ASCO special articles

# Therapy for Stage IV Non–Small-Cell Lung Cancer Without 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-non-da-living-guideline.*

**PURPOSE** To provide evidence-based recommendations updating the 2020 ASCO and Ontario Health (Cancer Care Ontario) guideline on systemic therapy for patients with stage IV non–small-cell lung cancer without driver alterations.

**METHODS** ASCO updated recommendations on the basis of an ongoing systematic review of randomized clinical trials from 2018 to 2021.

**RESULTS** This guideline update reflects changes in evidence since the previous update. Five randomized clinical trials provide the evidence base. Outcomes of interest include efficacy and safety.

**RECOMMENDATIONS** In addition to 2020 options for patients with high programmed death ligand-1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%), nonsquamous cell carcinoma (non-SCC), and performance status (PS) 0-1, clinicians may offer single-agent atezolizumab. With high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilumumab alone or nivolumab and ipilimumab plus chemotherapy. With negative (0%) and low positive PD-L1 expression (TPS 1%-49%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus chemotherapy. With high PD-L1 expression, SCC, and PS 0-1, clinicians may offer single-agent atezolizumab. With high PD-L1 expression, squamous cell carcinoma (SCC), and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or in combination with two cycles of platinum-based chemotherapy. With negative and low positive PD-L1 expression, SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or in combination with two cycles of platinum-based chemotherapy. With non-SCC who received an immune checkpoint inhibitor and chemotherapy as first-line therapy, clinicians may offer second-line paclitaxel plus bevacizumab. With non-SCC, who received chemotherapy with or without bevacizumab and immune checkpoint inhibitor therapy, clinicians should offer the options of third-line single-agent pemetrexed, docetaxel, or paclitaxel plus bevacizumab.

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 update the ASCO and Ontario Health (Cancer Care Ontario) guidelines on the systemic treatment of patients with nondriver alteration stage IV non–small-cell lung cancer (NSCLC) last published in 2020. 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 those whose cancer did not have driver alterations, in January 2020.[1]

This update is based on five randomized clinical trials (RCTs) that directly affected clinical questions 1, 2, and 3.

## THE BOTTOM LINE

### Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO Guideline

#### Guideline Question

What systemic therapy treatment options should be offered to patients with stage IV non–small-cell lung cancer (NSCLC) without driver alterations, depending on the subtype of the patient's cancer?

#### Target Population

Patients with stage IV NSCLC without driver alterations in epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) (with known *EGFR* and *ALK* status; plus programmed death ligand-1 [PD-L1] tumor proportion score [TPS] test results available to the clinician being optimal).

#### 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

***Recommendation 1.5 (note numbering change: 2020 1.5 will become 2022 1.8).*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%; Table 1), nonsquamous cell carcinoma (non-SCC), and performance status (PS) 0-1, clinicians may offer single-agent atezolizumab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 1.6.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer single-agent cemiplimab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 1.7.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

***Recommendation 2.7.*** In addition to 2020 options, for patients with negative (0%) and low positive PD-L1 expression (TPS 1%-49%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

***Recommendation 3.3 (note numbering change: 2020 3.3 will become 2022 3.6).*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), squamous cell carcinoma (SCC), and PS 0-1, clinicians may offer single-agent atezolizumab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 3.4.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer single-agent cemiplimab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 3.5.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

***Recommendation 4.5.*** In addition to 2020 recommendations 4.1-4.4, for patients with negative (TPS 0%) and low positive (TPS 1%-49%) PD-L1 expression, SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

***Recommendation 5.1.*** For patients with non-SCC who received an immune checkpoint inhibitor and chemotherapy as first-line therapy, clinicians may offer paclitaxel plus bevacizumab in the second-line setting (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

***Recommendation 6.1.*** For the majority of patients with non-SCC, who received chemotherapy with or without bevacizumab and immune checkpoint inhibitor therapy (in either sequence), clinicians should offer the options of single-agent pemetrexed or docetaxel or paclitaxel plus bevacizumab in the third-line setting (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

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## THE BOTTOM LINE (CONTINUED)

### 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.**

## GUIDELINE QUESTIONS

This clinical practice guideline addresses one clinical question with three subquestions: (1) What systemic therapy treatment options should be offered to patients with stage IV NSCLC without 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?

## METHODS

### Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative 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. 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 (EBMC) before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of evidence identified through online searches of PubMed June 2018 through December 2021 of phase III RCTs, 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:
- Programmed death ligand-1 (PD-L1) TPS test results available to the clinician being optimal and without driver alterations in epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) (with known *EGFR* and *ALK*) status.
- Interventions: Chemotherapy, monoclonal antibodies, immunotherapy, palliative care, and no treatment
- Comparisons: Chemotherapy, monoclonal antibodies, immunotherapy, 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:
- Minimum sample size of 20 patients for immune checkpoint therapy and 50 patients for chemotherapy.

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.[7] 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.[8,9] GRADE quality assessment labels (ie, high, moderate, low, and very low) were assigned for each outcome by the project methodologist in collaboration with

**TABLE 1.** Comparison of 2020 and 2022 Recommendations

| 2020 Recommendation (with older numbering scheme) | 2022 |
|---|---|
| Recommendation A1.a.: For patients with performance status (PS) of 0 or 1 receiving chemotherapy, a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications to platinum therapy. Chemotherapy may also be used to treat selected patients with PS of 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment | No change |
| Recommendation A1.b. Because there is no cure for patients with stage IV NSCLC, early concomitant palliative care assistance has improved the survival and well-being of patients and is therefore recommended | No change |
| For patients with high programmed death ligand-1 (PD-L1)/PD-1 expression (TPS ≥ 50%), in the absence of contraindications to immune checkpoint inhibitor therapies. Non-SCC PS 0-1:<br>1.1 Clinicians should offer single-agent pembrolizumab<br>Evidence quality: High; Strength of recommendation: Strong<br>1.2. Clinicians may offer pembrolizumab/carboplatin/pemetrexed<br>Evidence quality: High; Strength of recommendation: Strong<br>1.3 Clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab<br>Evidence quality: Intermediate; Strength of recommendation: Moderate<br>1.4. Clinicians may offer atezolizumab/carboplatin/nab-paclitaxel<br>Evidence quality: Low; Strength of Recommendation: Weak<br>1.5 There are insufficient data to recommend any other checkpoint inhibitors or to recommend combination checkpoint inhibitors or any other combinations of immune checkpoint inhibitors with chemotherapy in the first-line setting.<br>Evidence quality: High; Strength of recommendation: Strong | For patients with high programmed death ligand-1 (PD-L1)/PD-1 expression (TPS ≥ 50%), in the absence of contraindications to ICI therapies, non-SCC PS 0-1:<br>1.1. Clinicians should offer single-agent pembrolizumab<br>Evidence quality: High; Strength of recommendation: Strong<br>1.2. Clinicians may offer pembrolizumab/carboplatin/pemetrexed<br>Evidence quality: High; Strength of recommendation: Strong<br>1.3. Clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab<br>Evidence quality: Intermediate; Strength of recommendation: Moderate<br>1.4. Clinicians may offer atezolizumab/carboplatin/nab-paclitaxel<br>Evidence quality: Low; Strength of Recommendation: Weak<br>1.5. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer single-agent atezolizumab<br>Evidence quality: Moderate; Strength of recommendation: Strong<br>1.6. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer single-agent cemiplimab<br>Evidence quality: moderate; Strength of recommendation: strong<br>1.7. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy<br>Evidence quality: Moderate; Strength of recommendation: Weak<br>1.8. (previously 1.5) There are insufficient data to recommend any other checkpoint inhibitors or to recommend combination checkpoint inhibitors or any other combinations of ICIs with chemotherapy in the first-line setting.<br>Evidence quality: High; Strength of recommendation: Strong |
| Recommendation A2.a.1. For patients receiving carboplatin plus paclitaxel, the Update Committee recommends the addition of bevacizumab 15 mg/kg once every 3 weeks, except for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, Eastern Cooperative Oncology Group PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression (no change) | No change |
| There is insufficient evidence to recommend bevacizumab in combination with pemetrexed plus carboplatin for patients who do not have contraindications to bevacizumab | No change |
| For patients with negative (< 1% or unknown) and low positive (TPS 1%-49%) PD-L1 expression, non-SCC, PS 0-1, AND are eligible for chemotherapy and pembrolizumab<br>2.1. Clinicians should offer pembrolizumab/carboplatin/pemetrexed<br>Evidence quality: High; Strength of recommendation: Strong<br>2.2. Clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab. Evidence quality: Intermediate; Strength of recommendation: Moderate<br>2.3. Clinicians may offer atezolizumab/carboplatin/nab-paclitaxel<br>Evidence quality: Intermediate; Strength of recommendation: Moderate<br>2.4. (For patients who have the above characteristics) AND have contraindications to/declines immunotherapy, clinicians should offer standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update<br>Evidence quality: High; Strength of recommendation: Strong<br>2.5. (For patients with above characteristics) AND have contraindications to/declines immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer nonplatinum-based two-drug therapy as outlined in the 2015 update<br>Evidence quality: Low; Strength of recommendation: Weak<br>2.6. For patients with low positive PD-L1 expression (TPS 1%-49%), non-SCC, PS 0-1, AND who are ineligible for or decline combination of doublet platinum ± pembrolizumab, clinicians may offer single-agent pembrolizumab<br>Evidence quality: Low; Strength of Recommendation: Weak | For patients with negative (< 1% or unknown) and low positive (TPS 1%-49%) PD-L1 expression, non-SCC, PS 0-1, AND are eligible for chemotherapy and pembrolizumab:<br>2.1. Clinicians should offer pembrolizumab/carboplatin/pemetrexed<br>Evidence quality: High; Strength of recommendation: Strong<br>2.2. Clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab<br>Evidence quality: Intermediate; Strength of recommendation: Moderate<br>2.3. Clinicians may offer atezolizumab/carboplatin/nab-paclitaxel<br>Evidence quality: Intermediate; Strength of recommendation: Moderate<br>2.4. (For patients who have the above characteristics) AND have contraindications to/declines immunotherapy, clinicians should offer standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update<br>Evidence quality: High; Strength of recommendation: Strong<br>2.5. (For patients with above characteristics) AND have contraindications to/declines immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer nonplatinum-based two-drug therapy as outlined in the 2015 update<br>Evidence quality: Low; Strength of recommendation: Weak<br>2.6. For patients with low positive PD-L1 expression (TPS 1%-49%), non-SCC, PS 0-1, AND who are ineligible for or decline combination of doublet platinum ± pembrolizumab, clinicians may offer single-agent pembrolizumab<br>Evidence quality: Low; Strength of Recommendation: Weak<br>2.7. In addition to 2020 options, for patients with negative (0%) and low positive PD-L1 expression (TPS 1%-49%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy<br>Evidence quality: Moderate; Strength of recommendation: Weak |

