Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update Summary

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ASCO published the last full clinical practice guideline update on systemic therapy for patients with stage IV non–small-cell lung cancer (NSCLC) in 2017; that update is available online.[1] The purpose of this current (2019) guideline update (a partial update) is to revise the portion of the 2017 ASCO guideline on systemic treatment of patients with stage IV NSCLC that addresses those patients with NSCLC without effectively targeted driver alterations. ASCO undertook this current partial update due to potentially practice-changing evidence published since the 2017 full update,[1] for clinical questions addressing the specific population of patients without potentially actionable driver alterations (see Bottom Line Box and specific recommendations).[1] Notably, ASCO is developing a separate update on patients with cancers with effectively targeted driver alterations, updating the targeted therapy–relevant areas of the full clinical practice guideline update (2017). The 2017 update included target populations both with and without known driver alterations, as well as those with or without known results of immunotherapy predictive marker results (eg, PD-1) and multiple categories of interventions (chemotherapy, targeted therapy, palliative care).[1] The current guideline update includes the nonactionable alterations population and covers the interventions of immune checkpoint therapy, chemotherapy, and anti–vascular endothelial growth factor (VEGF) agents. Since the 2017 update, there have been advances in the management of these patients. In addition, since the 2017 update, ASCO published several other guidelines relevant to patients with stage IV NSCLC.[2-5] Although management of patients' immune-related adverse effects is outside of the scope of this guideline, the authors do believe that patient and family caregivers should receive timely and up-to-date education about the potential adverse effects of immunotherapies, as well as referrals, as necessary.

This update is based on five phase III randomized clinical trials (RCTs), which directly impacted clinical questions (out of the full list in the systematic review; Data Supplement), and the authors chose to discuss a sixth trial.[6-11] The current updated systematic review included clinical trial results that investigated interventions (care options), including immunotherapy and monoclonal antibodies, for example, nivolumab, pembrolizumab, atezolizumab, ipilimumab, and other agents. Additional information is available at https://www.asco.org/lung-cancer guidelines. Patient information is available at www.cancer.net.

WHAT IS PRACTICE CHANGING

This guideline reflects evidence-based changes in the first-line treatment of patients with stage IV lung cancer and reflects a shifting paradigm for the subset of patients whose NSCLC is without actionable mutation—away from primarily solely cytotoxic chemotherapy.

The guideline reflects the increasing importance of treatment based on the PD-L1 predictive maker. Results of testing can guide first-line treatment options to using factors like histology and actionable driver mutations discussed in previous versions of this guideline.

In a change from the previous guideline, this version includes a combination of immunotherapy and chemotherapy for the first time.

Although immunotherapy may not benefit every patient with stage IV NSCLC without known actionable mutations, which is important to communicate, clinicians may discuss increased treatment options, to bring immunotherapy with or without chemotherapy to the forefront in eligible patients who have access to the tests and recommended treatments. In addition, clinicians should knowledgeably communicate about immunotherapy-related adverse effects.

ASSOCIATED CONTENT

Data Supplement

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

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THE BOTTOM LINE

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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 based on a systematic review of the medical literature.

Recommendations

For patients with high PD-L1 expression (TPS $\geq$ 50%) and nonsquamous cell carcinoma (non-SCC), in the absence of contraindications to immune checkpoint therapies, treatment options include:

Recommendation 1.1. For patients with high PD-L1 expression (TPS $\geq$ 50%), non-SCC, and performance status (PS) 0 to 1, clinicians should offer single-agent pembrolizumab (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement: Although Recommendation 1.1 addresses many patients in the target population (eg those who are asymptomatic) for patients who are in other situations, as described in the manuscript, the guideline presents additional options that may be reasonable, based on the evidence reviewed. This statement applies to all recommendations with the word "should."

Readers should refer to the full text of the manuscript for discussion of other selected scenarios.

Recommendation 1.2. For patients with high PD-L1 expression (TPS $\geq$ 50%), non-SCC, and PS 0 to 1, clinicians may offer pembrolizumab/carboplatin/pemetrexed (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.3. For patients with high PD-L1 expression (TPS $\geq$ 50%), non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.4. For patients with high PD-L1 expression (TPS $\geq$ 50%), non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/nab-paclitaxel (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

Recommendation 1.5. There are insufficient data to recommend any other checkpoint inhibitors, combination checkpoint inhibitors, or any other combination of immune checkpoint inhibitors with chemotherapy in the first-line setting (Type: evidence based, benefits outweigh harm; Evidence quality: High; Strength of recommendation: strong).

