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

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abstract

PURPOSE The aim of this work is to provide evidence-based recommendations updating the 2017 ASCO guideline on systemic therapy for patients with stage IV non–small-cell lung cancer (NSCLC) without driver alterations. A guideline update for patients with stage IV NSCLC with driver alterations will be published separately.

METHODS The American Society of Clinical Oncology and Ontario Health (Cancer Care Ontario) NSCLC Expert Panel made updated recommendations based on a systematic review of randomized controlled trials from December 2015 to 2019.

RESULTS This guideline update reflects changes in evidence since the previous guideline update. Five randomized controlled trials provide the evidence base. Additional literature suggested by the Expert Panel is discussed.

RECOMMENDATIONS Recommendations apply to patients without driver alterations in epidermal growth factor receptor or ALK. For patients with high programmed death ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%) and non–squamous cell carcinoma (non-SCC), the Expert Panel recommends single-agent pembrolizumab. Additional treatment options include pembrolizumab/carboplatin/pemetrexed, atezolizumab/ carboplatin/paclitaxel/bevacizumab, or atezolizumab/carboplatin/nab-paclitaxel. For most patients with non-SCC and either negative (0%) or low positive (1% to 49%) PD-L1, the Expert Panel recommends pembrolizumab/ carboplatin/pemetrexed. Additional options are atezolizumab/carboplatin/nab-paclitaxel, atezolizumab/carboplatin/ paclitaxel/bevacizumab, platinum-based two-drug combination chemotherapy, or non–platinum-based two-drug therapy. Single-agent pembrolizumab is an option for low positive PD-L1. For patients with high PD-L1 expression (TPS ≥ 50%) and SCC, the Expert Panel recommends single-agent pembrolizumab. An additional treatment option is pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel). For most patients with SCC and either negative (0%) or low positive PD-L1 (TPS 1% to 49%), the Expert Panel recommends pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel) or chemotherapy. Single-agent pembrolizumab is an option in select cases of low positive PD-L1. Recommendations are conditional on the basis of histology, PD-L1 status, and/or the presence or absence of contraindications. Additional information is available at www.asco.org/lung-cancer-guidelines.

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INTRODUCTION

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, which is available online.[1] The purpose of this 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 as a result of 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 (Bottom Line Box and specific recommendations).[1] Of note, ASCO is developing a separate update on patients with cancers with effectively targeted driver alterations, updating the targeted therapy–relevant areas of 2017 full clinical practice guideline update. The 2017 update included target populations both with and without known driver alterations, as well as both those with or without known results of immunotherapy predictive

THE BOTTOM LINE

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

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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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).

THE BOTTOM LINE (CONTINUED)

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).

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 two-drug 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."

markers results (eg, programmed death 1 [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 agents. Since the 2017 update, there have been advances in the management of these patients. In addition, ASCO has published several other guidelines relevant to patients with stage IV NSCLC since the 2017 update.[2-5] While management of patients' immune-related adverse effects is outside the scope of this guideline, the authors 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 (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 came from the investigation of interventions (care options) that include immunotherapy and monoclonal antibodies (eg, nivolumab, pembrolizumab, atezolizumab, ramucirumab, ipilimumab, and other agents).

GUIDELINE QUESTIONS

This clinical practice guideline addresses three overarching clinical questions. For patients with stage IV NSCLC without driver alterations:

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

The guideline addresses patients with NSCLC in the following histologic or subgroups, including squamous cell carcinoma (SCC), nonsquamous cell carcinoma (non-SCC), and programmed death ligand 1 (PD-L1)/PD-1 positive or negative.

The update does not apply to patients with stage IV NSCLC and alterations in any of the following molecular targets: epidermal growth factor receptor (*EGFR*), *ALK, ROS1,* or *BRAF* (the latter driver alterations will be covered in a separate guideline update). The guideline also does not apply to patients with stage IV NSCLC with rarer histologies (eg, large cell, neuroendocrine, and so on).

METHODS

Guideline Update Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel that included two patient representatives and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel also included representatives from Ontario Health (Cancer Care Ontario) in an effort to avoid duplication of guidelines on topics of mutual interest (Appendix Table A1, online only). The Expert Panel, co-chaired by N.H. and G.M., met via teleconference and/or 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 2 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 guideline, which was then circulated for external review, and submitted to *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. After the ASCO process was completed, Ontario Health (Cancer Care Ontario) provided approval through its Program in Evidence-Based Care internal and external approval processes. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review (2015 to 2018) of phase II and phase III RCTs and clinical experience. Articles were selected for

inclusion in the systematic review of the evidence based on the following criteria:

- Patients with stage IV NSCLC without driver alterations (some trials that also included patients with stage IIIB NSCLC were included if separate analyses were conducted).
- Fully published presentations of English-language reports of phase II or III RCTs, rigorously conducted (see the Data Supplement for ASCO method of quality assessment) systematic reviews, or meta-analyses.
- Meeting abstracts with this population with fully available presentations: ASCO, European Society for Medical Oncology 2017 to 2018, and International Association for the Study of Lung Cancer 2018.
- Minimal sample size of 20 patients for immune checkpoint therapy and 50 patients for chemotherapy.
- Outcomes included progression-free survival, overall survival, treatment toxicity (adverse events), and quality of life (if reported).

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, or narrative reviews; or (3) published in a non-English language. Guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[12] In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation.

Detailed information about the methods used to develop this guideline update is available in the Methodology Manual at www.asco.org/methodology, including an overview (eg, panel composition, development process, and revision dates); literature search and data extraction; the recommendation development process (GLIDES and BRIDGE-Wiz); and quality assessment.

ASCO guidelines staff updated the literature search that was conducted for the 2017 update to inform its recommendations on Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer. MEDLINE was searched from December 2015 to August 2018. The updated search was restricted to articles published in English, as well as to systematic reviews, meta-analyses, and RCTs. The updated search was guided by the signals[13] approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. This approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the signals approach. This is the most

recent information as of the publication date. The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on a formal review of the emerging literature, ASCO will determine the need to update.

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/rwc). 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

A total of 20 RCTs met the eligibility criteria. Five of these RCTs were applicable to the 2019 clinical questions and are narratively summarized here. They form the evidentiary basis for the new/updated guideline recommendations. The other RCTs included were discussed during development but did not ultimately support the recommendations (including an additional trial narratively discussed that the Expert Panel chose not to use to support a recommendation).[6-11] The Expert Panel reviewed all 20 studies in the systematic review, and data extraction was performed per ASCO Systematic Review methodology and are presented in the Data Supplement. However, only evidence directly addressing updated Clinical Questions are included in the narrative summary. The additional study did not support/change a recommendation. Due to Expert Panel revision of 2017 Clinical Questions, they selected studies of the systematic review results that were likely to be relevant with regard to and address the Clinical Questions. The sixth study was reviewed in depth and is discussed outside of the recommendation sections (Special Commentary). Full results of the other 14 studies in the full systematic review for this specific update are available in the Data Supplement.

The five studies addressing the clinical questions were new RCTs published in 2018 to 2019 and are summarized in Tables 1-5. The RCTs compared a variety of interventions. The primary outcome for all of the trials was therapeutic efficacy, framed in a variety of ways, such as progression-free survival (PFS) and overall survival (OS).

Selected patient characteristics are listed in Table 2. Detailed characteristics of the studies' participants are in the Data Supplement. Table 1 outlines the characteristics of studies that were particularly pertinent to the development of the recommendations.

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed. Please refer to the Data Supplement and Methodology Manual for more information and definitions of ratings for overall potential risk of bias. Study quality was formally assessed for all included studies. Table 3 lists the results of study quality assessment for the five new RCTs narratively summarized in this publication. Other studies' quality assessments are included in the Data Supplement. Design aspects related to individual study quality were assessed by one reviewer, with such factors as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on, generally indicating a low-to-intermediate potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results. The Methodology Manual includes definitions of ratings for overall potential risk of bias.

Key Outcomes of Interest: Efficacy

Additional data on key outcomes of interest and key adverse events are reported in Tables 4 and 5 as well as in the Data Supplement.

RECOMMENDATIONS

Expert Panel Note

Each recommendation is accompanied by a rating of Evidence quality and Strength of recommendation. The ASCO Guidelines Methodology Manual (www.asco.org/guideline-methodology) contains detailed definitions of the possible ratings. For the purposes of this guideline, the authors provide recommendations according to a patient's histology and the primary biomarker predicting the potential benefit of immunotherap—that is, the tumor proportion score (TPS) of PD-L1 status (Appendix Table A2, online only). These guidelines do not use tumor mutation burden or T-effector gene expression (Teff), and it is not within the scope of this guideline to provide systematically reviewed guidance on the choice of biomarkers.[2] This guideline advises that clinicians review the results of patients' driver alteration testing before discussing immunotherapy. If patients have EGFR+ or ALK+ results, they should refer to the ASCO/OH (CCO) guideline update on Systemic Therapy for Patients with Stage IV NSCLC with Driver Alterations (forthcoming). In this guideline, the authors have chosen to use subset analyses that help provide guidance according to these characteristics; prespecified subsets were preferred. When the only evidence supporting a recommendation was from a subset analysis from a single RCT, the guideline rated the evidence quality as intermediate (or lower) based on formal quality assessment of risk of bias of individual studies.