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**TABLE 1.** Comparison of 2020 and 2022 Recommendations (continued)

| 2020 Recommendation (with older numbering scheme) | 2022 |
|---|---|
| Recommendation A2.b. In the context of shared decision making, combination therapy, single-agent therapy, or palliative therapy alone may be used for patients in this population with PS of 2 (chemotherapy [Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak]; palliative care [Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong]) | No change |
| For patients with high PD-L1 expression (TPS ≥ 50%) SCC, and PS 0-1, in the absence of contraindications to ICI therapy:<br>3.1. Clinicians should offer single-agent pembrolizumab)<br>Evidence quality: High; Strength of recommendation: Strong<br>3.2. Clinicians may offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel)<br>Evidence quality: Intermediate; Strength of recommendation: Moderate<br>3.3. There are insufficient data to recommend any other checkpoint inhibitors or to recommend combination checkpoint inhibitors or any other combinations of ICIs with chemotherapy in the first-line setting<br>Evidence quality: High; Strength of recommendation: Strong | For patients with high PD-L1 expression (TPS ≥ 50%) SCC, and PS 0-1, in the absence of contraindications to ICI therapy:<br>3.1. Clinicians should offer single-agent pembrolizumab<br>Evidence quality: High; Strength of recommendation: Strong<br>3.2. Clinicians may offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel)<br>Evidence quality: Intermediate; Strength of recommendation: Moderate<br>3.3. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer single-agent atezolizumab<br>Evidence quality: Moderate; Strength of recommendation: Strong<br>3.4. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer single-agent cemiplimab<br>Evidence quality: moderate; Strength of recommendation: strong<br>3.5. In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy<br>Evidence quality: Moderate; Strength of recommendation: Weak<br>3.6. (previously 3.3) There are insufficient data to recommend any other checkpoint inhibitors or to recommend combination checkpoint inhibitors or any other combinations of ICIs with chemotherapy in the first-line setting<br>Evidence quality: High; Strength of recommendation: Strong |
| For patients with negative (TPS 0%, < 1%, or unknown) and/or low positive (TPS 1%-49%) PD-L1 expression and SCC, in the absence of contraindications to ICI therapies:<br>4.1. Clinicians should offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel)<br>Evidence quality: Intermediate; Strength of recommendation: Strong<br>4.2. (For patients who have the above characteristics)—<br>AND with contraindications to immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with non-platinum-based two drug combinations as outlined in the 2015 update<br>Evidence quality: High; Strength of recommendation: Strong<br>4.3. For patients with contraindications to immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with non-platinum-based two drug combinations as outlined in the 2015 update<br>Evidence quality: Intermediate; Strength of recommendation: Weak<br>4.4. Patients with low positive PD-L1 (TPS 1%-49%) AND who are ineligible for or decline combination of doublet platinum/pembrolizumab AND have contraindications to doublet-chemotherapy, clinicians may offer single-agent pembrolizumab, in the absence of contraindications to immune checkpoint therapies.<br>Evidence quality: Low; Strength of recommendation: Weak | For patients with negative (TPS 0%, < 1%, or unknown) and/or low positive (TPS 1%-49%) PD-L1 expression and SCC, in the absence of contraindications to ICI therapies:<br>4.1. Clinicians should offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel<br>Evidence quality: Intermediate; Strength of recommendation: Strong<br>4.2. (For patients who have the above characteristics)—<br>AND with contraindications to immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with non-platinum-based two drug combinations as outlined in the 2015 update<br>Evidence quality: High; Strength of recommendation: Strong<br>4.3. For patients with contraindications to immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with nonplatinum-based two drug combinations as outlined in the 2015 update<br>Evidence quality: Intermediate; Strength of recommendation: Weak<br>4.4. Patients with low positive PD-L1 (TPS 1%-49%) AND who are ineligible for or decline combination of doublet platinum/pembrolizumab AND have contraindications to doublet-chemotherapy, clinicians may offer single-agent pembrolizumab, in the absence of contraindications to immune checkpoint therapies<br>Evidence quality: Low; Strength of recommendation: Weak<br>4.5. In addition to 2020 recommendations 4.1-4.4, for patients with negative (TPS 0%) and low positive (TPS 1%-49%) PD-L1 expression, SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy<br>Evidence quality: Moderate; Strength of recommendation: Weak |
| Recommendation A3.a. In the context of shared decision making, combination chemotherapy, single-agent therapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3a. (chemotherapy: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: weak. Palliative care: type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong) | No change |

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**TABLE 1.** Comparison of 2020 and 2022 Recommendations (continued)

| 2020 Recommendation (with older numbering scheme) | 2022 |
|---|---|
| No changes (therefore, carried over from 2017)<br>Recommendation B1. Squamous and nonsquamous and negative/unknown *EGFR* mutation, *ALK* or *ROS1* gene rearrangement.<br>i. For patients who received first-line chemotherapy and have not received prior immune checkpoint inhibitor therapy, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab in patients with positive tumor PD-L1 expression (TPS ≥ 1%, 22C3 assay), in the absence of contraindications to immune checkpoint therapy (type: evidence based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong)<br>ii. For patients with negative or unknown tumor PD-L1 expression (TPS < 1%) who received first-line chemotherapy, clinicians should use single-agent nivolumab or atezolizumab in the absence of contraindications to immune checkpoint therapy (type: evidence based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong)<br>iii. There are insufficient data to recommend combination checkpoint inhibitors or immune checkpoint inhibitors with chemotherapy in the second-line setting<br>iv. For patients who received an immune checkpoint inhibitor as first-line therapy, clinicians should offer standard platinum-based chemotherapy as outlined in the 2015 update (type: evidence based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong), or nonplatinum-based two-drug therapy if platinum contraindicated as outlined in the 2015 update (type: informal consensus; benefits outweigh harms; evidence quality: low; strength of recommendation: strong)<br>v. For patients with contraindications to immune checkpoint inhibitor therapy after first-line chemotherapy, docetaxel is recommended as second-line therapy (type: evidence-based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)<br>Nonsquamous only<br>vi. Patients with non-SCC who have not previously received pemetrexed-based first-line or maintenance therapy should be offered pemetrexed second-line (type: evidence based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong) | 5.1. In addition to previously recommended regimens, for patients with non-SCC who received an ICI and chemotherapy as first-line therapy, clinicians may offer paclitaxel plus bevacizumab in the second-line setting<br>Evidence quality: Low; Strength of recommendation: Weak |
| The evidence does not support the selection of a specific second-line chemotherapy drug or combination on the basis of age alone. This recommendation has not changed. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC | No change |
| Recommendation C1. For the majority of patients who received chemotherapy with or without bevacizumab and immune checkpoint therapy, clinicians should offer the options of single-agent pemetrexed or docetaxel in the third-line setting (type: informal consensus; benefits outweigh harms; evidence quality: low; strength of recommendation: strong) | 6.1. For the majority of patients with non-SCC, who received chemotherapy with or without bevacizumab and ICI therapy (in either sequence), clinicians should offer the options of single-agent pemetrexed or docetaxel or paclitaxel plus bevacizumab in the third-line setting<br>Evidence quality: Low; Strength of recommendation: Weak |
| Recommendation D1. Data are not sufficient to make a recommendation for or against using cytotoxic drugs as fourth-line therapy; patients should consider experimental treatment, clinical trials, and continued best supportive (palliative) care | No change |

NOTE. Recommendations from 2017 and earlier that were not updated in 2020 are not included in this table.

Abbreviations: ICI, immune checkpoint inhibitor; non-SCC, nonsquamous cell carcinoma; NSCLC, non–small-cell lung cancer; PD-L1, programmed death ligand-1; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score.

