	Medical oncology
Narjust Duma, MD	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Peter M. Ellis, MD, PhD	Juravinski Cancer Center, Hamilton, ON, Canada	Medical oncology
Ivy B. Elkins, MBA	EGFR Resisters, Buffalo Grove, IL	Patient representative
Rami Y. Haddad, MD	Affiliated Oncologists, LLC, Chicago Ridge, IL	Medical oncology PGIN rep
Paul J. Hesketh, MD	Lahey Hospital and Medical Center, Burlington, MA	Medical oncology/hematology
Dharamvir Jain, MD	Houston Methodist Cancer Center, Houston, TX	Medical oncology
David H. Johnson, MD	University of Texas Southwestern Medical Center, Dallas, TX	Medical oncology
Natasha B. Leighl, MD	Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada	Medical oncology
Hirva Mamdani, MD	Karmanos Cancer Institute/Wayne State University, Detroit, MI	Medical oncology
Gregory Masters, MD	Helen F. Graham Cancer Center and Research Institute, Newark, DE	Medical oncology
Pamela R. Moffitt, MD	Galva, IA	Patient representative
Tanyanika Phillips, MD	City of Hope, Duarte, CA	Medical oncology PGIN rep
Gregory J. Riely, MD, PhD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Andrew G. Robinson, MD	Kingston General Hospital, Queen's University, Ontario, Canada	Medical oncology
Rafael Rosell, MD	Catalan Institute of Oncology, Barcelona, Catalonia, Spain	Medical oncology
Joan H. Schiller, MD	Inova Schar Cancer Institute, Falls Church, VA	Medical oncology
Bryan J. Schneider, MD	University of Michigan Health System, Ann Arbor, MI	Medical oncology
David R. Spigel, MD	Sarah Cannon Research Institute, Nashville, TN	Medical oncology
Sarah Temin, MSPH	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO practice guideline staff (health research methods)

Abbreviation: PGIN, Practice Guideline Implementation Network.