First, the guideline presents the overall results of each of the primary outcomes that new studies prespecified. The number of patients in each study for each of those given outcomes, as well as patient characteristics, is listed in Table 1. All evidence that supports unchanged recommendations was

TABLE 1. Study Characteristics

Study	Inclusion Criteria	Comparison	No. Analyzed	Follow Up
West et al (IMpower 130)[6]	Non-SCC, ECOG PS 0-1, no previous chemotherapy for stage IV nonsquamous NSCLC	Atezolizumab + carboplatin + nab-paclitaxel	451	N/A
		Carboplatin + nab-paclitaxel	228	
Gandhi et al (KEYNOTE-189)[11]	Non-SCC, pathologically confirmed metastatic nonsquamous NSCLC without sensitizing *EGFR* or *ALK* mutations; had received no previous systemic therapy for metastatic disease; PS 0-1, ≥ 1 measurable lesion, enough tissue for sample; stratified results by PD-L1 (≥ 1% v 1%)	Pembrolizumab + pemetrexed/platin	410	10.5 months median
		Placebo + pemetrexed/platin	206	
Mok et al (KEYNOTE-042)[7]	PD-L1 TPS ≥ 1%, ECOG PS 0-1, both squamous NSCLC and nonsquamous NSCLC (stratified ≥ 50% v 1%–49%); approximately 22% of each arm were never smokers	Pembrolizumab	637	12.8 months median
		Carboplatin + paclitaxel or carboplatin + pemetrexed	637	
Socinski et al (IMpower 150)[10]	Non-SCC, PS 0-1, any PD-L1 IHC status, "Patients who had received previous adjuvant or neoadjuvant chemotherapy were eligible if the last treatment was at least 6 months before randomization"; "Patients with *EGFR* or *ALK* genomic alterations were included if they had had disease progression with or unacceptable side effects from treatment with at least one approved tyrosine kinase inhibitor"	ABCP	400 (356 wild type, 155 Teff high)	20 months
		BCP	400 (336 wild type, 129 Teff high)	
Paz-Ares et al (KEYNOTE-407)[8]	SCC, PS 0-1, included PD-L1 all statuses (< 1%, ≥ 1%, and not evaluable), no previous systemic therapy for metastatic disease (NOTE. Some patients did have previous treatment of nonmetastatic)	Pembrolizumab + carboplatin/taxane	278	7.8 months median (0.1-19.1)
	SCC, PS 0-1, included PD-L1 all statuses (< 1%, ≥ 1%, and not evaluable), no previous systemic therapy for metastatic disease (NOTE. Some patients did have previous treatment of nonmetastatic)	Saline + carboplatin/taxane	281	

Abbreviations: ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; *ALK*, anaplastic lymphoma kinase; BCP, bevacizumab + carboplatin + paclitaxel; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; IHC, immunohistochemistry; N/A, not applicable; NSCLC, non–small-cell lung cancer; PD-L1, programmed death ligand 1; PS, performance status; SCC, squamous cell carcinoma; Teff, T effector; TPS, tumor proportion score.

systematically reviewed in past updates of this guideline and is not rereviewed here (eg, KEYNOTE-024).[14]

Literature Review Update and Analysis

In the KEYNOTE-042 trial,[7] 1,251 of 1,274 randomly assigned participants received either single-agent pembrolizumab or a chemotherapy doublet (carboplatin/paclitaxel or carboplatin/pemetrexed). Participants had either SCC or non-SCC and performance status (PS) of 0 to 1. Eligibility criteria required patients' PD-L1 TPS to be ≥ 1%. Patients with cancers with sensitizing *EGFR* or *ALK* alterations were excluded from the trial. The primary outcome was OS, stratified by TPS status. Results in this overall population favored the intervention. For TPS ≥ 1%, OS was 16.7 months (95% CI, 13.9 to 19.7 months) versus 12.1 months (95% CI, 11.3 to 13.3 months; hazard ratio (HR), 0.81; 95% CI, 0.71 to 0.93; $P = .0018$). PFS, a secondary outcome, did not significantly improve TPS ≥ 1% (5.4 months [95% CI, 4.3 to 6.2 months] v 6.5 months [95% CI, 6.3 to 7.0 months]; HR, 1.07; 95% CI, 0.94 to 1.21).

KEYNOTE-042 demonstrated improved PFS and OS for pembrolizumab compared with combination chemotherapy in patients with SCC (approximately one third of participants) as well as in those with non-SCC NSCLC.[7] The PFS curves split around 3 months and considerably favor patients who received pembrolizumab thereafter. Similarly, the OS curves split immediately and strongly favor patients who received pembrolizumab. The authors did not present results in the PFS subgroup by histology and TPS level.

Grade 3 to 5 adverse events were lower in the intervention arm (17.8% v 41%). Adverse effects that were immune mediated, including infusion reactions, were higher among patients in the intervention (27.5% v 7.2%). See Recommendations 1.1, 2.6, 3.1, and 4.4.

The KEYNOTE-189 trial[11] randomly assigned patients to pembrolizumab/carboplatin/pemetrexed (intervention arm) versus placebo plus carboplatin/pemetrexed treatments (control arm). The study included 616 participants (with non-SCC) and the study's primary outcomes were OS and PFS. The study's 616 participants all had non-SCC, including those with any PD-L1 TPS expression (≥ 1% v < 1%).

TABLE 2. Patient Characteristics

Phase III RCTs	Intervention or Comparison	No. of Patients (randomly assigned)	No. of Patients (analyzed)	Median Age, Years (range)	M, %	F, %	PD-L1 (low or high)	Histology	EGFR and/or ALK Alterations, %
				Patient Characteristics			**Disease Characteristics**		
West et al (IMpower 130), Arm 1[6]	Atezolizumab + carboplatin + nab-paclitaxel	483	451	64 (18-86)	59	41	High, low positive, negative	Adenocarcinoma 96%	7
IMpower 130, Arm 2[6]	Carboplatin + nab-paclitaxel	240 NOTE. ITT WT	228 NOTE. ITT WT	65 (38-85)	59	41		96%	5
Gandhi et al (KEYNOTE-189), Arm 1[11]	Pembrolizumab + chemotherapy	410	410	65.0 (34-84)	62.0	38	High, low positive, negative	Adenocarcinoma 96.1%	0
KEYNOTE-189, Arm 2	Placebo + chemotherapy	206	206	63.5 (34-84)	52.9	47.1		96.1%	
Mok et al (KEYNOTE-042), Arm 1[7]	Pembrolizumab	637	637	63 (57-69)	71	29	High (≥ 50%), low positive[a]	Non-squamous cell 62% 61%	0
KEYNOTE-042, Arm 2[7]	Platinum-based chemotherapy doublet	637	637	63 (57-69)	71	29		Squamous cell carcinoma 38% 39%	
Socinski et al, (IMpower 150), Arm 1[10]	ABCP[b]	400	400	63 (31-89)	60	40	High, low positive, negative	Adenocarcinoma 94.5%	EGFR 8.8 ALK 3.2
IMpower 150, Arm 2[10]	BCP	400	400	63 (31-90)	59.8	40.2		94.2%	EGFR 11.3 ALK 5.2
Paz-Ares et al (KEYNOTE-407), Arm 1[8]	Pembrolizumab + chemotherapy	278	278	65 (29-87)	79.1	20.9	High, low positive, negative	Squamous cell carcinoma 97.5%	N/R
KEYNOTE-407, Arm 2[8]	Placebo + chemotherapy	281	281	65 (36-88)	83.6	16.4		97.5%	
		Arm 1: NOTE. PD-L1 TPS: < 1% 95 (34.2%), ≥ 1% 176 (63.3%)	Arm 2: NOTE. PD-L1 TPS < 1% 99 (35.2%), ≥ 1% 177 (63%)						

NOTE. Definition: high ≥ 50%; low positive: 1% to 49%; negative: < 1%.

Abbreviations: ABCP, Atezolizumab + bevacizumab + carboplatin + paclitaxel; BCP, Bevacizumab + carboplatin + paclitaxel; F, female; ITT, intention to treat; M, male; N/R, not reported; PD-L1, programmed death ligand 1; RCTs, randomized controlled trials; SCC, squamous cell carcinoma; TPS, tumor proportion score; WT, wild type.

[a]For primary analysis.

[b]Third arm: atezolizumab/carboplatin/paclitaxel was the third arm and not part of primary analysis.

Patients with cancers with sensitizing EGFR or ALK alterations were excluded from the trial. The study's primary outcomes were OS and PFS. OS in the intervention arm was not reached during the 10.5-month follow-up period. The control arm had an OS of 11.3 months (95% CI, 8.7 to 15.1 months); therefore, it was statistically significantly greater with pembrolizumab/carboplatin/pemetrexed (HR, 0.49; 95% CI, 0.38 to 0.64; P < .001). PFS and response rate results were also statistically significantly different in favor of the intervention arm. PFS was 8.8 months (95% CI, 7.6 to 9.2 months) versus 4.9 months (95% CI, 4.7 to 5.5 months; HR, 0.52; 95% CI, 0.43 to 0.64; P < .001). There was no difference in the incidence of adverse events between arms. Some adverse effects were numerically greater in the intervention arms (eg, diarrhea, neutropenia, and febrile neutropenia) and others were greater in the control arm (eg, dyspnea) but not statistically significant. In reports of the risk difference with CI (Data Supplement, Figure S6 of the Appendix), grade 3 to 5 ≥ 5%, there were no adverse events with CIs that did not cross one that were better with intervention.[11] See Recommendations 1.2 and 2.1 for the subgroup results.

TABLE 3. Quality Assessment

Study	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-Up	ITT	Insignificant COI	Overall Risk of Bias
West H et al (IMpower 130)[6]	Yes	Partially	Yes	Yes	No	Yes	Yes	Yes	No	Intermediate
Gandhi et al (KEYNOTE-189)[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Low
Mok et al (KEYNOTE-042)[7]	Yes	Partially	Yes	Yes	No	Yes	Yes	Yes	No	Intermediate
Socinski et al (IMpower 150)[10]	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	No	Low
Paz-Ares et al (KEYNOTE-407)[8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	High

NOTE. Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.
Abbreviations: COI, conflict of interest; N/A, not applicable; ITT, intention to treat.

IMpower 150[10] was a three-arm study that randomly assigned patients with non-SCC to carboplatin/bevacizumab/paclitaxel (CPB) versus atezolizumab/carboplatin/paclitaxel/bevacizumab (ACPB) versus atezolizumab/carboplatin/paclitaxel (ACP). The two reported arms both included bevacizumab (CPB and ACPB), one with atezolizumab and the other without; the publication did not report results from the ACP arm. These two arms included a total of 800 participants. Participants table with advanced NSCLC with non-SCC and any PD-L1 TPS status were eligible. Patients with cancers with sensitizing EGFR or ALK alterations were eligible if they had prior tyrosine kinase inhibitor therapy and disease progression or unacceptable adverse effects, representing approximately 14% of patients in the study. However, the primary analysis was for patients with EGFR/ALK (wild type [WT]) cancers with the primary outcome of PFS (investigator assessed) in the WT population. Of note, the study made a protocol amendment, changing the primary analysis populations from the intention-to-treat (ITT) population, including both the WT population and patients with EGFR or ALK genomic rearrangements and with the marker of PD-L1 TPS expression, to the WT population using the Teff marker-high WT population (another marker for immune checkpoint inhibitor therapy effectiveness). The Teff categories are not used in other studies in this guideline.