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

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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 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, five RCTs remained, forming the evidentiary basis for the guideline recommendations (Fig 1).[3,5,6,10,11]

The identified trials were published between 2020 and 2021. The randomized trials compared similar interventions. The primary outcome for five of the trials was therapeutic efficacy,[3,5,6,10,11] although they were framed in a variety of ways such as PFS and OS. Tables 2-11 present the included articles from the literature search pertinent to the development of the recommendations.

### 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 3-11, study quality was formally assessed for the five RCTs identified. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, etc, generally indicating a low to moderate potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results.

Additional data on key outcomes of interest and key AEs are reported in Tables 3-11. Data analysis regarding unchanged recommendations is reviewed in the prior 2020 update.

## RECOMMENDATIONS (NEW ± MODIFIED RECOMMENDATIONS)

### Clinical Question 1

For patients with stage IV NSCLC without driver alterations, what are the most effective first-line therapies?

### For High PD-L1 Expression and Non-SCC

***Recommendation 1.5 (note numbering change: 2020 1.5 will become 2022 1.8).*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer single-agent atezolizumab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 1.6.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer single-agent cemiplimab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 1.7.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

Note: 2020 options:

- Single-agent pembrolizumab (Evidence quality: High; Strength of recommendation: Strong)
- Pembrolizumab + carboplatin + pemetrexed (Evidence quality: High; Strength of recommendation: Strong)
- Atezolizumab + carboplatin + paclitaxel + bevacizumab in the absence of contraindications to bevacizumab (Evidence quality: Intermediate; Strength of recommendation: Moderate)
- Atezolizumab + carboplatin + nab-paclitaxel (Evidence quality: Low; Strength of recommendation: Weak)
- There are insufficient data to recommend any other checkpoint inhibitors or to recommend combination checkpoint inhibitors or any other combinations of immune checkpoint inhibitors (ICIs) with chemotherapy in the first-line setting (Evidence quality: High; Strength of recommendation: Strong).

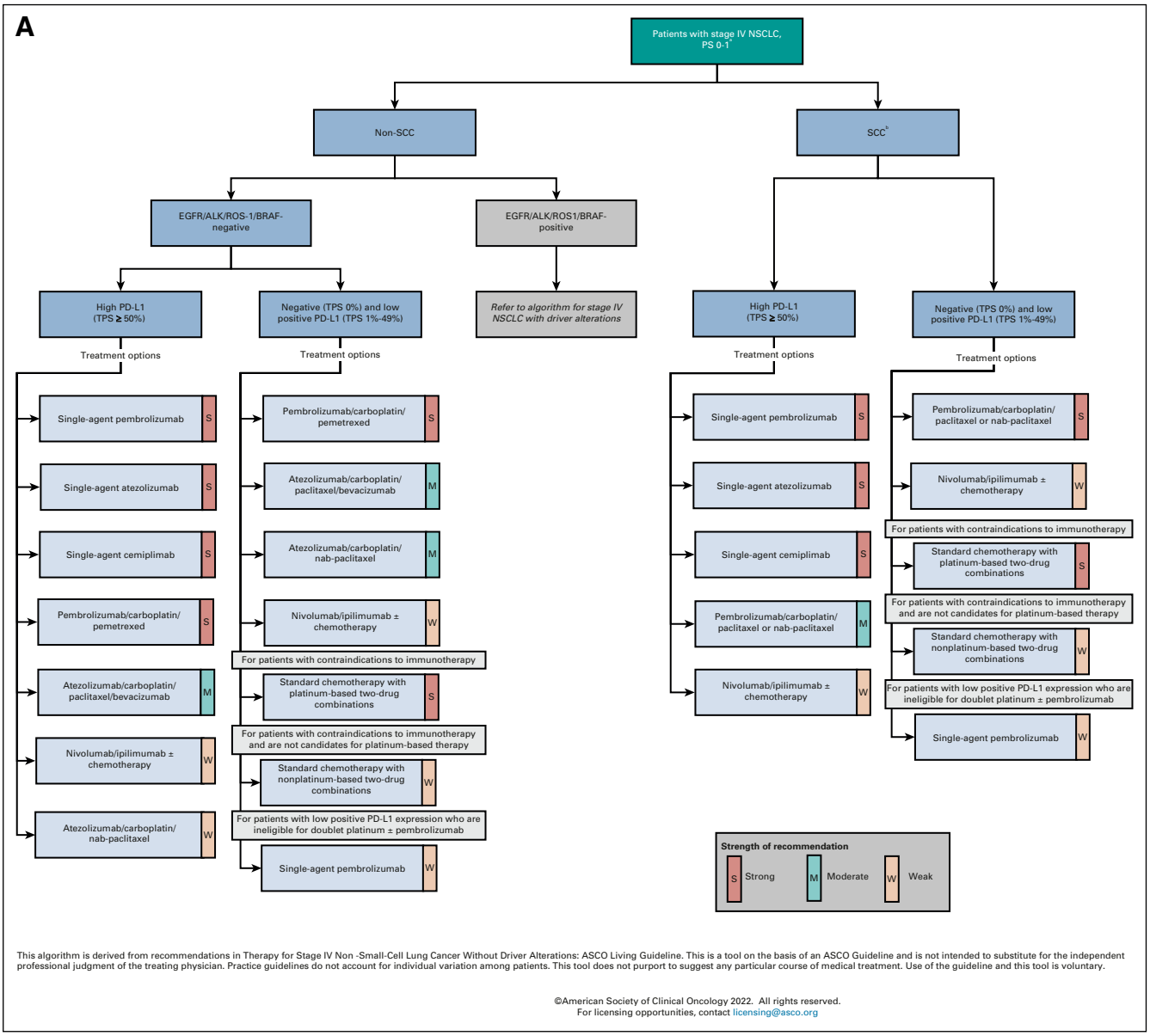


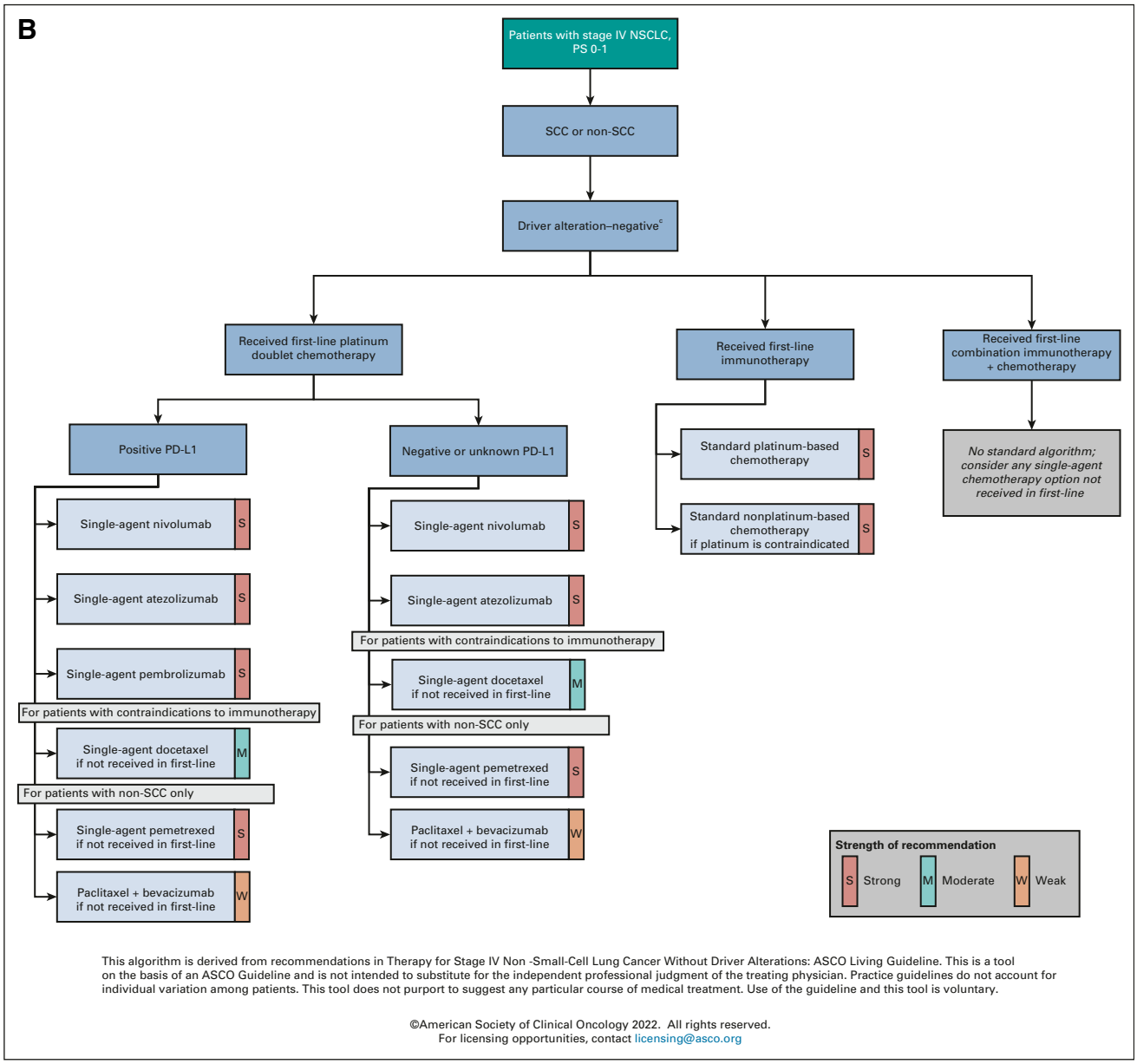

**FIG 1.** Algorithm. (A) First-line treatment options for patients with stage IV NSCLC without driver alterations. (B) Third-line treatment options for patients with stage IV non-small cell lung cancer without driver alterations. (C) Third-line treatment options for patients with stage IV NSCLC without driver alterations. [a]This does not apply to patients with stage IV NSCLC with rarer histologies, eg, large cell neuroendocrine, etc. [b]Kalemkerian et al.[26] [c]Driver alterations including *EGFR*, *ALK*, *ROS-1*, *BRAF* V600E, *MET* exon 14, *NTRK, KRAS*, and *RET*. *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; non-SCC, nonsquamous cell carcinoma; NSCLC, non–small-cell; lung cancer; PD-L1, program death ligand-1; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score. (continued on next page)