For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, and non-SCC, in the absence of contraindications to immune checkpoint therapies, treatment options include:

Recommendation 2.1. For patients with negative (0%) and low positive PD-L1 expression (TPS 1% to 49%), non-SCC, and PS 0 to 1, and who are eligible for chemotherapy and pembrolizumab, clinicians should offer pembrolizumab/carboplatin/pemetrexed (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.2. For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/paclitaxel/bevacizumab in the absence of contraindications to bevacizumab (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.3. For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, clinicians may offer atezolizumab/carboplatin/nab-paclitaxel (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Recommendation 2.4. For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, and who have contraindications to or decline immunotherapy, clinicians should offer standard chemotherapy with platinum-based two-drug combinations as outlined in the 2015 update (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 2.5. For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, non-SCC, and PS 0 to 1, and who have contraindications to or decline immunotherapy and not deemed candidates for platinum-based therapy, clinicians should offer non–platinum-based two-drug therapy as outlined in the 2015 update (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).

Recommendation 2.6. For patients with low positive PD-L1 expression (TPS 1% to 49%), non-SCC, and PS 0 to 1, and who are ineligible for or decline combination of doublet platinum with or without pembrolizumab, clinicians may offer single-agent pembrolizumab (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

For patients with high PD-L1 expression (TPS ≥ 50%) and squamous cell carcinoma (SCC), in the absence of contraindications to immune checkpoint therapy, treatment options include:

Recommendation 3.1. For patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0 to 1, clinicians should offer single-agent pembrolizumab (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. For patients with high PD-L1 expression (TPS ≥ 50%), SCC, and PS 0 to 1, clinicians may offer pembrolizumab/carboplatin/paclitaxel or nab-paclitaxel (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.3. There are insufficient data to recommend any other checkpoint inhibitors, combination checkpoint inhibitors, or any other combination of immune checkpoint inhibitors with chemotherapy in the first-line setting (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

For patients with negative (TPS 0%) and/or low positive (TPS 1% to 49%) PD-L1 expression and SCC, in the absence of contraindications to immune checkpoint therapies, treatment options include:

Recommendation 4.1. For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, SCC, and PS 0 to 1, clinicians should offer pembrolizumab/carboplatin/paclitaxel or nab-paclitaxel (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 4.2. For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, SCC, and PS 0 to 1, and with contraindications to immunotherapy, clinicians should offer standard chemotherapy with platinum-based twodrug combinations as outlined in the 2015 update (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Recommendation 4.3. For patients with negative (TPS 0%) and low positive (TPS 1% to 49%) PD-L1 expression, SCC, and PS 0 to 1, 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 (Type: evidence based; Evidence quality: intermediate; Strength of recommendation: weak).

Recommendation 4.4. For patients with low positive PD-L1 expression (TPS 1% to 49%), SCC, and PS 0 to 1, and who are ineligible for or decline a 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 (Type: evidence based; Evidence quality: low; Strength of recommendation: weak).

NOTE. For all recommendations, benefits outweigh harms. The type of recommendation is evidence based, except where otherwise noted (in this case, all data were from RCTs).

NOTE: According to ASCO Guideline Methods, Recommendations are labeled evidence based to distinguish them from consensus based (informal consensus or formal consensus). The evidence-based label connotes that "there was sufficient evidence from published studies to inform a recommendation to guide clinical practice."

*ASCO and OH (CCO) are developing a separate guideline update on systemic therapy for patients with stage IV NSCLC with driver alterations (eg, patients with EGFR, ALK, ROS1), that is, updating selected recommendations addressing these populations in the previous version of the ASCO/OH (CCO) 2017 guideline in Hanna et al.)[1]

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 Data Supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/lung-cancer-guidelines. The Methodology Manual (available at www.asco.org/guidelines-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

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REFERENCES

1. Hanna NH, Schneider BJ, Temin S, et al: Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. J Clin Oncol 10.1200/JCO.19.03022 [epub ahead of print on January 28, 2020]
2. Kalemkerian GP, Narula N, Kennedy EB, et al: Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology clinical practice guideline update. J Clin Oncol 36:911-919, 2018
3. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35:3618-3632, 2017
4. Brahmer JR, Lacchetti C, Schneider BJ, et al: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 36:1714-1768, 2018
5. Osman H, Shrestha S, Temin S, et al: Palliative care in the global setting: ASCO resource-stratified practice guideline. J Glob Oncol 4:1-24, 2018
6. West H, McCleod M, Hussein M, et al: Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 20:924-937, 2019
7. Mok TSK, Wu YL, Kudaba I, et al: Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. Lancet 393:1819-1830, 2019
8. Paz-Ares L, Luft A, Vicente D, et al: Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 379:2040-2051, 2018
9. Hellmann MD, Ciuleanu TE, Pluzanski A, et al: Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 378:2093-2104, 2018
10. Socinski MA, Jotte RM, Cappuzzo F, et al: Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 378:2288-2301, 2018
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378: 2078-2092, 2018

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