In an interim analysis for OS in the WT group (regardless of PD-L1 TPS expression), OS was greater in the ACPB arm (19.2 months) than in the CPB arm (14.7 months) and was statistically significant (HR, 0.78; 95% CI, 0.64 to 0.96; the efficacy boundary had not been crossed by the time of publication). PFS in the WT/all PD-L1 TPS expressions' populations was longer (8.3 months v 6.8 months; HR, 0.62; 95% CI, 0.52 to 0.74; $P < .001$). In PFS subgroup analyses by PD-L1 TPS status, results of the five PD-L1 subcategories were statistically significantly greater with the four-agent combination intervention (greatest in the category the study defined as high PD-L1 expression; see also Recommendations 1.3 and 2.2). OS by PD-L1 TPS subgroups was not provided in the publication. Grade 3 to 4 treatment-related adverse events where the incidence

was ≥ 5% (note: for all grades with incidence ≥ 10%) of the more common adverse events, neutropenia, decreased platelet count, febrile neutropenia, and diarrhea were numerically greater with ACPB. Objective response (unconfirmed, investigator assessed) was 63.5% versus 48% for all patients with WT non-SCC. See Recommendations 1.3 and 2.2.

The IMpower 130[6] study enrolled patients with non-SCC, regardless of PD-L1 TPS status, and randomly assigned patients to atezolizumab/carboplatin/nab-paclitaxel (ACnP) versus carboplatin/nab-paclitaxel (CnP).[6] The efficacy analysis portion of the study consisted of 679 participants. There were two primary end points: investigator-assessed PFS and OS in the ITT WT population (ie, EGFR WT/ALK negative). The PD-L1 subgroups included the following percentages of the 679 participants: high (TPS ≥ 50%; tumor cell [TC] or tumor-infiltrating immune cells [IC 3]), 19.5%; low (TPS ≥ 1% to < 50%; TC1/2 or IC1/2), 28%; and negative (< 1%; TPS TC0 and IC0), 52%.

The overall study results were as follows: OS in the ITT WT population was ACnP: 18.6 months (95% CI, 16 to 21.2 months) versus CnP: 13.9 months (95% CI, 12 to 18.7 months; HR, 0.79; 95% CI, 0.64 to 0.98; $P = .033$). Investigator-assessed PFS in ITT WT population was also longer (ACnP, 7 months [95% CI, 6.2 to 7.3 months] v 5.5 months [95% CI, 4.4 to 5.9 months]; HR, 0.64; 95% CI, 0.54 to 0.77; $P < .0001$). The secondary outcome of response rate was greater in the atezolizumab arm (49.2% v 31.9%).

Grade 3 to 5 treatment-related adverse events for the whole safety population of participants (grade 3 to 4, 73% v 60%) were higher in the atezolizumab arm. Two adverse events of special interest were numerically greater in atezolizumab arm (hypothyroidism, 3 patients [0.6%] v none; and colitis, 5 patients [1.1%] v none). Adverse events were not measured by subgroup. See Recommendations 1.4 and 2.3.

The KEYNOTE-407 study[8] included patients with only SCC and compared pembrolizumab plus carboplatin/paclitaxel with saline plus carboplatin/taxane. Previous versions of

TABLE 4. Efficacy Outcomes

Study	Comparison	Primary Outcome	Median OS, Months (95% CI)	Median PFS, Months (95% CI)	Subgroups With Significant Interactions for OS	Subgroups With Significant Interactions for PFS, Months (95% CI)	Other (ORR or 1-year survival)
West et al (IMpower 130)[6]	Atezolizumab + carboplatin + nab-paclitaxel	OS: ITT-WT, PFS/ TTP: ITT-WT	18.6 (95% CI, 16 to 21.2)	7 (95% CI, 6.2 to 7.3)		PFS (ITT-WT), by PD-L1 subgroup:	
						a. High 6.4 v 4.6, HR, 0.51 (95% CI, 0.34 to 0.77)	
	Carboplatin + nab-paclitaxel		13.9 (95% CI, 12 to 18.7)	5.5 (95% CI, 4.4 to 5.9)		b. Low 8.3 v 6, HR, 0.61 (95% CI, 0.43 to 0.85)	
			statistic and significance: HR, 0.79 (95% CI, 0.64 to 0.98); P = .033;	statistic and significance: HR, 0.64 (95% CI, 0.54 to 0.77); P < .0001;		c. Negative 6.2 v 4.7; HR, 0.72 (95% CI, 0.56 to 0.91)	
			NOTE. OS (ITT-WT)	NOTE. Investigator-assessed PFS (ITT-WT)			
Gandhi et al (KEYNOTE-189)[11]	Pembrolizumab + pemetrexed/ platin	OS	N/R	8.8 (95% CI, 7.6 to 9.2)	12-month OS based on PD-L1 TPS:		The 12-month survival rates were:
							TPS < 1%, 61.7% v 52.2%
							HR for death, 0.59 (95% CI, 0.38 to 0.92)
	Placebo + pemetrexed/ platin	PFS/TTP	11.3 (95% CI, 8.7 to 15.1),	4.9 (95% CI, 4.7 to 55)	PD-L1 TPS < 1%, 61.7% v 52.2%; HR, 0.59 (95% CI, 0.38 to 0.92)		TPS: 1% to 49% 71.5% v 50.9% (HR, 0.55; 95% CI, 0.34 to 0.90)
			Statistic and significance: HR, 0.49; (95% CI, 0.38 to 0.64); P < .001	statistic and significance: HR, 0.52 (95% CI, 0.43 to 0.64); P < .001			TPS ≥ 50%, 73.0% v 48.1%; (HR, 0.42; 95% CI, 0.26 to 0.68)

(continued on following page)

TABLE 4. Efficacy Outcomes (continued)

Study	Comparison	Primary Outcome	Median OS, Months (95% CI)	Median PFS, Months (95% CI)	Subgroups With Significant Interactions for OS	Subgroups With Significant Interactions for PFS, Months (95% CI)	Other (ORR or 1-year survival)
Mok et al (KEYNOTE-042)[7]	Pembrolizumab	OS: TPS ≥ 50% and ≥ 1%	TPS ≥ 1%, 16.7 (95% CI, 13.9 to 19.7) v 12.1 (95% CI, 11.3 to 13.3); HR, 0.81 (95% CI, 0.71 to 0.93); P = .0018	TPS ≥ 1%, 5.4 (95% CI, 4.3 to 6.2) v 6.5 (95% CI, 6.3 to 7.0); HR, 1.07 (95% CI, 0.94 to 1.21)	PD-L1 TPS ≥ 50% Median, 20 (95% CI, 15.4 to 24.9) v 12.2 (95% CI, 10.4 to 14.2)	PD-L1 TPS ≥ 50%, 7.1 (95% CI, 5.9 to 9.0) v 6.4 (95% CI, 6.1 to 6.9); HR, 0.81 (95% CI, 0.67 to 0.99); P = .0170 (protocol-specified boundary not met)	2-year survival improvement TPS ≥ 50%, 45% v 30%
	Carboplatin + paclitaxel or carboplatin + pemetrexed				HR, 0.69 (95% CI, 0.56 to 0.85); P = .0003 (both histologies)	PD-L1 TPS ≥ 50% (both histologies)	
					PD-L1 TPS ≥ 20%, 17.7 (95% CI, 15.3 to 22.1) v 13 (95% CI, 11.6 to 15.3); HR, 0.77 (95% CI, 0.64 to 0.92)		
					PD-L1 TPS ≥ 20% SCC HR, 0.65 (95% CI, 0.49 to 0.87)		
					PD-L1 TPS ≥ 50% SCC was HR, 0.53 (95% CI, 0.38 to 0.75)		
					PD-L1 TPS ≥ 1% SCC HR, 0.75 (95% CI, 0.60 to 0.93)		

TABLE 4. Efficacy Outcomes (continued)

Study	Comparison	Primary Outcome	Median OS, Months (95% CI)	Median PFS, Months (95% CI)	Subgroups With Significant Interactions for OS	Subgroups With Significant Interactions for PFS, Months (95% CI)	Other (ORR or 1-year survival)
Socinski et al (IMpower 150)[10]	ABCP	PFS/TTP: The WT population and the Teff-high WT population (investigator assessed)	19.2	8.3		HR for disease progression or death by PD-L1 subgroup (in WT population)	36.5% (95% CI, 31.2 to 41.9) rate of 12-month PFS
						Subgroup, median PFS ABCP v BCP, HR	18.0% (95% CI, 13.4 to 22.6)
						TC3 or IC3: 12.6 v 6.8; 0.39 (95% CI, 0.25 to 0.60)	
						TC1/2/3 or IC1/2/3: 11.0 v 6.8; 0.50 (95% CI, 0.39 to 0.64)	Statistic and significance: 0.62 (95% CI, 0.52 to 0.74); P < .001
	BCP		14.7			TC1/2 or IC1/2: 8.3 v 6.6; 0.56 (95% CI, 0.41 to 0.77)	Teff-high WT population (284); PFS (median, 11.3 mo v 6.8 mo; stratified HR, 0.51; 95% CI, 0.38 to 0.68; P < .001)
			statistic and significance: HR, 0.78 (95% CI, 0.64 to 0.96); P = .02	6.8, HR, 0.62 (95% CI, 0.52 to 0.74); P < .001		TC0/1/2 and IC0/1/2: 8.0 v 6.8; 0.68 (95% CI, 0.56 to 0.82)	
						TC0 and IC0: 7.1 v 6.9; 0.77 (95% CI, 0.61 to 0.99)[a]	
Paz-Ares et al (KEYNOTE-407)[8]	Pembrolizumab + carboplatin/taxane	OS	15.9 (95% CI, 13.2 to NR)	6.4 (95% CI, 6.2 to 8.3)	a. PD-L1 TPS < 1%, 73/194, HR, 0.61 (95% CI, 0.38 to 0.98)	TPS < 1% HR, 0.68 (95% CI, 0.47 to 0.98), ≥ 1% HR, 0.49 (95% CI, 0.38 to 0.65), 1% to 49% HR, 0.56 (95% CI, 0.39 to 0.80), ≥ 50% HR, 0.37 (95% CI, 0.24 to 0.58)	1-year OS, 65.2% v 48.3%
	Saline + carboplatin/ taxane	PFS/TTP	11.3 (95% CI, 9.5 to 14.8)	4.8 (95% CI, 4.3 to 5.7)	b. PD-L1 TPS ≥ 1%, 129/353, HR, 0.65 (95% CI, 0.45 to 0.92)		
			Statistic and significance: HR, 0.64 (95% CI, 0.49 to 0.85); P < .001	Statistic and significance: HR, 0.56 (95% CI, 0.45 to 0.70); P < .001	c. PD-L1 TPS 1% to 49%, 76/207 HR, 0.57 (95% CI, 0.36 to 0.90)		

Abbreviations: ABC, atezolizumab + bevacizumab + carboplatin; ABCP, atezolizumab + bevacizumab + carboplatin + paclitaxel; BCP, bevacizumab/carboplatin/paclitaxel; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; mo, month; N/R, not reached; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PS, performance status; SCC, squamous cell carcinoma; Teff, T effector; TPS, tumor proportion score; WT, wild type.