### Negative or Low PD-L1 Expression and Non-SCC

***Recommendation 2.7.*** In addition to 2020 options, for patients with negative (0%) and low positive PD-L1 expression (TPS 1%-49%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

Note: 2020 options:

- Pembrolizumab + carboplatin + pemetrexed (Evidence quality: High; Strength of recommendation: Strong)
- Atezolizumab + carboplatin + paclitaxel + bevacizumab in the absence of contraindications to bevacizumab (Evidence quality: Intermediate; Strength of recommendation: Moderate).




This algorithm is derived from recommendations in Therapy for Stage IV Non -Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline. This is a tool on the basis of an ASCO Guideline and is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients. This tool does not purport to suggest any particular course of medical treatment. Use of the guideline and this tool is voluntary.



**FIG 1.** (Continued).

- Atezolizumab + carboplatin + nab-paclitaxel (Evidence quality: Intermediate; Strength of recommendation: Moderate).
- If have contraindications to ± declines immunotherapy, clinicians should offer standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update (Evidence quality: High; Strength of recommendation: Strong).
- If have contraindications to ± declines immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer nonplatinum-based two-drug therapy as outlined in the 2015 update (Evidence quality: Low; Strength of recommendation: Weak).
- (1%-49% only): If ineligible for or decline combination of doublet platinum ± pembrolizumab, clinicians may offer single-agent pembrolizumab (Evidence quality: Low; Strength of Recommendation: Weak).

### High PD-L1 Expression and Squamous Cell Carcinoma (SCC)

***Recommendation 3.3.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer single-agent atezolizumab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 3.4.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and

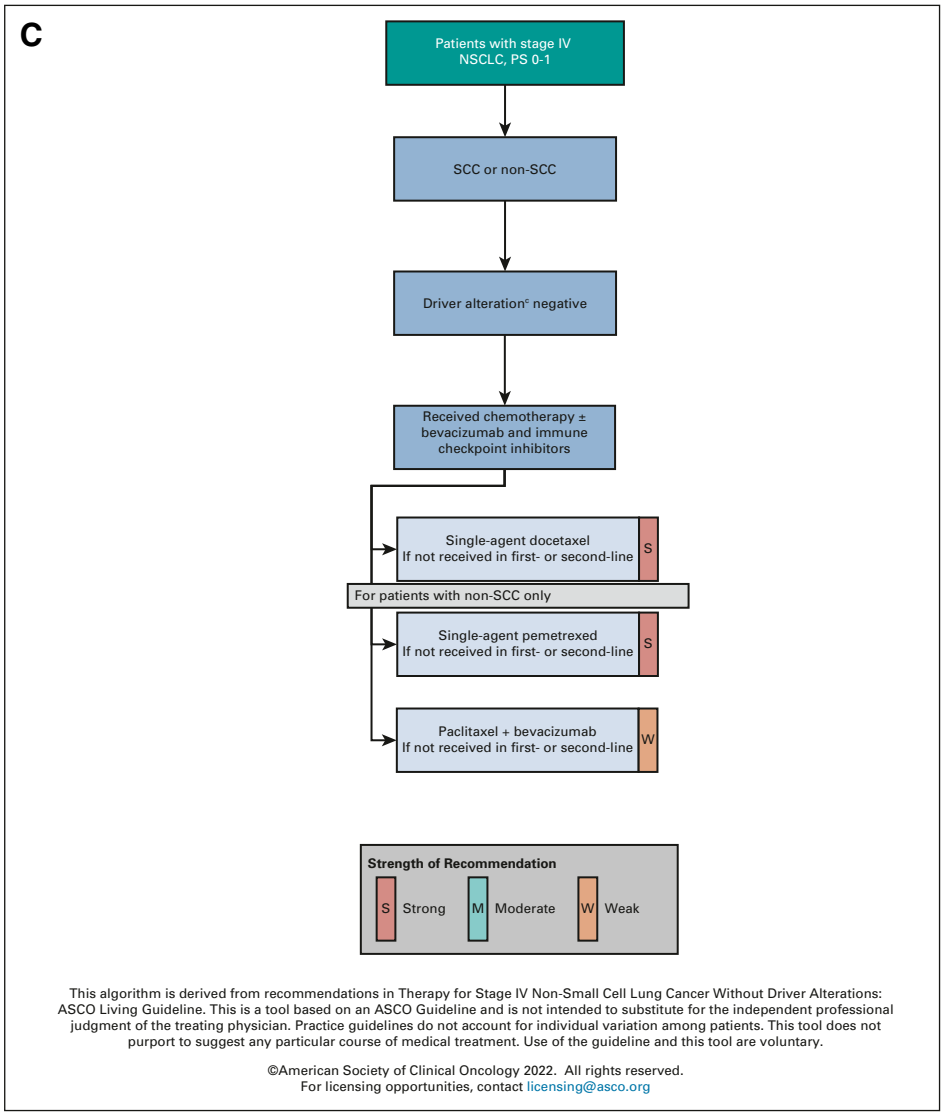



**FIG 1.** (Continued).

PS 0-1, clinicians may offer single-agent cemiplimab (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Strong).

***Recommendation 3.5.*** In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

Note: 2020 options:

- Single-agent pembrolizumab (Evidence quality: High; Strength of recommendation: Strong)
- Pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel (Evidence quality: Intermediate; Strength of recommendation: Moderate).
- There are insufficient data to recommend any other checkpoint inhibitors or to recommend combination checkpoint inhibitors or any other combinations of ICIs with chemotherapy in the first-line setting (Evidence quality: High; Strength of recommendation: Strong).

**Literature review update and analysis.** The updated systematic review identified four RCTs in the non-SCC and SCC settings.[3,6,10,11] Herbst 2021, IMpower 110 was a RCT of 554 participants comparing atezolizumab with platinum-based chemotherapy.[10] In the primary outcome of OS, the results for 155 participants with non-SCC showed a modest benefit in the absolute effect estimate of 150/1,000 fewer deaths (95% CI, 255 fewer to 14 fewer). For PFS, 205 participants with non-SCC showed similar results in absolute effect estimate and hazard ratio (HR). With a moderate certainty, atezolizumab probably improves OS and PFS in patients with high PD-L1 compared with platinum-based chemotherapy. In AE results, there were lower numbers of grade 3-5 AEs, with a relative risk of 0.60 (95% CI, 0.49 to 0.73), with the

**TABLE 2.** Characteristics of Studies Identified in the Literature Search

| Author Year Reference | Interventions [or] Comparisons | No. of Patients | Patient Characteristics: Median Age, years | Sex, % Male | Sex, % Female | Never Smokers, % | Histology: Non-SCC, % | Histology: SCC, % | PD-L1 Status: High | PD-L1 Status: Low | PD-L1 Status: Negative |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Herbst et al 2020[10] IMpower110 | Atezolizumab<br>Chemotherapy[a] | 277<br>277 | 64 (30-81)<br>65 (30-87) | 70.8<br>69.7 | 29.2<br>30.3 | 13.4<br>12.6 | 69.3<br>69.7 | 30.7<br>30.3 | n = 107<br>n = 98 | b | |
| Paz-Ares et al 2021[3] and Reck et al 2020[4] (Checkmate 9LA) | Nivolumab + ipilimumab + chemotherapy<br>Chemotherapy | 361<br>358 | ≥ 65- < 75: 41%<br>41% | 70<br>70 | 30<br>30 | 13<br>14 | 69<br>69 | 31<br>31 | 22<br>20 | 38<br>32 | 40<br>39 |
| Cortot et al 2020[5] | Weekly paclitaxel + bevacizumab<br>Docetaxel | 111<br>55 | 59.6%<br>59.7% | 70.3<br>72.3 | | 8.1<br>16.4 | 90.1<br>92.7 | NR | NR | NR | NR |
| Sezer et al 2021[6] | Cemiplimab<br>Platinum-doublet chemotherapy | 283<br>280[c] | 63 (58-69)<br>64 (58-70) | 88<br>83 | 12<br>18 | NR | 57<br>57 | 43<br>43 | 100<br>100 | | |
| Boyer et al 2021[11] | Pembrolizumab + ipilimumab<br>Pembrolizumab + placebo | 284<br>284 | 64 (35-85) | 71.1<br>67.3 | | 10.2<br>8.8 | 72.9<br>71.5 | 27.1<br>28.5 | 100<br>100 | | |

Abbreviations: non-SCC, nonsquamous cell carcinoma; NR, not reported; PD-L1, programmed death ligand-1; SCC, squamous cell carcinoma.
[a]Cisplatin or carboplatin in addition to pemetrexed.
[b]High or intermediate, n = 166 atezolizumab, n = 162 control.
[c]Intent-to-treat population.

caveat that the investigators analyzed AEs in patients with either histology and any PD-L1 status.

