Therapy for Stage IV Non-Small Cell Lung Cancer Without Driver Alterations

ASCO Living Guideline Version 2023.1

Singh et al.

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1 Background & Methodology

Introduction

- In 2022, ASCO launched living clinical practice guidelines for systemic therapy for patients with stage IV non–small-cell lung cancer (NSCLC) with[1] and without driver alterations[2] and both have been updated recently.[3-6]
- Based on routine literature searches (up to November 30, 2022), this version[7] of the stage IV NSCLC without driver alterations living guideline reviews new evidence to assess if recommendations are up to date.
- The ASCO living guideline on therapy for stage IV NSCLC with driver alterations accompanies this guideline.[8]

ASCO Living Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) living guideline process includes:
  - an ongoing literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This living guideline update addresses recommendations for two clinical questions:

- What is the most effective first-line therapy for patients with non-SCC and PD-L1 TPS 0-49%, without known EGFR, ALK, or ROS-1 alterations, and PS 0-1?
- What is the most effective first-line therapy for patients with SCC and PD-L1 TPS 0-49%, without known EGFR, ALK, or ROS-1 alterations, and PS 0-1?

Target Population and Audience

Target Population

- Patients with stage IV NSCLC without driver alterations in *EGFR* or *ALK* (with known *EGFR* and *ALK*) status (plus PD-L1 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.

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2 Summary of Updated Recommendations

Summary of Updated Recommendations

Clinical Question

- What is the most effective first-line therapy for patients with non-SCC and PD-L1 TPS 0-49%, without known EGFR, ALK, or ROS-1 alterations, and PS 0-1?

These updated recommendations are in addition to 2020 options.

Recommendation 2.8

- For patients with non-SCC, PD-L1 TPS 0-49% and PS 0 to 1, clinicians may offer cemiplimab plus chemotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Updated Recommendations

Recommendation 2.9

- For patients with non-SCC, PD-L1 TPS 0-49% and PS 0 to 1, clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Updated Recommendations

Clinical Question

- What is the most effective first-line therapy for patients with SCC and PD-L1 TPS 0-49%, without known EGFR, ALK, or ROS-1 alterations, and PS 0-1?

These updated recommendations are in addition to 2020 options.

Recommendation 4.6

- For patients with SCC, PD-L1 TPS 0-49% and PS 0 to 1, clinicians may offer cemiplimab plus chemotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Updated Recommendations

Recommendation 4.7

- For patients with SCC, PD-L1 TPS 0-49% and PS 0 to 1, clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

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3 Summary of Previous Recommendations

Summary of Previous Recommendations

Clinical Question

- Which patients with stage IV NSCLC should be treated with chemotherapy?

Recommendation

- For patients with 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.

Summary of Previous Recommendations

Recommendation

- 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.

Summary of Previous Recommendations

Clinical Question 1

- What is the most effective first-line therapy for patients with non-SCC and high PD-L1 (TPS ≥ 50%) status, and PS 0-1?

For patients with high PD-L1/PD1 expression (TPS ≥ 50%), in the absence of contraindications to immune checkpoint inhibitor therapies, non-SCC PS 0-1:

Recommendation 1.1

- clinicians should offer single-agent pembrolizumab.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 1.2

- clinicians may offer pembrolizumab/carboplatin/pemetrexed.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 1.3

- clinicians may offer atezolizumab/carboplatin/nab-paclitaxel.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

Summary of Previous Recommendations

Recommendation 1.4

- For patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, PS 0-1, clinicians may offer atezolizumab/carboplatin/nab-paclitaxel.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Recommendation 1.5

- In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0 to 1, clinicians may offer single-agent atezolizumab.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Previous Recommendations

Recommendation 1.6

- In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0 to 1, clinicians may offer single-agent cemiplimab.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 1.7

- In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0 to 1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Previous Recommendations

Recommendation 1.8

- 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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Clinical Question 7

- What is the most effective first-line therapy for patients with stage IV NSCLC, non-SCC and no contraindications to bevacizumab?

Recommendation 7.1

- 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, ECOG PS > 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression (no change).

Summary of Previous Recommendations

Recommendation 7.2

- Bevacizumab should not be added to pemetrexed plus carboplatin or given as maintenance with pemetrexed for patients who do not have contraindications to bevacizumab. Note that first line platinum chemotherapy alone without immunotherapy is not considered standard of care but may be considered in patients ineligible for immunotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Previous Recommendations

Clinical Question 2

- What is the most effective first-line therapy for patients with stage IV NSCLC with non-SCC, and negative or unknown PD-L1 status (TPS 0-49%), and PS 0-1?