[a]Socinski definitions of PD-L1 levels: Tumor cell (TC) 3/tumor-infiltrating immune cell (IC) 3 = PD-L1 ≥ 50% or ≥ 10% tumor-infiltrating immune cells = high PD-L1; TC1/2/3 or IC1/2/3 = PD-L1 ≥ 1% or tumor-infiltrating immune cells ≥ 1% = PD-L1 positive; TC1/2 or IC1/2 = ≥ 1% tumor cells or tumor-infiltrating immune cells and (< 50% tumor cells or < 10% tumor-infiltrating immune cells) = low PD-L1; TC0/1/2 and IC0/1/2 = PD-L1 < 50% AND < 10% tumor-infiltrating immune cells = low or negative PD-L1; TC0 and IC0 = PD-L1 < 1% and tumor-infiltrating immune cells < 1% = negative PD-L1.

TABLE 5. Adverse Events Outcomes

Study	Overall AEs, %	Hematologic AEs, %	GI and Other AEs, %	Other AEs, %
West et al Lancet (IMpower 130)[6]	Overall: 96.2 v 92.7; Grade 3-4: 73.2 v 60.3; Grade 5: 1.7 v 0.4 (treatment related); SAEs: 50.7 v 37.9	Neutropenia, arm 1: 32; neutropenia, arm 2: 28; Thrombocytopenia, arm 1: 9; thrombocytopenia, arm 2: 6; Anemia, arm 1: 29; anemia, arm 2: 20	Diarrhea, arm 1: 5; diarrhea, arm 2: 5; Nausea, arm 1: 3; nausea, arm 2: 2	
Gandhi et al (KEYNOTE-189)[11]	Overall: grade ≥ 3: 67.2 v 65.8	Neutropenia, arm 1: n = 64, 15.8; neutropenia, arm 2: n = 24, 11.9; Thrombocytopenia, arm 1: n = 32, 7.9; thrombocytopenia, arm 2: n = 14, 6.9; Anemia, arm 1: n = 66, 16.3; anemia, arm 2: n = 31, 15.3	Diarrhea, arm 1: n = 21, 5.2; diarrhea, arm 2: n = 6, 3.0	Fatigue, arm 1: n = 23, 5.7; fatigue, arm 2: 5, 2.5; Dyspnea: n = 15, 3.7; dyspnea n = 11, 5.4
Mok et al (KEYNOTE-042)[7]	Overall: n = 399, 63 v n = 553, 90; SAEs: grade 3-5, n = 113, 18 v n = 252, 41	Neutropenia, arm 1, < 1; neutropenia, arm 2, 7; Thrombocytopenia: arm 1, < 1; thrombocytopenia: arm 2, 2; Anemia: arm 1, < 1; anemia: arm 2, 13	Diarrhea: arm 1, < 1; diarrhea: arm 2, < 1; Nausea: arm 1, 0; nausea: arm 2, 1	Neuropathy, arm 1: 0; neuropathy, arm 2: 1
Socinski et al (IMpower 150)[10]	Overall: n = 188, 47.7; v n = 9, 2.3	Neutropenia, arm 1: n = 54, 13.7; neutropenia, arm 2: n = 44, 11.2*; FN, arm 1: n = 36, 9.2; FN, arm 2: n = 23, 5.8; Thrombocytopenia, arm 1: n = 16, 4.1; thrombocytopenia, arm 2: n = 17, 4.3; Decreased neutrophil count, n = 34, 8.7; decreased neutrophil count n = 25, 6.3; Hypertension, n = 25, 6.4; hypertension n = 25, 6.3	Diarrhea, arm 1: n = 11, 2.8; diarrhea, arm 2: n = 2, 0.5; Nausea, arm 1: n = 15, 3.8; nausea, arm 2: 8, 2.0	Neuropathy: arm 1: n = 11, 2.8; neuropathy, arm 2: 9, 2.3; Rash, arm 1: 5, 1.3; rash, arm 2: n = 0
Paz-Ares et al (KEYNOTE-407)[8]	Overall: Grade ≥ 3: 69.8 v 68.2; SAEs: any event grade ≥ 3: n = 194, 69.8 v n = 191, 68.2	Neutropenia, arm 1: n = 63, 22.7; neutropenia, arm 2: n = 69, 24.6; Thrombocytopenia, arm 1: n = 19, 6.8; thrombocytopenia, arm 2: n = 18, 6.4; Anemia, arm 1: n = 43, 15.5; anemia, arm 2: n = 57, 20.4	Diarrhea, arm 1: n = 11, 4.0; diarrhea, arm 2: n = 6, 2.1; Nausea, arm 1: n = 3, 1.1; nausea, arm 2: n = 4, 1.4; Asthenia, arm 1: n = 6, 2.2; arm 2: n = 10 3.6	Neuropathy, arm 1: n = 3, 1.1; neuropathy, arm 2: n = 2, 0.7; Fatigue: arm 1: n = 9, 3.2; fatigue: arm 2: n = 11, 3.9; Pneumonitis and autoimmune hepatitis immune-mediated adverse events and infusion reactions, 10.8 and 3.2

*NOTE. This and the other AEs were those with incidences ≥ 10%.

Abbreviations: AE, adverse events; FN, febrile neutropenia; SAE, serious adverse event.

this guideline did not recommend any combinations of immunotherapy and chemotherapy for patients with SCC; new evidence supports a change. The primary outcomes of this study were OS and PFS. The study included 559 total participants, all of whom had SCC, with any PD-L1 TPS status (n = 177 ≥ 1%). The *EGFR/ALK* inclusion criteria were not specified.

The results for the whole population, regardless of PD-L1 TPS status, showed statistically significant increases in OS and PFS (OS overall was 15.9 months [95% CI, 13.2 months to not reached] *v* 11.3 months [95% CI, 9.5 to 14.8 months]; HR, 0.64; 95% CI, 0.49 to 0.85; $P < .001$). PFS overall was 6.5 months (95% CI, 6.2 to 8.3 months) versus 4.8 months (95% CI, 4.3 to 5.7 months; HR, 0.56; 95% CI, 0.45 to 0.70; $P < .001$). Subgroup descriptions and outcomes are presented in Recommendations 3.2 and 4.1.

Adverse events were similar between arms. Diarrhea was slightly higher in the intervention arm, but not statistically significantly. Pneumonitis and autoimmune hepatitis were higher with pembrolizumab (Data Supplement, Figure S7), whereas immune-mediated adverse events and infusion reactions were higher with pembrolizumab (both numerically).

CLINICAL QUESTION 1

For patients with stage IV NSCLC without driver alterations, what are the most effective first-line therapies? The following recommendations apply to patients with non-SCC, in the absence of contraindications to immune checkpoint therapy (unless noted) and high PD-L1 TPS (≥ 50%).

Recommendation 1.1

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

Literature review update and analysis. Single-agent pembrolizumab was an option in the 2017 update, and this update presents this as the preferred choice. New evidence further supports this recommendation. In the KEYNOTE-042 trial,[7] of the 1,274 randomly assigned participants, 47% had a TPS ≥ 50%, and cancers of 62% and 61% of those in the single-agent pembrolizumab and chemotherapy doublet (carboplatin/paclitaxel or carboplatin/pemetrexed; control) arms, respectively, were non-SCC. The primary outcome was OS stratified by TPS status.

For all patients with TPS ≥ 50%, the OS result was an HR of 0.69 (95% CI, 0.56 to 0.85; $P = .0003$, both histologies). In the population with TPS ≥ 50% and non-SCC, ITT OS results were not statistically significantly greater with pembrolizumab single-agent therapy (HR, 0.82; 95% CI, 0.63 to 1.07; $P =$ NS), but the numerical difference favored the group that received pembrolizumab. For all patients with TPS ≥ 1%, the analysis presented results stratified by histology. For patients with non-SCC, the OS was HR of 0.86

(95% CI, 0.77 to 1.03). For patients with TPS ≥ 50% (both histologies), PFS was 7.1 months (95% CI, 5.9 to 9.0 months) versus 6.4 months (95% CI, 6.1 to 6.9 months; HR, 0.81; 95% CI, 0.67 to 0.99; $P = .0170$). The analysis did not meet the protocol-specified boundary. The estimated 2-year survival improvement for patients with TPS ≥ 50% was 45% versus 30%; data favored KEYNOTE-042's positive result. Treatment-related adverse events (grades 3 to 5) for all patients with TPS ≥ 1% favored the intervention, occurring less often with the intervention (17.8% *v* 41%).

The updated literature search found a secondary publication on exploratory quality-of-life (QoL) end points from KEYNOTE-024.[15] The Expert Panel included and reviewed KEYNOTE-024 in the 2017 update[1] (see the Data Supplement for QoL results), and this current update will not rereview the efficacy/adverse events findings from KEYNOTE-024 publications.