This study is also relevant to first-line treatment for patients with high PD-L1 expression (TPS ≥ 50%) and SCC. Fifty patients in the SCC, high PD-L1 subgroup were included for the OS analysis. It is unclear whether atezolizumab increases survival in the immature analysis. For 12-month PFS, atezolizumab improved PFS compared with platinum-based chemotherapy in the 205 patients in this subgroup. There was a statistically significant decrease in relative risks of grade 3-5 serious adverse events with the immunotherapy.

The CheckMate-9LA trial study[3] randomly assigned patients to nivolumab and ipilimumab plus chemotherapy versus chemotherapy. There were 174 patients in the subgroup of patients with stage IV NSCLC and high PD-L1 expression (TPS ≥ 50%). For these patients, nivolumab

**TABLE 3.** Studies Informing the Evidence Review—Immunotherapy

| Author Trial Year Reference | No. of Patients Randomly Assigned | Comparison | Significance $P < .05$ OS | Grade 3-5 Adverse Events, % | PFS |
|---|---|---|---|---|---|
| Herbst et al 2020[10] IMpower110 | 277<br>277 | Atezolizumab<br>Cisplatin or carboplatin in addition to pemetrexed (non-SCC) OR platinum/gemcitabine (SCC) | ↑ | ↑ | 34<br>57 |
| Paz-Ares et al 2021[3] and Reck et al 2020[4] (CheckMate 9LA) | 361 (22% ≥ 50%); (40% < 1%)<br>358 (29% ≥ 50%); (39% < 1%)<br>69% non-SCC | Nivolumab + ipilimumab + chemotherapy<br>Chemotherapy | ↑ | ↑ | 47<br>38 |
| Paz-Ares et al 2021[3] and Reck et al 2020[4] SCC | 113/361<br>111/358<br>31% SCC each arm (by PD-L1, any histology 127 *v* 106 [1%-49%]) | | | | |
| Sezer et al 2021[6] | 283<br>280 | Cemiplimab<br>Platinum-doublet chemotherapy | ↑ | ↑ | 14<br>39 |
| Boyer et al 2021[11] | 284<br>284 | Pembrolizumab + ipilimumab<br>Pembrolizumab + placebo | — | — | 62<br>50 |

Abbreviations: non-SCC, nonsquamous cell carcinoma; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; SCC, squamous cell carcinoma.
↑ Favors intervention $P < .05$.
↓ Favors control $P < .05$.
— No significant differences.

**TABLE 4.** High, Non-SCC—Atezolizumab

**Population: Patients With Nondriver-Mutated, Stage IV, High PD-L1 Expression (TPS ≥ 50%), Non-SCC NSCLC, PS 0-1 (Herbst et al[10])**
**Intervention: Atezolizumab**
**Comparator: Cisplatin or Carboplatin in Addition to Pemetrexed**

| Outcome Time Frame | Study Results and Measurements | Absolute Effect Estimates | | Certainty of the Evidence (quality of evidence) | Plain Text Summary |
|---|---|---|---|---|---|
| | | Platinum-Based Chemotherapy | Atezolizumab | | |
| OS[a] (primary outcome) at 12 months | HR: 0.62 (95% CI, 0.4 to 0.96) on the basis of data from 155 patients in one study[b] Follow-up 15.7 months | 494 per 1,000 | 344 per 1,000 Difference: 150 fewer per 1,000 (95% CI, 255 fewer to 14 fewer) | Moderate[c] | Atezolizumab probably improves OS in PD-L1-high patients compared with platinum-based chemotherapy |
| PFS at 12 months | HR: 0.63 (95% CI, 0.45 to 0.88) On the basis of data from 205 patients in one study[b,d] Follow-up 15.7 months | 784 per 1,000 | 619 per 1,000 Difference: 165 fewer per 1,000 (95% CI, 286 fewer to 44 fewer) | Moderate[c] | Atezolizumab probably improves PFS in PD-L1-high patients compared with platinum-based chemotherapy |
| Grade 3-5 AEs | Relative risk: 0.60 (95% CI, 0.49 to 0.73) On the basis of data from 549 patients in one study[e] Follow-up 15.7 months | 567 per 1,000 | 340 per 1,000 Difference: 227 fewer per 1,000 (95% CI, 289 fewer to 153 fewer) | Moderate[c,f] | Atezolizumab probably decreases grade 3-4 AE compared with platinum-based chemotherapy. Includes patients with all PD-L1 expressions and both histologies |

Abbreviations: AE, adverse event; HR, hazard ratio; non-SCC, nonsquamous cell carcinoma; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score.

[a]Median follow-up for the high PD-L1 expression population was 15.7 months.

[b]Only patients in PD-L1 TPS ≥ 50%, non-SCC subgroup. Number of events in high PD-L1, non-SCC subgroup NR. Baseline/comparator: control arm of reference used for intervention. Estimated from 50.6% of patients in subgroup alive at 12 months.

[c]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; inadequate concealment of allocation during random assignment process, resulting in potential for selection bias; indirectness: differences between the population of interest and those studied (includes all histologic types); imprecision: only data from one study; publication bias: commercially funded study.

[d]Baseline/comparator control arm of reference used for intervention. Estimated from 21.6% of patients in subgroup alive at 12 months.

[e]Includes all patients, not just those with high PD-L1 expression, non-SCC; 286 in intervention and 263 in control. One hundred forty-nine in control group out of 263 had grade 3-5 events. Ninety-seven in intervention arm out of 286 had events. Relative risk and CI for adverse events generated from data in paper using Medcalc's Relative Risk Calculator.[12]

[f]Indirectness: adverse event data for all patients regardless of PD-L1 status and histologic type.

plus ipilimumab probably improved the OS in patients with high PD-L1 compared with chemotherapy, with a HR of 0.66 (95% CI, 0.44 to 0.89), as well as for all patients with SCC NSCLC (n = 227; HR, 0.62 [95% CI, 0.45 to 0.86]) and non-SCC NSCLC (n = 492; HR, 0.69 [95% CI, 0.55 to 0.87]). In this subgroup of patients with advanced NSCLC and high PD-L1 expression, PFS was also improved with nivolumab plus ipilimumab (HR, 0.61 [95% CI, 0.42 to 0.89]) as it was for all patients (irrespective of PD-L1 expression) with SCC NSCLC (HR, 0.57 [95% CI, 0.42 to 0.78]) and non-SCC NSCLC (HR, 0.74 [95% CI, 0.60 to 0.92]). Grade 3-4 treatment-related adverse events (TRAEs) were increased with the immunotherapy and chemotherapy intervention (in either histology or PD-L1 subgroup). The certainty of the evidence was low, due to indirectness; therefore, the strength of recommendation is weak.

In addition, this study included data on first-line treatment for patients with advanced NSCLC and either negative (< 1%) or low PD-L1 expression (TPS 1%-49%) SCC.[3] The subgroup analysis of OS included patients in low PD-L1 (n = 233) and negative PD-L1 (n = 264) subgroups. Nivolumab + ipilimumab + chemotherapy probably improved OS in patients with low (HR, 0.61 [95% CI, 0.44 to 0.84]) and negative (HR, 0.62 [95% CI, 0.45 to 0.85]) PD-L1 expression compared with chemotherapy alone. Similarly, for PFS, the triplet combination may have improved PFS compared with platinum-based chemotherapy in both subgroups of patients, namely those with low PD-L1 (HR, 0.69 [95% CI, 0.51 to 0.94]) and negative PD-L1 (HR, 0.71 [95% CI, 0.53 to 0.94]) expression. There was a statistically significant increase in relative risks of grade 3-4 TRAEs with the immunotherapy and chemotherapy regimen.

An additional study was identified of pembrolizumab and ipilimumab[11] (see Table 9 for the data). The trial was negative and did not support changing a recommendation.