For patients with negative (<1% or unknown) and low positive (TPS 1%-49%) PD-L1 expression, non-squamous cell carcinoma, PS 0-1, AND are eligible for chemotherapy and pembrolizumab,

Recommendation 2.1

- clinicians should offer pembrolizumab/carboplatin/pemetrexed

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 2.2

- clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

Recommendation 2.3

- clinicians may offer atezolizumab/carboplatin/nab-paclitaxel.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

Summary of Previous Recommendations

Recommendation 2.4

- (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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 2.5

- (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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Summary of Previous Recommendations

Recommendation 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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Recommendation 2.7

- In addition to 2020 options, for patients with negative (0%) and low positive PD-L1 expression (TPS 1% to 49%), non-SCC, and PS 0 to 1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Previous Recommendations

Clinical Question

- What is the most effective first-line therapy for patients with stage IV NSCLC with PS 2, non-SCC?

Recommendation

- 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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Intermediate chemotherapy	Weak chemotherapy
Intermediate palliative care	Strong palliative care

Summary of Previous Recommendations

Clinical Question 3

- What is the most effective first-line therapy for patients with stage IV NSCLC with SCC, and high PD-L1 status (TPS ≥ 50%), and PS 0-1?

For patients with high PD-L1 expression (TPS ≥ 50%) squamous cell carcinoma, PS 0-1, in the absence of contraindications to immune checkpoint inhibitor therapy:

Recommendation 3.1

- clinicians should offer single-agent pembrolizumab.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Previous Recommendations

Recommendation 3.2

- clinicians may offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel).

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

Recommendation 3.3

- In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0 to 1, clinicians may offer single-agent atezolizumab.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Summary of Previous Recommendations

Recommendation 3.4

- In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0 to 1, clinicians may offer single-agent cemiplimab.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Strong

Recommendation 3.5

- In addition to 2020 options, for patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0 to 1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Moderate	Weak

Summary of Previous Recommendations

Clinical Question 4

- What is the most effective first-line therapy for patients with stage IV NSCLC with squamous cell carcinoma, and negative or unknown PD-L1 status (TPS 0-49%), and PS 0-1?

For patients with negative (TPS 0%, <1%, or unknown) and/or low positive (TPS 1%-49%) PD-L1 expression and squamous cell carcinoma, in the absence of contraindications to immune checkpoint inhibitor therapies:

Recommendation 4.1

- clinicians should offer pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Intermediate	Strong

Summary of Previous Recommendations

Recommendation 4.2

- (For patients who have the above characteristics) 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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Intermediate	Weak

Summary of Previous Recommendations

Recommendation 4.4

Evidence-based

Evidence Quality	Strength of Recommendation
High	Strong

- 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.

Recommendation 4.5

Evidence-based

Evidence Quality	Strength of Recommendation
Moderate	Weak

- In addition to 2020 recommendations 4.1-4.4, for patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, SCC, and PS 0 to 1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy.

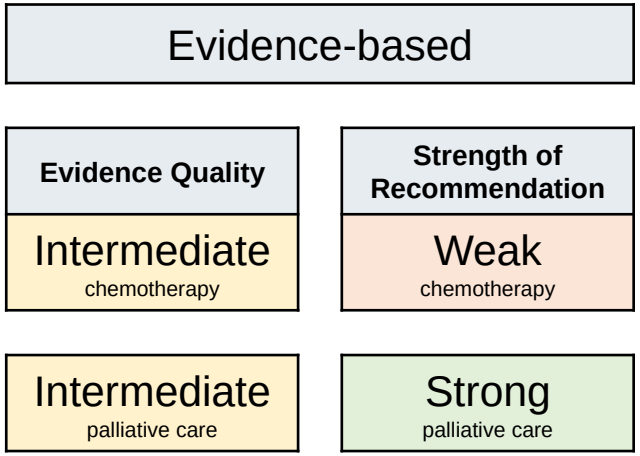
Summary of Previous Recommendations

Clinical Question

- What is the most effective first-line therapy for patients with stage IV NSCLC, SCC, and PS 2?

Recommendation

- 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.



Summary of Previous Recommendations

Clinical Question 5

- What is the most effective therapy for patients with non-SCC who have received one prior chemotherapy regimen?

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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Summary of Previous Recommendations

Recommendation

- The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. This recommendation has not changed. Age alone is not a contraindication to chemotherapy for NSCLC.

Summary of Previous Recommendations

Clinical Question 6

- What is the most effective third-line therapy for patients with stage IV NSCLC and PS 0-1?

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.

Evidence-based	
Evidence Quality	**Strength of Recommendation**
Low	Weak

Summary of Previous Recommendations

Clinical Question

- Is there a role for cytotoxic therapy for patients who have received three prior regimens and good PS?

Recommendation

- 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.

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4 Additional Information

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/living-guidelines

- Patient information is available at www.cancer.net

Abbreviations

- *ALK*, anaplastic lymphoma kinase
- ASCO, American Society of Clinical Oncology
- EBMC, Evidence Based Medicine Committee
- *EGFR*, epidermal growth factor receptor
- NSCLC, non-small cell lung cancer
- PD-L1, programmed death ligand 1
- PS, performance status
- RCT, randomized controlled trial
- SCC, squamous cell carcinoma
- TPS, tumor proportion score

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