Clinical interpretation. The Expert Panel concluded that the KEYNOTE-042 study[7] further supports the 2017 recommendation of the use of pembrolizumab monotherapy in patients with advanced NSCLC and PD-L1 TPS expression ≥ 50%, building on the results of previous randomized trials, including updated results of KEYNOTE-024.[16] The number of patients with non-SCC and PD-L1 TPS expression ≥ 50% with single-agent pembrolizumab versus chemotherapy was greater in the study reviewed here and in studies reviewed in previous ASCO guideline updates.[1] Of note, patients with cancers with sensitizing *EGFR or ALK* alterations were excluded from the trial. Although this trial included patients with NSCLC of any histology and PD-L1 TPS ≥ 1%, the exploratory analysis of patients with TPS of 1% to 49% failed to show a survival benefit of pembrolizumab over platinum doublet chemotherapy (see Recommendation 2.6). The overall 2-year survival improvement of 20% (50% *v* 30%), median follow up of 12.8 months with pembrolizumab versus chemotherapy, and combined with a superior toxicity profile make this a preferred treatment of patients with advanced NSCLC with PD-L1 TPS expression ≥ 50% who are eligible for immune checkpoint therapy.

Of interest, the results in the subset of patients enrolled in KEYNOTE-042 with non-SCC histology and PD-L1 TPS ≥ 50% did not show a clear survival benefit of pembrolizumab versus chemotherapy alone; however, there was no significant interaction. The Expert Panel has no obvious explanation for this finding but believes this may be due to as-yet-unknown patient selection factors. The Expert Panel recognizes the critical importance of PD-L1 TPS analysis as part of the initial evaluation to spare patients the toxicity of chemotherapy or chemotherapy-immunotherapy combinations if tests identify PD-L1 TPS expression ≥ 1%. Regarding QoL results, there are inconsistent and insufficient data to compare across studies; therefore, the guideline does not suggest decision making based on QoL alone.

Future research may further define subgroups of patients who do not benefit from immunotherapy and/or have tumors that are absolutely refractory, which define positive or negative predictive factors. Overall, the Expert Panel deemed the quality of evidence to be high and the strength of the recommendation strong.

Recommendation 1.2

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

Literature review update and analysis. The study by Gandhi et al,[11] KEYNOTE-189, compared pembrolizumab/carbo-platin/pemetrexed with placebo plus carboplatin/pemetrexed treatments. The study stratified results by PD-L1 TPS (≥ 1% v < 1%). For the purpose of this recommendation, 132 versus 70 participants had PD-L1 TPS ≥ 50% in the pembrolizumab and control arms, respectively. In the pre-specified stratified analysis of PD-L1 TPS status, all subgroups had greater OS in the intervention arm, including the PD-L1 TPS ≥ 50% subgroup (70 of 202; HR, 0.42; 95% CI, 0.26 to 0.68), as well as for PFS (Table 4).

Clinical interpretation. The options for patients with PD-L1 TPS ≥ 50% are either chemotherapy plus immunotherapy or immunotherapy alone, but it is difficult to compare these two options directly in the absence of randomized trial data. Therefore, physicians and patients will have to engage in individual decision making.

The Expert Panel believes single-agent pembrolizumab is the treatment of choice in most patients when the PD-L1 TPS is known and is ≥ 50%, given the increased cost and adverse effects with the three-drug combination. The goal of therapy is preservation of/improvement in QoL, and the adverse effect profile of the proposed treatment should always be factored into the decision-making process. However, in select cases in which the PD-L1 TPS status is unknown or unobtainable, or the treating physician deems other clinically appropriate situations, pembrolizumab/ carboplatin/pemetrexed is a reasonable treatment option for patients with advanced, non-SCC NSCLC. Examples of scenarios include patients with a high symptom and/or disease burden and/or large-volume visceral tumor involvement. Currently, no objective predictive criteria are validated to globally define the appropriate responses.

The caveats of subgroup analyses and small numbers apply to the interpretation of these data. In the trial, the response rate of this triplet therapy was 61.4% when TPS was ≥ 50%. The risk of increased toxicity and financial implications should be part of the decision-making process when clinicians and patients discuss this combination. The Expert Panel notes that KEYNOTE-189 compared the combination of immunotherapy plus chemotherapy with placebo plus chemotherapy and not with single-agent immunotherapy. Overall, the Expert Panel deemed the quality of evidence to be high and the strength of the recommendation strong.

Recommendation 1.3

For patients with high PD-L1 expression (TPS ≥ 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).

Literature review update and analysis. This recommendation presents another immunotherapy plus chemotherapy combination for the high PD-L1 TPS subgroup. The recommendation for this specific four-agent combination of ACPB was supported by one three-arm study, IMpower 150.[10] The outcomes were primarily reported for the ACPB arm versus the CPB arm. The publication did not report results from the third arm (ACP).

The primary analysis was investigator-assessed PFS by PD-L1 TPS expression for patients with *EGFR* or *ALK* WT cancers (see page 9). In an interim analysis for OS in the WT group (regardless of TPS expression), OS was greater with ACPB. The publication did not report the details of OS by TPS subgroup. PFS in the WT group was also statistically significantly longer with ACPB. In PFS subgroup analyses by PD-L1 TPS status, all PD-L1 subcategory results were statistically significantly greater with the four-agent combination (the greatest in the category the study defined as high PD-L1 expression). The high PD-L1 PFS result was 12.6 months versus 6.8 months (investigator-assessed unstratified HR, 0.39; 95% CI, 0.25 to 0.60). Grade 3 to 4 treatment-related adverse events were higher with ACPB and were not presented by subgroup.

Clinical interpretation. The Expert Panel believes single-agent pembrolizumab is the treatment of choice when the patients' PD-L1 TPS is known and is ≥ 50%. However, in select cases in which the PD-L1 TPS status is unknown or unobtainable or the treating physician deems other clinically appropriate situations, carboplatin/paclitaxel/atezolizumab plus bevacizumab is a treatment option for advanced, non-squamous NSCLC, provided that the patient does not have contraindications to bevacizumab (see 2017 Recommendation A2.a.1.; Data Supplement). Examples of scenarios include patients with a high symptom and/or disease burden and/or large-volume visceral tumor involvement. Currently, no objective predictive criteria have been validated to globally define the appropriate responses. This trial did include patients with sensitizing *EGFR* or *ALK* alterations; however, these cohorts were analyzed separately in secondary or exploratory analyses. The response rate of the four-drug regimen was 63.5% in the WT patient cohort. The risk of increased toxicity and financial implications should be part of the decision-making process when considering this combination, as the cost of this four-drug regimen in the

United States is almost two-fold greater than that of pembrolizumab alone.

Of note, the IMpower 150 trial was a three-arm study and the nonbevacizumab arm (ACP) was not reported. Therefore, a comparison of treatment with and without bevacizumab has not been described, and the clinical benefit of adding bevacizumab to chemotherapy plus immunotherapy remains unclear. In addition, investigators have not published a comparison of treatment with and without bevacizumab, and the clinical benefit of adding bevacizumab to chemotherapy remains unclear. Therefore, the Expert Panel deemed the quality of evidence to be intermediate and the strength of the recommendation moderate. There is no direct comparison of this four-drug regimen with single-agent immune checkpoint therapy or alternate chemotherapy/immunotherapy combinations, and physicians will need to individualize care based on the clinical scenario and patient preference.

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).

Literature review update and analysis. The systematic review found that the IMpower 130[6] study supports this recommendation. IMpower 130 randomly assigned patients to atezolizumab/carboplatin/nab-paclitaxel versus carboplatin/nab-paclitaxel. All patients had non-SCC NSCLC and were enrolled regardless of PD-L1 TPS status (data below are from the ITT WT population). The subcategory relevant to this recommendation included participants with PD-L1 TPS expression $\geq$ 50% (aka TC3 or IC3 in $\geq$ 50% of TC or $\geq$ 10% of IC), including 19.5% in the atezolizumab-containing arm and 18.4% in the control arm. The two coprimary outcomes were OS and PFS.

The coprimary outcome of OS in this subgroup showed a difference in the PD-L1 TPS $\geq$ 50% group of 17.3 months versus 16.9 months (HR, 0.84; 95% CI, 0.51 to 1.39) that was not statistically significant. For the other coprimary outcome of PFS, the resulting difference of 6.4 months versus 4.6 months (a difference of 1.8 months) was statistically significant (HR, 0.51; 95% CI, 0.34 to 0.77). In this study overall, there was not a statistically significant OS improvement in any of three PD-L1 subgroups. Adverse events were not measured by subgroup.

Clinical interpretation. The Expert Panel believes single-agent pembrolizumab is the treatment of choice when the patient's PD-L1 TPS is known and TPS is $\geq$ 50%. However, in select cases in which the PD-L1 TPS status is unknown or unobtainable or the treating physician deems other clinically appropriate situations, carboplatin/nab-paclitaxel/atezolizumab is a treatment option for patients with advanced, non-SCC NSCLC who may have a contraindication to pemetrexed. The results suggest a modest improvement in median PFS and no statistically significant improvement

in median OS when atezolizumab was added to carboplatin/nab-paclitaxel. The overall response rate was 49.2% for the triplet regimen in the ITT patient population. Because there was no OS difference in the TPS $\geq$ 50% subgroup, the Expert Panel rated the evidence quality as low and the strength of recommendation as weak.

Recommendation 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 (Type: evidence based, benefits outweigh harm; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. One example found in the systematic review that investigated other combinations was from the Checkmate 026 trial,[17] a study of patients with PD-L1 $\geq$ 1% and both histologies, which did not change recommendations.

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).

Literature review update and analysis. This recommendation, like Recommendation 1.2, is based on the KEYNOTE-189 study,[11] which is described above (in which 616 total participants had non-SCC NSCLC). There were 31.2% participants with TPS 1% to 49% (and non-SCC) in the pembrolizumab arm and 28.2% participants in the control arm. Approximately 31% in each arm had PD-L1 < 1%. In the prespecified stratified analysis by PD-L1 TPS status, OS results for patients with TPS 1% to 49% status included 65 of 186 events. Twelve-month survival rates were 71.5% versus 50.9% (HR, 0.55; 95% CI, 0.34 to 0.90). PFS HR was 0.55 (95% CI, 0.37 to 0.81) based on 114 of 186 events. Therefore, both are statistically significant. In a planned subgroup analysis, the triplet regimen results for survival in patients with PD-L1 TPS < 1% and both histologies were statistically significant (HR, 0.59; 95% CI, 0.38 to 0.92). The study did not analyze adverse events by histology and PD-L1 TPS subgroup.