**Clinical interpretation.** Patients with advanced or metastatic NSCLC (who do not harbor sensitizing *EGFR* mutations or *ALK* rearrangements) and have high PD-L1 expression (≥ 50%) have been consistently shown to have better outcomes (OS, PFS, and relative risk) when treated with monotherapy that may either be a PD-1 ICI (pembrolizumab) or a PD-L1 ICI (atezolizumab or cemiplimab) versus standard

**TABLE 5.** High, Non-SCC—Nivolumab + Ipilimumab

**Population: Patients With Nondriver-Mutated, Stage IV, High PD-L1 Expression (TPS ≥ 50%) Non-SCC, NSCLC (Reck et al[4] and Paz-Ares et al[3])**
**Intervention: Nivolumab + Ipilimumab + Chemotherapy**
**Comparator: Chemotherapy Alone**

| Outcome Time Frame | Study Results and Measurements | Absolute Effect Estimates | | Certainty of the Evidence (quality of evidence) | Plain Text Summary |
|---|---|---|---|---|---|
| | | Chemotherapy | Nivolumab + Ipilimumab + CT | | |
| OS in PD-L1 high | HR: 0.66 (95% CI, 0.44 to 0.89)<br>On the basis of data from 174 patients in one study[a]<br>Follow-up 12.7 months | 622 per 1,000 | 474 per 1,000<br>Difference: 148 fewer per 1,000 (95% CI, 274 fewer to 43 fewer) | Low[b] | Nivolumab + ipilimumab + chemotherapy probably improves OS in patients with PD-L1-high compared with chemotherapy alone |
| OS in non-SCC (all PD-L1 levels) | HR: 0.69 (95% CI, 0.55 to 0.87)<br>On the basis of data from 492 patients in one study[a]<br>Follow-up 12.7 months | 646 per 1,000 | 512 per 1,000<br>Difference: 134 fewer per 1,000 (95% CI, 211 fewer to 51 fewer) | Low[c] | Nivolumab + ipilimumab + chemotherapy may improve OS in patients with non-SCC compared with chemotherapy alone (all PD-L1 expressions) |
| PFS | HR: 0.68 (95% CI, 0.57 to 0.82)<br>On the basis of data from 719 patients in one study<br>Follow-up 12.7 months | 820 per 1,000 | 688 per 1,000<br>Difference: 132 fewer per 1,000 (95% CI, 196 fewer to 65 fewer) | Low[d] | Nivolumab + ipilimumab + chemotherapy may improve PFS compared with chemotherapy alone. Includes patients with all PD-L1 expressions and both histologies |
| Grade 3 or 4 TRAEs[e] | Relative risk: 1.24 (95% CI, 1.04 to 1.48)<br>On the basis of data from 707 patients in one study<br>Follow-up 12.7 months | 378 per 1,000 | 469 per 1,000<br>Difference: 91 more per 1,000 (95% CI, 15 more to 181 more) | Low[d] | Nivolumab + ipilimumab + chemotherapy may increase grade 3 or 4 treatment-related adverse events compared with chemotherapy alone. Includes patients with all PD-L1 expressions and both histologies |
| PFS in non-SCC (Data Supplement) | HR: 0.74 (95% CI, 0.6 to 0. 0.92)<br>On the basis of data from 492 patients in one study<br>Follow-up 12.2 months | 736 per 1,000 | 627 per 1,000<br>Difference: 109 fewer per 1,000 (95% CI, 186 fewer to 30 fewer) | Low[c] | Nivolumab + ipilimumab + chemotherapy may improve PFS compared with chemotherapy alone. Includes patients with all PD-L1 expressions |

Abbreviations: CT, chemotherapy; HR, hazard ratio; non-SCC, nonsquamous cell carcinoma; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PS, performance status; SAE, serious adverse event; TPS, tumor proportion score.

[a]Primary study. Baseline/comparator. Control arm of reference used for intervention.

[b]Serious risk of bias: open-label study; serious indirectness: data for both histologic types. not serious: single study, commercially funded. Risk 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; and inadequate concealment of allocation during random assignment process.

[c]Risk 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; inadequate concealment of allocation during random assignment process, resulting in potential for selection bias; indirectness: serious. Differences between the population of interest and those studied (all PD-L1 levels included).

[d]Risk of bias: serious. 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; indirectness: serious. Due to inclusion of all PD-L1 expression groups and both histologic subtypes.

[e]Relative risk and CI for adverse events generated from data in paper using Medcalc's Relative Risk Calculator.[12]

**TABLE 6.** Negative or Low, Non-SCC

**Population: Patients With Nondriver-Mutated, Stage IV, Negative (< 1%) or Low (< 50%) PD-L1 Expression Non-SCC NSCLC (Reck et al[4] and Paz-Ares et al[3])**
**Intervention: Nivolumab + Ipilimumab + Chemotherapy**
**Comparator: Chemotherapy Alone**

| Outcome Time Frame | Study Results and Measurements | Absolute Effect Estimates | | Certainty of the Evidence (quality of evidence) | Plain Text Summary |
|---|---|---|---|---|---|
| | | Chemotherapy | Nivolumab + Ipilimumab + CT | | |
| OS in PD-L1 low | HR: 0.61 (95% CI, 0.44 to 0.84)<br>On the basis of data from 233 patients in one study[a]<br>Follow-up 12.7 months | 736 per 1,000 | 556 per 1,000<br>Difference: 180 fewer per 1,000 (95% CI, 293 fewer to 63 fewer) | Moderate[b] | Nivolumab + ipilimumab + chemotherapy probably improves OS in PD-L1 low patients compared with chemotherapy alone |
| OS in PD-L1-negative | HR: 0.62 (95% CI, 0.45 to 0.85)<br>On the basis of data from 264 patients in one study[a]<br>Follow-up 12.7 months | 690 per 1,000 | 516 per 1,000<br>Difference: 134 fewer per 1,000 (95% CI, 211 fewer to 51 fewer) | Moderate[b] | Nivolumab + ipilimumab + chemotherapy probably improves OS in PD-L1 negative patients compared with chemotherapy alone |
| PFS | HR: 0.68 (95% CI, 0.57 to 0.82)<br>On the basis of data from 719 patients in one study<br>Follow-up 12.7 months | 820 per 1,000 | 688 per 1,000<br>Difference: 132 fewer per 1,000 (95% CI, 196 fewer to 65 fewer) | Low[c] | Nivolumab + ipilimumab + chemotherapy may improve PFS compared with chemotherapy alone. Includes patients with all PD-L1 expressions and both histologies |
| Grade 3 or 4 TRAEs[3] | Relative risk: 1.23 (95% CI, 1.04 to 1.46)<br>On the basis of data from 707 patients in one study<br>Follow-up 12.7 months | 378 per 1,000 | 469 per 1,000<br>Difference: 91 more per 1,000 (95% CI, 15 more to 181 more) | Low[c,d] | Nivolumab + ipilimumab + chemotherapy may increase grade 3 or 4 treatment-related adverse events compared with chemotherapy alone. Includes patients with all PD-L1 expressions and both histologies |
| PFS[e]<br>SCC all PD-L1 levels (Data Supplement) | HR: 0.57 (95% CI, 0.42 to 0.82)<br>On the basis of data from 361 patients in one study[e]<br>Follow-up 12.2 | 750 per 1,000 | 546 per 1,000<br>Difference: 204 fewer per 1,000 (95% CI, 309 fewer to 71 fewer) | Low[f] | Nivolumab + ipilimumab + chemotherapy may improve PFS compared with chemotherapy alone. Includes patients with all PD-L1 expressions and SCC |

Abbreviations: CT, chemotherapy; HR, hazard ratio; non-SCC, nonsquamous cell carcinoma; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PS, performance status; SAE, serious adverse event; SCC, squamous cell carcinoma; TPS, tumor proportion score.

[a]Primary study. Baseline/comparator control arm of reference used for intervention.

[b]Risk 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; inadequate concealment of allocation during random assignment process, resulting in potential for selection bias, due to abstract data only; indirectness: serious. Differences between the population of interest and those studied (both histologies included).

[c]Due to serious risk of bias, due to serious indirectness risk of bias: serious. 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, due to abstract data only. Indirectness: serious. Due to inclusion of all PD-L1 expression groups and both histologic subtypes.

[d]Relative risk and CI for adverse events generated from data in paper using Medcalc's Relative Risk Calculator.[12]

[e]Data Supplement.

[f]Serious risk of bias: open-label study; serious indirectness: data for both histologic types. Not serious: single study, commercially funded; serious indirectness: data for all PD-L1 expressions. Differences between the population of interest and those studied (ie, all histologic subtypes included) were deemed to be not serious indirectness for anti–PD-1/PD-L1 therapies.

**TABLE 7.** All PD-L1 Expression, SCC

**Population: Patients With Nondriver-Mutated, Stage IV, All PD-L1 Expressions SCC NSCLC (Reck et al[4] and Paz-Ares et al[3])**
**Intervention: Nivolumab + Ipilimumab + Chemotherapy**
**Comparator: Chemotherapy Alone**

| Outcome Time Frame | Study Results and Measurements | Absolute Effect Estimates | | Certainty of the Evidence (quality of evidence) | Plain Language Summary |
|---|---|---|---|---|---|
| | | Chemotherapy | Nivo + Ipi + CT | | |
| OS in SCC[a] (all PD-L1 levels) | HR: 0.62 (95% CI, 0.45 to 0.86)<br>On the basis of data from 227 patients in one study. Follow-up 12.7 months | 741 per 1,000 | 567 per 1,000<br>Difference: 174 fewer per 1,000 (95% CI, 185 fewer to 54 fewer) | Low[b] | Nivolumab + ipilimumab + chemotherapy may improve OS in patients with SCC compared with chemotherapy alone |
| PFS[c] SCC all PD-L1 levels | HR: 0.57 (95% CI, 0.42 to 0.78)<br>On the basis of data from 361 patients in one study. Follow-up 12.7 months | 750 per 1,000 | 546 per 1,000<br>Difference: 204 fewer per 1,000 (95% CI, 309 fewer to 71 fewer) | Low[b] | Nivolumab + ipilimumab + chemotherapy may improve PFS compared with chemotherapy alone. Includes patients with all PD-L1 expressions and both histologies |
| Grade 3 or 4 TRAEs[d] | Relative risk: 1.24 (95% CI, 1.04 to 1.48)<br>On the basis of data from 707 patients in one study. Follow-up 12.7 months | 378 per 1,000 | 469 per 1,000<br>Difference: 91 more per 1,000 (95% CI, 15 more to 181 more) | Low[e] | Nivolumab + ipilimumab + chemotherapy may increase grade 3 or 4 treatment-related adverse events |

Abbreviations: CT, chemotherapy; HR, hazard ratio; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PS, performance status; SAE, serious adverse event; SCC, squamous cell carcinoma; TPS, tumor proportion score.