Clinical interpretation. The Expert Panel believes that this is the preferred treatment of patients with advanced non-SCC NSCLC, when patients' PD-L1 TPS status is unknown or when TPS is < 50%, including those with TPS < 1%. KEYNOTE-189 demonstrated an approximate 20% improvement in 1-year survival when pembrolizumab was added to carboplatin and pemetrexed. In a planned subgroup analysis, the triplet regimen improved survival. Of note, patients with sensitizing *EGFR* or *ALK* alterations were excluded from the trial.

This recommendation is based on subset analyses from a single RCT. The panel rated the evidence quality as high. As all patients in this study, regardless of TPS score, had greater median OS and PFS with the addition of pembrolizumab to chemotherapy, the Expert Panel rated the recommendation as strong. This recommendation is rated strong also because there was a fully published RCT with a prespecified analysis for these subgroups.

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).

Literature review update and analysis. This recommendation was based on the IMpower 150 study,[10 (16,22)] a fully published RCT described above (pages 9, 15). The authors described the low PD-L1 category differently from some of the other studies (TC1/2 or IC1/2 meant 1% TC or IC and < 50% tumor cells or < 10% IC). The study also used the following categories: TC0/1/2 and IC0/1/2 was equivalent to PD-L1 < 50% and < 10% IC was called low or negative PD-L1; TC0 and IC0 = PD-L1 < 1% and IC < 1% was called negative PD-L1.

In the PD-L1 subcategory TC1/2 or IC1/2 (as for the other PD-L1 subgroups), investigator-assessed PFS was statistically significantly greater with the four-agent combination intervention (8.3 months v 6.6 months; unstratified HR, 0.56; 95% CI, 0.41 to 0.77; similar in low or negative). The results in low were statistically but not clinically different. The results for the whole WT population (page 9) apply here as well (ie, OS in the overall WT group was greater in the ACPB arm [the efficacy boundary was not crossed]). Other end points were not reported by PD-L1 subcategory.

Clinical interpretation. The Expert Panel believes this four-drug combination is a treatment option when patients' PD-L1 TPS is known and < 50% TPS, including those with PD-L1 < 1%, particularly for patients who have a contraindication to pemetrexed. The IMpower 150 trial demonstrated a response rate of 63.5% plus an improvement of interim median OS of almost 5 months when atezolizumab was added to the CPB regimen (ACPB) for patients with WT, non-SCC NSCLC as defined in the protocol. Subset analysis of patients with PD-L1–negative status (defined TC0 and IC0; approximately one half of the patients enrolled) failed to demonstrate a meaningful clinical benefit with the addition of atezolizumab to CPB (ACPB median PFS, 7.1 months v 6.9 months; HR, 0.77; 95% CI, 0.61 to 0.99) despite the analysis reaching statistical significance ($P = .039$). OS was not reported in this subgroup.

Of note, the IMpower 150 trial was a three-arm study. One arm included carboplatin/paclitaxel/atezolizumab and one arm included these three agents plus bevacizumab. The study did not report results from the carboplatin/paclitaxel/atezolizumab arm. Because of this, a comparison of treatment with and without bevacizumab has not been reported; therefore, the clinical benefit of bevacizumab added to chemotherapy plus immunotherapy remains unclear. Overall, the Expert Panel deemed the quality of evidence to be intermediate and the strength of the recommendation moderate based on lack of final median OS data, lack of OS data in PD-L1 subgroups, and the use of nonstandard definitions of PD-L1 expression.

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).

Literature review update and analysis. The IMpower 130 study[6] is described under Recommendation 1.4. The subcategory relevant to this recommendation (low PD-L1, non-SCC) included participants in IMpower 130 with PD-L1 TPS of 0% to 49% (low [PD-L1 TPS ≥ 1% to < 50%] and negative [PD-L1 TPS < 1%]). The study defined the subgroups as PD-L1-low (TC1/2 or IC1/2; ie, patients with PD-L1 TPS expression in ≥ 1% and < 50% of tumor cells or ≥ 1% and < 10% of infiltrating cells. Negative was defined as PD-L1 TPS < 1% (TC0 and IC0; ie, PD-L1 TPS expression in < 1% of TC and < 1% of IC. In this study overall, there was no statistically OS improvement in any of three PD-L1 subgroups.

Of patients, 28.4% in the atezolizumab-containing arm were in the PD-L1 TPS ≥ 1% to 50% subgroup and 28.5% were in the control arm. OS was 23.7 months versus 15.9 months (HR, 0.7; 95% CI, 0.45 to 1.08) and therefore not statistically significant. PFS in this subgroup was 8.3 months versus 6 months (HR, 0.61; 95% CI, 0.43 to 0.85). Approximately 52% of participants were in the PD-L1 TPS < 1% subgroup (OS, 15.2 months v 12.0 months; HR, 0.81; 95% CI, 0.61 to 1.08; and PFS, 6.2 months v 4.7 months; HR, 0.72; 95% CI, 0.56 to 0.91). The study did not analyze adverse events by PD-L1 subgroup.

Clinical interpretation. Whereas OS and PFS results for the entire population of patients with advanced non-SCC NSCLC favored those receiving carboplatin plus nab-paclitaxel plus atezolizumab over those receiving carboplatin plus nab-paclitaxel alone, results of a subset analysis of OS for those with low (or absent) PD-L1 scores were not statistically significant between the two groups. A major challenge with interpreting these data is the PD-L1 scoring assay chosen for the study. The purpose of this guideline is not to provide guidance on any molecular tests, including PD-L1 assays (the College of American Pathology will be developing a guideline on this subject). For discussion purposes only, the IMpower 130 study used the Ventana SP142 assay (Ventana Medical Systems, Inc.,1910 East Innovation Park

Drive, Tucson, AZ 85755), which recorded patients as PD-L1 low if PD-L1 expression was $\geq$ 1% but < 50% of tumor cells or $\geq$ 1% but < 10% of tumor-infiltrating immune cells. In the Blueprint comparison project significantly supported by the International Association for the Study of Lung Cancer, this assay exhibited fewer stained tumor cells overall compared with the 22C3, 28-8, or SP263 assays.[18] This difference in scoring system may account for the differences observed in subset analyses of the IMpower 130 study. The Expert Panel also acknowledges that not all forms of PD-L1 assays are universally available. Due to the lack of meaningful statistical differences in OS, despite the improvements in PFS in low or negative PD-L1 subgroups, as well as the challenges of interpreting the PD-L1 assay in this study, the Expert Panel agreed to an intermediate level recommendation for this regimen for this patient subset and to assign a moderate level of evidence quality.

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). NOTE. This corresponds to the first part of Recommendation A2.a.iii in 2017: "For patients with low PD-L1 expression (TPS < 50%), clinicians should offer standard chemotherapy with platinum-based two-drug combinations as outlined in the 2015 update (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) or (see below)".[1(p6)]

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).

Literature review update and analysis. This recommendation was based on KEYNOTE-042[7] in which there was an exploratory analysis with results for patients in the TPS 1% to 49% subgroup (with both histologies). The study

is described under Recommendation 1.1. Approximately 53% of participants in each arm had TPS 1% to 49% regardless of histology. OS was longer but not statistically significant (OS, 13.4 months [95% CI, 10.7 to 18.2 months] v 12.1 months [95% CI, 11.0 to 14.0 months]; HR, 0.92 [95% CI, 0.77 to 1.11]; PFS results for patients $\geq$ 1% TPS was not statistically significant). OS for patients with cancers with TPS $\geq$ 20% was 17.7 months (95% CI, 15.3 to 22.1 months) versus 13 months (95% CI, 11.6 to 15.3 months; HR, 0.77; 95% CI, 0.64 to 0.92) overall (irrespective of histology). However, 72% of these patients had a TPS of $\geq$ 50%. In subgroup analyses of OS, for those with TPS $\geq$ 20% and non-SCC, HR was not statistically significant (and were for TPS $\geq$ 1%). Results overall for TPS $\geq$ 1% (irrespective of histology) was 16.7 months (95% CI, 13.9 to 19.7 months) versus 12.1 months (95% CI, 11.3 to 13.3 months; HR, 0.81; 95% CI, 0.71 to 0.93; P = .0018). Of these patients, 47% had a TPS of $\geq$ 50%. The study did not report subgroups within the 1% to 49% range (ie, the 20% to 49%, and so on). The study did not analyze PFS or adverse events by this PD-L1 TPS subgroup.

The Expert Panel rated the evidence quality low because the TPS 1% to 49% analysis of participants' OS was not preplanned; therefore, the recommendation strength was weak; TPS $\geq$ 20% was preplanned and the latter did show a statistically significant benefit (but not for the non-SCC subgroup); however, the latter is probably due to the 70% of patients in this group who had a PD-L1 TPS of $\geq$ 50%. The guideline listed this as an option for patients who are ineligible for or who decline the combination of doublet platinum/pembrolizumab (see also Recommendation 4.4).

Clinical interpretation. In the KEYNOTE-042 clinical trial, the primary end points were OS in patients with a PD-L1 TPS of $\geq$ 50%, $\geq$ 20%, and $\geq$ 1% in the ITT population. The study required patients to have a PD-L1 TPS $\geq$ 1%; therefore, the Expert Panel cannot make comparisons of pembrolizumab with chemotherapy for those with PD-L1 TPS < 1%. Whereas the OS was statistically significantly better for all three cutoffs favoring pembrolizumab, the greatest improvement in OS was in the TPS $\geq$ 50% subgroup (47% of all study participants). Therefore, the large population of patients deriving benefit from pembrolizumab in the TPS $\geq$ 50% group strongly influences the analysis of OS benefit in the subset of patients with $\geq$ 1% and $\geq$ 20% PD-L1 TPS. Analysis of the patients with PD-L1 TPS 1% to 49% subset was considered exploratory. In this subset analysis, OS numerically favored treatment with chemotherapy (for those patients) until the approximate 1-year mark. At that point, the Kaplan-Meier curves cross and the survival curves from that point until the 3-year mark favor the treatment with pembrolizumab patients. This analysis suggests that there are two populations of patients, those deriving more benefit from chemotherapy and those deriving more benefit from pembrolizumab. PFS curves for those with PD-L1 TPS of $\geq$ 1% favored those on

chemotherapy for the first 6 months, then the curves cross to favor those receiving pembrolizumab. Similarly, the study also showed a trend for PD-L1 TPS $\geq$ 50% and $\geq$ 20%; the magnitude of difference (favoring chemotherapy early) was larger for patients with lower PD-L1 TPS scores. In addition, only 20% of patients who received chemotherapy received subsequent immunotherapy treatments, as trial crossover was not permitted in this study, which is significantly lower than what would be expected and recommended in current practice. For these reasons, the Expert Panel rated evidence quality as low to support offering single-agent pembrolizumab in this subset of patients, with a weak recommendation. The Expert Panel indicated that patients refusing chemotherapy or with contraindications to chemotherapy with a PD-L1 TPS 1% to 49% may discuss pembrolizumab monotherapy with clinicians, otherwise combination chemotherapy and pembrolizumab is preferentially indicated.

Summary comment. As in Recommendation 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 (eg, nivolumab) in the non-SCC PD-L1 < 50% population.

Recommendation 3.1

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

Literature review update and analysis. The Expert Panel did not change this recommendation from the previous update that recommended single-agent pembrolizumab as an option for patients with $\geq$ 50% TPS and SCC. The KEYNOTE-042 study[7] provides further support to this recommendation (described under Recommendations 1.1 and 2.6). There were 38.1% plus 39.1% participants with SCC of the 1,274 total study population and 211 participants with PD-L1 TPS $\geq$ 50%. In OS for all patients with TPS $\geq$ 50%, the subgroup results for those with SCC was a HR of 0.53 (95% CI, 0.38 to 0.75) favoring pembrolizumab. The prespecified analysis for PFS was statistically significantly greater for results for TPS $\geq$ 50% regardless of histology (see Recommendation 1.1), but this result did not meet the prespecified superiority boundary.

Clinical interpretation. Substantial evidence exists to recommend single-agent pembrolizumab for the treatment of patients with SCC NSCLC and a PD-L1 TPS $\geq$ 50%, and the Expert Panel believes this is the treatment of choice when patients' cancers fits these criteria. Overall, PFS and OS considerably favor patients who received pembrolizumab. KEYNOTE-042 observed similar results in the subset of patients with PD-L1 TPS $\geq$ 50% in both histologies (see Recommendation 2.1). Approximately one third of patients in KEYNOTE-042 had SCC. The OS strongly

favored pembrolizumab in the subset of patients with SCC histology and a PD-L1 TPS $\geq$ 50% (HR, 0.56). Given the totality of evidence, the Expert Panel agreed to strongly recommend pembrolizumab monotherapy in patients with SCC and PD-L1 TPS $\geq$ 50%. The Expert Panel assessed the level of evidence as high.

Recommendation 3.2

For patients with high PD-L1 expression (TPS $\geq$ 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).

Literature review update and analysis. This recommendation was based on the KEYNOTE-407 study[8] that compared pembrolizumab plus carboplatin/paclitaxel with saline plus carboplatin/taxane for patients with SCC. The primary outcomes of this study were OS and PFS. Of the participants' cancers, 146 had PD-L1 TPS $\geq$ 50% (approximately 26% per arm) of the 177 participants with TPS $\geq$ 1%. In subgroup analyses of those with PD-L1 TPS $\geq$ 50%, the HR for OS was 0.64 (95% CI, 0.37 to 1.10) and 1-year survival for these patients was 63.4% for those receiving chemotherapy plus pembrolizumab versus 51% for chemotherapy alone. Neither was statistically significant. PFS HR results were statistically significant at 8.0 months versus 4.2 months (HR, 0.37; 95% CI, 0.24 to 0.58).

Clinical interpretation. In KEYNOTE-407, all patients had SCC and approximately one quarter had a PD-L1 TPS $\geq$ 50%. The benefit of OS with adding pembrolizumab to chemotherapy was observed in all prespecified subgroups, including those with a PD-L1 TPS $\geq$ 50%; however, the estimated 1-year OS was only statistically significant in the < 1% and 1% to 49% PD-L1 TPS subgroups (see Recommendation 4.1). In the PD-L1 TPS $\geq$ 50% subgroup, the 1-year survival not significantly different. In contrast, the PFS in this same subset significantly (statistically and clinically) favored the pembrolizumab plus chemotherapy group. As OS was not statistically significantly different in this subgroup, the Expert Panel rated the level of evidence as intermediate only.

Recommendation 3.3

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 (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

Literature review update and analysis. One example found in the systematic review was Checkmate 026,[17] a study of patients with PD-L1 $\geq$ 1% and both histologies that did not change recommendations.

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).

Literature review update and analysis. The KEYNOTE-407 study[8] of pembrolizumab/chemotherapy versus chemotherapy is described above (and under Recommendation 3.2) and included 207 patients in the low PD-L1 expression (TPS < 50%) subgroup; approximately 37% of each arm (all participants had SCC). The estimated 1-year OS was statistically significant in the < 1% and 1% to 49% PD-L1 TPS subgroups. OS results were statistically significant for the subgroup of patients with PD-L1 TPS 1% to 49% (HR, 0.57; 95% CI, 0.36 to 0.90), unlike in the PD-L1 TPS ≥ 50% subgroup. PFS in the PD-L1 TPS 1% to 49% subgroup was 7.2 months versus 5.2 months (HR, 0.56; 95% CI, 0.39 to 0.80) based on 102 of 207 events.

Clinical interpretation. In KEYNOTE-407, PFS and OS results for patients with PD-L1 TPS of < 50% (and with SCC) strongly favored pembrolizumab plus chemotherapy compared with chemotherapy alone. This represented approximately 75% of the patients treated. Within that group, approximately one third of patients had PD-L1 TPS < 1% and 37% had PD-L1 TPS 1% to 49%. PFS and OS were statistically superior for the addition of pembrolizumab in both of these subgroups. The PFS and OS curves separate early, favoring the addition of pembrolizumab, and never cross throughout the entirety of follow up on study. For these reasons, the Expert Panel concurred on highly recommending pembrolizumab plus chemotherapy in patients with SCC and a PD-L1 TPS score of < 50%.

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 two-drug combinations** as outlined in the 2015 update (Type: evidence based; Evidence quality: high; Strength of recommendation: strong). NOTE. Similar to first part of Recommendation A3.iii in 2017 "For patients with low (TPS < 50%) or unknown PD-L1 expression, clinicians should offer standard chemotherapy with platinum-based, two-drug combinations as outlined in the 2015 update (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)."[1(p25)]

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). NOTE. Similar to the second part of Recommendation A3.iii in 2017 "For patients with low (TPS < 50%) or unknown PD-L1 expression, clinicians should offer standard chemotherapy with…non–platinum-based, two-drug therapy as outlined in the 2015 update for patents not deemed candidates for platinum-based therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak)."[1(p25)]

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).

Literature review update and analysis. This recommendation is supported by the KEYNOTE-042[7] subgroup analysis of patients with cancers with PD-L1 TPS 1% to 49% (please see above and Recommendations 1.1, 2.6, and 3.1 for study descriptions). As above, approximately 38% of participants of the total study population had SCC regardless of PD-L1 status. In analyses of OS for all patients with TPS ≥ 1%, including patients with both TPS ≥ 1% to 49% and TPS ≥ 50%, the results for the subgroup of patients with SCC and TPS ≥ 20% was HR of 0.65 (95% CI, 0.49 to 0.87) favoring pembrolizumab alone (for all with TPS ≥ 1%: HR, 0.75; 95% CI, 0.60 to 0.93).[7] The guideline describes the exploratory analysis for the TPS 1% to 49 subgroup under Recommendation 2.6. Recommendation 2.6 states that the OS was not statistically significantly different for this subgroup. (OS results were statistically significantly greater in all patients with TPS ≥ 1% regardless of histology and as this includes PD-L1 TPS ≥ 50% and both histologies, this does not provide evidence specifically for SCC and PD-L1 TPS 1% to 49%.) An exploratory analysis for PFS in the TPS 1% to 49 subgroup was not published. The same comments for Recommendation 2.6 apply here. Accordingly, the Expert Panel noted this recommendation has low evidence quality and weak strength (including due to this exploratory analysis with nonsignificant results [see also Recommendations 2.6 and 3.1]).

Clinical interpretation. KEYNOTE-042 offers the best available evidence at this writing to evaluate the utility of pembrolizumab monotherapy in patients with PD-L1 TPS < 50% and SCC histology. Details of the clinical interpretation of this trial for the low PD-L1 TPS group can be found under Recommendation 2.6. There are no data to evaluate the role of pembrolizumab monotherapy compared with

chemotherapy in patients with PD-L1 TPS < 1%; therefore, the analysis is based on those with PD-L1 TPS 1% to 49%. Analysis of the PD-L1 TPS 1% to 49% subset from KEYNOTE-042 was exploratory. In patients with SCC (but not non-SCC), those with a PD-L1 TPS > 1% had improved OS compared with chemotherapy; however, this subset analysis includes all patients entered into the trial, including those with PD-L1 TPS > 20% and PD-L1 TPS > 50%, subgroups in which the patients who received pembrolizumab disproportionately benefited. Details on patients with SCC and PD-L1 TPS 1% to 49% were not provided. For these reasons, the Expert Panel settled on a low evidence quality, supporting the use of single-agent pembrolizumab in this subset of patients with a weak recommendation strength. The Expert Panel indicated that patients refusing chemotherapy or with contraindications to chemotherapy with a PD-L1 TPS 1% to 49% may discuss pembrolizumab monotherapy with clinicians, otherwise combination chemotherapy and pembrolizumab is preferentially indicated.

CLINICAL QUESTION 2

For patients with stage IV NSCLC without driver alterations, what is the most effective second-line therapy?

These recommendations are unchanged from the 2017 Update (see the Data Supplement for recommendations).

Literature update and analysis. The systematic review included new publications on second-line treatment but no new evidence that would change these or any of the other second-line and beyond recommendations. For example, the systematic review found a pooled analysis of nivolumab versus docetaxel in second-line by Horn et al.[30] This publication included data reviewed in the systematic review for the 2017 update and did not change 2017 recommendations.[1]

CLINICAL QUESTION 3

For patients with stage IV NSCLC without driver alterations, what is the most effective third-line therapy and beyond?