[a]Absolute estimate is from SCC histology with all PD-L1 expressions. Primary study. Baseline/comparator: control arm of reference used for intervention.

[b]Risk 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; inadequate concealment of allocation during random assignment process, resulting in potential for selection bias, indirectness: serious. Differences between the population of interest and those studied (all PD-L1 levels included).

[c]Refer the Data Supplement for SCC.

[d]Relative risk and CI for adverse events generated from data in paper using Medcalc's Relative Risk Calculator.[12]

[e]Risk of bias: serious. 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, due to abstract data only. Indirectness: serious. Due to inclusion of all PD-L1 expression groups and both histologic subtypes.

platinum-doublet chemotherapy. This approach is also associated with a more favorable side-effect and toxicity profile with monoimmunotherapy compared with chemotherapy. Pembrolizumab efficacy and safety has a much longer follow-up from the KEYNOTE-024 trial including 5-year OS data,[13-15] and no ambiguity regarding PD-L1 testing method (IHC 22C3 assay). By contrast, the IMpower110 trial involving atezolizumab is associated with complexity in both PD-L1 testing methods used (IHC SP142, SP263, and 22C3 assays) as well as the hierarchical testing design for primary outcome. Moreover, in the updated OS analysis,[16] even for the high PD-L1 expression group, the 95% CI of the HR (0.76) ranged from 0.54 to 1.09, although the median OS (20.2 months *v* 14.7 months for chemotherapy) and the safety data both continued to favor atezolizumab over chemotherapy. Cemiplimab is the third PD-L1 immune check point inhibitor (immunotherapy) to have been tested as monotherapy for high PD-L1 advanced or metastatic NSCLC without a targetable oncogenic driver. Although not practice-changing, the EMPOWER-Lung 1 trial does reinforce the findings of previous trials (involving pembrolizumab and subsequently atezolizumab) in this setting, thereby making cemiplimab another immunotherapy drug that can be offered to eligible patients for this particular indication. The dual immunotherapy and chemotherapy approach (nivolumab and ipilimumab) while improving clinical outcomes versus chemotherapy alone for patients with high PD-L1 advanced or metastatic NSCLC is also associated with increased adverse effects and toxicities that are not insignificant and therefore shows no advantage for monoimmunotherapy alone for routine clinical practice (the reason for a weak recommendation). In patients with high symptom burden or disease burden, clinicians may choose an option of a combination of chemotherapy with immunotherapy despite a high PD-L1 value on the basis of the results of the KEYNOTE-189 and KEYNOTE-407 trials involving pembrolizumab for non-SCC and SCC histologic types, respectively (data with atezolizumab being much less impressive). Although there is no head-to-head comparison between the triple combination strategy (PD-1 ICI + doublet chemotherapy) with the quadruple combination strategy (PD-1 ICI + cytotoxic

**TABLE 8.** All PD-L1 Expression, Both Histologies

**Population: Patients With High PD-L1 Expression (TPS ≥ 50%), Both SCC and Non-SCC (approximately 57% non-SCC); Lung Cancer, PS 0-1 (Sezer et al[6])**
**Intervention: Cemiplimab**
**Comparator: Platinum-Doublet Chemotherapy**

| Outcome Time Frame | Study Results and Measurements | Absolute Effect Estimates | | Certainty of the Evidence (quality of evidence) | Plain Text Summary |
|---|---|---|---|---|---|
| | | Platinum-Doublet Chemotherapy | Cemiplimab | | |
| OS | HR: 0.57 (95% CI, 0.42 to 0.77)<br>On the basis of data from 563 patients in one study<br>Follow-up 11 months | 375 per 1,000 | 235 per 1,000<br>Difference: 140 fewer per 1,000 (95% CI, 196 fewer to 71 fewer) | Moderate<br>Given that cemiplimab met the prespecified boundary for demonstration of superior OS benefit over chemotherapy, the IDMC recommended that the randomized portion of the study should be stopped[a] | Cemiplimab probably increases OS (assessed in patients with ≥ 50% PD-L1) |
| PFS | HR: 0.54 (95% CI, 0.43 to 0.68)<br>On the basis of data from 563 patients in one study<br>Follow-up 11 months | 704 per 1,000 | 482 per 1,000<br>Difference: 222 fewer per 1,000 (95% CI, 296 fewer to 141 fewer) | Moderate<br>Given that cemiplimab met the prespecified boundary for demonstration of superior OS benefit over chemotherapy, the IDMC recommended that the randomized portion of the study should be stopped[b] | Cemiplimab probably increases PFS (assessed in patients with ≥ 50% PD-L1) |
| Grade 3-5 AEs | HR: 0.36 (95% CI, 0.27 to 0.48)<br>On the basis of data from 697 patients in one study<br>Follow-up 11 months | 392 per 1,000 | 164 per 1,000<br>Difference: 228 fewer per 1,000 (95% CI, 266 fewer to 180 fewer) | Moderate<br>Given that cemiplimab met the prespecified boundary for demonstration of superior OS benefit over chemotherapy, the IDMC recommended that the randomized portion of the study should be stopped[c] | Cemiplimab probably decreases grade 3-5 AEs. AE assessment in ITT population, which included patients < 50% PD-L1 |

Abbreviations: AE, adverse event; HR, hazard ratio; IDMC, independent data monitoring committee; non-SCC, nonsquamous cell carcinoma; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score.

[a]Risk of bias: no serious. 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; trials stopping earlier than scheduled, resulting in potential for overestimating benefits; imprecision: no serious. Only data from one study; publication bias: no serious. Commercially funded study.

[b]Risk of bias: no serious. 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; trials stopping earlier than scheduled, resulting in potential for overestimating benefits; imprecision: no serious. Only data from one study; publication bias: no serious. Commercially funded study.

[c]Risk of bias: no serious. 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; trials stopping earlier than scheduled, resulting in potential for overestimating benefits; imprecision: no serious. Only data from one study; publication bias: no serious. Commercially funded study.

T-cell lymphocyte-4 ICI + doublet chemotherapy), clinicians should keep the additive toxicity of two ICIs in mind while making decisions regarding choice of treatment in these settings.

### Negative ± Low PD-L1 Expression and SCC

***Recommendation 4.5.*** In addition to 2020 recommendations 4.1-4.4, for patients with negative (TPS 0%) and low positive (TPS 1%-49%) PD-L1 expression, SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Type: Evidence based; Evidence quality: Moderate; Strength of recommendation: Weak).

Note: 2020 options:

- Pembrolizumab + carboplatin + (paclitaxel or nab-paclitaxel (Evidence quality: Intermediate; Strength of recommendation: Strong).
- With contraindications to immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with non-platinum-based two drug combinations as outlined in the 2015 update (Evidence quality: High; Strength of recommendation: Strong).
- For patients with contraindications to immunotherapy AND not deemed candidates for platinum-based therapy, clinicians should offer standard chemotherapy with nonplatinum-based two drug combinations as outlined in the 2015 update (Evidence quality: Intermediate; Strength of recommendation: Weak).
- (TPS 1%-49%) ineligible for or decline combination of doublet platinum + pembrolizumab AND have contraindications to doublet-chemotherapy, clinicians may offer single-agent pembrolizumab, in the absence of contraindications to immune checkpoint therapies

**TABLE 9.** High PD-L1 Expression, Both Histologies

**Population: Patients With High PD-L1 Expression (TPS ≥ 50%) Non-SCC and SCC (72%-73% non-SCC) Lung Cancer, PS 0-1 (Boyer et al[11])**
**Intervention: Pembrolizumab + Ipilimumab**
**Comparator: Pembrolizumab + Placebo**

| Outcome Time Frame | Study Results and Measurements | Absolute Effect Estimates | | Certainty of the Evidence (quality of evidence) | Plain Text Summary |
|---|---|---|---|---|---|
| | | Pembrolizumab + Placebo | Pembrolizumab + Ipilimumab | | |
| OS | HR: 1.08 (95% CI, 0.85 to 1.37)<br>On the basis of data from 568 patients in one study<br>Follow-up 20.6 months | 475 per 1,000 | 501 per 1,000<br>Difference: 26 more per 1,000 (95% CI, 53 fewer to 111 more) | High[a] | Pembrolizumab + ipilimumab has little or no difference on OS. 21.4 months (95% CI, 16.6 to NR) *v* 21.9 months (95% CI, 18.0 to NR) |
| PFS | HR: 1.06 (95% CI, 0.86 to 1.30)<br>On the basis of data from 568 patients in one study<br>Follow-up 20.6 months | 648 per 1,000 | 669 per 1,000<br>Difference: 21 more per 1,000 (95% CI, 55 fewer to 95 more) | High[b] | Pembrolizumab + ipilimumab has little or no difference on PFS. 8.2 (6.0 to 10.5) *v.* 8.4 (6.3 to 10.5) months |
| Grade ≥ 3 AEs | Relative risk: 1.25 (95% CI, 1.08 to 1.45)<br>On the basis of data from 563 patients in one study<br>Follow-up 20.6 months | 502 per 1,000 | 628 per 1,000<br>Difference: 126 more per 1,000 (95% CI, 40 more to 226 more) | High[c] | Pembrolizumab + ipilimumab increases grade ≥ 3 AEs |

Abbreviations: AE, adverse event; HR, hazard ratio; non-SCC, nonsquamous cell carcinoma; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score.

[a]Risk of bias: no serious. Note: the results from first interim analysis. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits; imprecision: no serious. Only data from one study; publication bias: no serious. Commercially funded study.

[b]Risk of bias: no serious. Note: the results from first interim analysis. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits; imprecision: no serious. Only data from one study; publication bias: no serious. Commercially funded study.

[c]Risk of bias: no serious. Note: the results from first interim analysis. Trials stopping earlier than scheduled, resulting in potential for overestimating benefits; imprecision: no serious. Only data from one study; publication bias: no serious. Commercially funded study.

(Evidence quality: Low; Strength of recommendation: Weak).

**Literature review update and analysis.** See discussion under Recommendations 1.6, 2.7, and 3.4 above.

**Clinical interpretation.** Treatment of stage IV (metastatic) NSCLC—both SCC and non-SCC histologic types—with low (TPS = 1%-49%) or negative (TPS = 0%) PD-L1 expression continues to be a combination of chemotherapy and immunotherapy, in the absence of any contraindications for either of the two therapies. The strongest data for this combination continue to be from the KEYNOTE-189[17] (non-SCC) and KEYNOTE-407[18] (SCC) trials where pembrolizumab was combined with pemetrexed-platinum and paclitaxel or nab-paclitaxel + carboplatin, respectively. The results of other trials including IMPOWER-150[19] (paclitaxel + carboplatin + bevacizumab + atezolizumab) and IMPOWER-130[20] (nab-paclitaxel + carboplatin + atezolizumab) both for non-SCC NSCLC have been less impressive and some such as IMPOWER-131[21] (nab-paclitaxel + carboplatin + atezolizumab for SCC NSCLC) and IMPOWER-132[22] (pemetrexed + platinum + atezolizumab for non-SCC NSCLC) failed to demonstrate improvement in OS (the majority of these studies are described in the 2020 guideline). The CheckMate-9LA trial adopted a different strategy of two cycles of chemotherapy with a combination of two ICIs (PD-1 inhibitor nivolumab and cytotoxic T-cell lymphocyte-4 inhibitor ipilimumab) and did demonstrate improvements in both OS and PFS for all histologic types and for all levels of PD-L1 expression (including when the latter was either low or negative). However, the concerns related to using four drugs (including two ICIs) with the associated increase in toxicities (especially immune-related adverse events) do not offer any significant advantages over the pembrolizumab-chemotherapy combination; data that are more robust and have greater follow-up are available.

### Clinical Question 2 and Clinical Question 3

(2) What is the most effective second-line therapy? (3) Is there a role for a third-line therapy, or beyond?

***Recommendation 5.1 (there were no new second- or third-line recommendations in 2020 guideline, all carried over from prior updates—please see the Data Supplement [online***

**TABLE 10.** Additional Study Informing the Evidence Review

| Author, Trial Year | No. of Patients Randomly Assigned | PD-L1 Expression | Histology | Comparison | Significance $P < .05$ OS | Significance $P < .05$ PFS | Grade 3-5 AEs, % |
|---|---|---|---|---|---|---|---|
| Cortot et al,[5] 2020 | 111<br>55 | NR | Non-SCC | Weekly paclitaxel + bevacizumab<br>Docetaxel | — | ↑ | 45.9<br>54.5 |

Abbreviations: AEs, adverse events; non-SCC, nonsquamous cell carcinoma; NR, not reported; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.
↑ Favors Intervention $P < .05$.
↓ Favors Control $P < .05$.
— No significant differences.

***only]).*** For patients with non-SCC who received an ICI and chemotherapy as first-line therapy, clinicians may offer paclitaxel plus bevacizumab in the second-line setting (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

***Recommendation 6.1.*** For the majority of patients with non-SCC, who received chemotherapy with or without bevacizumab and ICI therapy (in either sequence), clinicians should offer the options of single-agent pemetrexed or docetaxel or paclitaxel plus bevacizumab in the third-line setting (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

**Literature review update and analysis.** The systematic review identified one relevant trial[5] (Tables 10 and 11). The RCT by Cortot et al[5] included 166 participants with non-SCC histology with prior treatment and allocated them to paclitaxel and bevacizumab versus docetaxel. The RCT's primary outcome was 6-month PFS. The result was HR 0.61 (95% CI, 0.44 to 0.86) and indicate the doublet may improve PFS. Grade 3-4 AEs showed no significant differences. Using the GRADE methodology,[9] study quality was downgraded from high to low because patients with *EGFR* mutations and *ALK* rearrangement were included, although the numbers are not reported.

**Clinical interpretation.** For the majority of patients with stage IV NSCLC (without an oncogenic driver alteration), the treatment options at progression or after relapse on first-line therapy (a platinum doublet chemotherapy and immunotherapy combination) typically include single-agent chemotherapy with a different agent than what was used previously. Docetaxel (all histologic types), pemetrexed (non-SCC NSCLC), and weekly paclitaxel and bevacizumab (non-SCC NSCLC) are all options that can be discussed in this setting. For patients in whom the initial treatment was not a chemoimmunotherapy combination should receive the treatment not given earlier, i.e., platinum doublet chemotherapy (if the initial treatment was monotherapy

**TABLE 11.** Treatment Regardless of Programmed Death Ligand-1
**Population: Previously Treated Stage III or IV, Non-SCC NSCLC (Cortot et al[5])**
**Intervention: Paclitaxel Plus Bevacizumab**
**Comparator: Docetaxel**

| Outcome Time Frame | Study Results and Measurements | Absolute Effect Estimates[a] DOC | Absolute Effect Estimates[a] PAC-BEV | Certainty of the Evidence (quality of evidence) | Plain Text Summary |
|---|---|---|---|---|---|
| PFS[a] at 6 months | HR: 0.61 (95% CI, 0.44 to 0.86)<br>On the basis of data from 166 patients in one study | 731 per 1,000 | 551 per 1,000<br>Difference: 180 fewer per 1,000 (95% CI, 292 fewer to 54 fewer) | Low<br>Due to serious indirectness[b] | PAC-BEV may improve PFS |
| AEs (grade 3-4) | Relative risk: 0.84 (95% CI, 0.61 to 1.15)<br>On the basis of data from 164 patients in one study | 545 per 1,000 | 458 per 1,000<br>Difference: 87 fewer per 1,000 | Low<br>Due to serious indirectness[c] | PAC-BEV may have little or no effect on AEs |

Abbreviations: AEs, adverse events; *ALK*, anaplastic lymphoma kinase; BEV, bevacizumab; DOC, docetaxel; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; non-SCC, nonsquamous cell carcinoma; NSCLC, non–small-cell lung cancer; PAC, paclitaxel; PFS, progression-free survival; SCC, squamous cell carcinoma.
[a]Rates were estimated from Kaplan-Meier curves.
[b]Risk of bias: no serious. Open label; indirectness: serious. Patients with *EGFR* mutations and *ALK* rearrangement were included although the numbers are not reported; imprecision: no serious. Only data from one study.
[c]Risk of bias: no serious. Blinding not addressed; indirectness: serious. Patients with *EGFR* mutations and *ALK* rearrangement were included although the numbers are not reported.

with an ICI) and immunotherapy (if the initial treatment was platinum doublet chemotherapy).

## 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 21 written comments received. A total of 89% of the 21 of the responses either agreed or agreed with slight modifications to the recommendations and 11 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, including those regarding cemiplimab, 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 OS data for atezolizumab was interim, uncertainties in the role of tumor mutational burden, and for Checkmate 9LA, indirectness in analysis by both histologic and PD-L1 subgroups. The Expert Panel suggests more research on these topics.

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 Care[23] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[24] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations[1] https://ascopubs.org/doi/10.1200/JCO.19.03022
- Therapy for Stage IV Non–Small-Cell Lung Cancer With Driver Alterations[25] https://ascopubs.org/doi/10.1200/JCO.20.03570
- Molecular Testing for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors[26] http://ascopubs.org/doi/10.1200/JCO.2017.76.7293
- Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy[27] https://ascopubs.org/doi/10.1200/JCO.21.01440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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.

## EQUAL CONTRIBUTION

I.J. and N.S. were Expert Panel co-chairs.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00825.

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## 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 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<br>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 | 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, Ontario, 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, Ontario, 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 | Galva, IA | Patient representative |
| Tanyanika Phillips, MD | City of Hope, Duarte, CA | Medical Oncology<br>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 |
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