These recommendations are unchanged from the 2017 Update (see the Data Supplement for recommendations).

SPECIAL COMMENTARY

Checkmate 227 Trial

The systematic review found one study (Checkmate 227) looking at another combination of checkpoint inhibitors (which involved immunotherapy). Checkmate 227 was the sixth study mentioned above.[9] The first-line recommendations for patients PD-L1 TPS ≥ 50% include Recommendation 1.5, which reflects that there were insufficient data to recommend other checkpoint inhibitors or to recommend combination checkpoint inhibitors in this setting (apart from recommendations for the specific combinations for this patient population [ie, Recommendations 1.2, 1.3, 1.4, 2.1, 2.2, 2.3, 3.2, and 4.1]). The Expert Panel reviewed

the systematic review results that tested other combinations and found no new evidence to support changing this recommendation in this current update.

Checkmate 227 was a multi-arm trial that evaluated patients with known PD-L1 TPS status receiving nivolumab plus ipilimumab, chemotherapy alone, nivolumab alone, or chemotherapy plus nivolumab and enrolled patients with PD-L1 TPS < 1% and ≥ 1%; first published in 2018. The results were stratified by PD-L1 status; however, the primary analysis did not include PD-L1 < 1%. The study randomly assigned patients to one of six arms with stratification. (NOTE. In the two nivolumab-alone arms, there were different nivolumab doses in each group). The primary analysis included patients who received nivolumab/ipilimumab versus chemotherapy (excluding the nivolumab and nivolumab/chemotherapy arms). The study conducted coprimary analysis on the basis of tumor mutation burden (TMB), an emerging biomarker (which none of the other included studies used—and on OS in those four arms based on PD-L1 stratification. It is outside the scope of this guideline to systematically review the biomarker literature. This publication did not include OS results for this end point. PFS by TMB results (unstratified HR for disease progression or death) were reported for all patients with high TMB. Within those results, subgroup analysis by PD-L1 showed a statistically significant HR result for those with PD-L1 "high" status, as did the PD-L1 "low" group. In the late stages of developing this guideline, the authors became aware of additional results, published more than 1 year after than the ASCO systematic review date parameter end, that presented OS results.[19] This analysis found that the combination showed an OS benefit for patients with cancers with PD-L1 TPS > 1%. The publication also reported on the secondary end point of OS results for patients with cancer with low or negative PD-L1 (< 1%) OS results. This publication would not change the approved recommendations; the authors include this citation for completeness. The Expert Panel will likely review these data in a future update.[19]

At the time of publication, the investigators did not have/use a companion diagnostic for TMB in the study (there was no United States—approved assay); therefore, the Expert Panel has concerns regarding the reproducibility of randomization. In addition, this is a single study of this combination of immunotherapy and there is insufficient evidence to make a recommendation on this combination. If there are future trial results of this combination fitting the inclusion criteria, the Expert Panel will reconsider such data.

TMB is emerging a predictive marker for response to checkpoint inhibitors. The optimal cutoff for a tumor as "high," "intermediate," and "low" TMB is not well defined. Whereas TMB may be an independent predictive biomarker from PD-L1, most clinical trials in patients with NSCLC have not used this biomarker in subset analyses. Consequently, studies have not reported the relative

benefits of "high" TMB with respect to PD-L1 expression in trials evaluating such agents as pembrolizumab. Some evidence exists that suggests that patients with tumors with "high" TMB and high PD-L1 expression may have the highest likelihood of achieving a response to checkpoint inhibitors. The Checkmate 227 trial, a multi-arm trial including 70% to 73% of patients with PD-L1 ≥ 1% tumors, included exploration of TMB's role. The study amended its protocol to include TMB-based efficacy analyses after enrollment was completed, but before the database lock and breaking of the coded treatments. PFS among patients with high TMB (defined as ≥ 10 mutations/per megabase) was longer for those receiving nivolumab plus ipilimumab versus chemotherapy. The objective response rate was also higher (45.3% v 26.9%). This benefit favoring nivolumab plus ipilimumab over chemotherapy was seen in patients regardless of PD-L1 status and tumor histology. Durable responses were also more frequent in patients receiving nivolumab plus ipilimumab. The Expert Panel encourages additional study of TMB as a biomarker, including in trials using other checkpoint inhibitors. The role of combination immunotherapy (eg, PD-1 or PD-L1 combined with a CTLA-4 inhibitor) is still not defined. Combination immunotherapy may result in a higher incidence of immunologic-related toxicities. If durable responses are more frequent (when compared with single-agent checkpoint inhibitors), resulting in more long-term survivors, the Expert Panel will review relevant publications on combination immunotherapy to discuss relative efficacies versus toxicities of combination versus single-agent immunotherapy.

PATIENT AND CLINICIAN COMMUNICATION

Immunotherapy may have adverse effects that did not appear in the clinical trials. Clinicians should discuss potential adverse effects and precautions that should be taken by patients receiving immunotherapy. This Expert Panel suggests that readers refer to the ASCO guideline on immunotherapy adverse events.[4] For general recommendations and appropriate strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline[3] as well as the patient-clinician communication section in the ASCO immunotherapy adverse events guideline.[4] With ever-increasing use of immune mediated therapies, oncology professionals must strive to work with colleagues in primary care, emergency medicine, and other subspecialties who may be at the forefront of providing care for patients, particularly elderly and vulnerable populations exposed to these agents who may be unaware of adverse events, including pneumonitis or thyroiditis, to arm them with tools to appropriately recognize, treat, and notify oncology providers so that appropriate decision making occurs.

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline makes the point that "Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible immune mediated adverse events prior to initiating therapy and throughout treatment and survivorship."[4(p1715)] In addition, it states that "there should be a high level of suspicion that new symptoms are treatment related."[4(p1715)]

HEALTH EQUITY

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[20-23] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. The Expert Panel is planning an editorial to further discuss issues of health equity and immunotherapy.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[24,25] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[26,27]

Discussion of cost can be an important part of shared decision making.[28] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for the treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[28]

Table 6 shows estimated US Centers for Medicare & Medicaid Services reimbursement rates for the available treatment options addressed in this guideline. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be

TABLE 6. US Centers for Medicare & Medicaid Services Reimbursement Table

Agent, Route, Treatment Setting	HCPCS Code	HCPCS Code Dosing Unit, mg	Medicare Payment Limit Per HCPCS Unit, USD	Schedule	Medicare Payment Limit/ Expected Reimbursement, USD	
					1 Cycle	4 Cycles
Pembrolizumab injection, first line	J9271	1	48.987	200 mg (flat dose) every 3 weeks (NOTE. In KEYNOTE-042 (Mok et al[7] and Gandhi et al[11]), 200 mg every 3 weeks up to 35 cycles, (NOTE. Same as Reck et al[14])	9,797	39,189
Atezolizumab injection	J9022	10	77.759	1,200 mg (flat dose) every 3 weeks (in combination with bevacizumab and chemotherapy doublet; 1,200 mg in Socinski et al[10])	9,331	37,324
Nivolumab injection in previous versions and in second line	J9299	1	27.50	3 mg/kg every 2 weeks (per Horn et al[30] and Hellman et al[9])	14,635 (2 doses = 1 cycle/month of treatment)	58,542
				Package insert dosing (240 mg every 2 weeks or 480 mg every 4 weeks)	13,200	52,800
Bevacizumab injection	J9035	10	81.179	15 mg/kg every 3 weeks	10,801	43,203
Pemetrexed injection	J9305	10	68.12	500 mg/m^2 every 3 weeks	7,091	28,365

NOTE. Regimens and prices for treatment of stage IV NSCLC, nondriver alteration. For a patient with BSA of 2.082 m^2 (weight, 88.7 kg; height, 175.9 cm) from January 2019 reimbursement data for Medicare Plan B (from Medicare for 88.7 kg and 15 mg/kg). Source for prices: Prices per dose from CMS Payment Allowances for Med Part B Drugs…doc: Jan 2019 ASP Pricing File 121118' Effective January 1, 2019 through March 31, 2019. Weight and height from Anthropometric Reference Data for Children and Adults: United States, 2007–2010 (No. 252), National health statistics reports. Hyattsville, MD, National Center for Health Statistics, PHS 2013-1603 https://www.cdc.gov/nchs/products/series/series11.htm. Males age 20 years or older, all racial and ethnic groups (US sample), mean weight, 88.7 kg (Table 5); mean height, 175.9 cm. Females, all racial and ethnic groups (US sample) age 20 years or older; mean weight, 75.4 kg (Table 3); mean height, 162.1 cm (Table 9). BSA calculator https://qxmd.com/calculate/calculator_28/bmi-and-bsa-mosteller: Man 2.082 m^2, Women 1.843 m^2. BSA male 2; height, 176 cm; weight, 88 kg results in 4.15 mg Medscape: Mosteller. Female BSA 2; height, 162 cm; weight, 75 kg results in 3.67 (https://reference.medscape.com/calculator/bsa-dosing). Note from 2009[31]: Drug costs may vary by plan and by pharmacy where a prescription is filled (eg, preferred or nonpreferred pharmacies). In some cases, coverage for orally administered drugs may be provided by either Part B or Part D. We have selected the Medicare Part B price in these cases. Drug prices are dynamic, and the prices listed in the table may not reflect current prices. In some cases, the recorded out-of-pocket price per dose is equivalent to the price per cycle. This may represent a minimum price per fill set by the health plan.

Abbreviations: BSA, body surface area; HCPCS, Healthcare Common Procedure Coding System; USD, United States dollars.

made aware of any financial counseling services available to address this complex and heterogeneous landscape.[28]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options, which was not pursued for the current update.

OPEN COMMENT

The draft recommendations were released to the public for open comment from June 4, 2019, through June 18, 2019. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree, see comments" were captured for every proposed recommendation with four written comments received. A total of three of the four respondents either agreed or agreed with slight modifications to the recommendations, and one of the respondents disagreed with a subset of the recommendations. 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 clinical practice guidelines committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. 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 Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in the *Journal of Clinical Oncology* and a summary in the *JCO Oncology Practice*.

LIMITATIONS OF THE RESEARCH AND FUTURE RESEARCH

The limitations in the evidence reviewed for this guideline include:

- The majority of the recommendations are based on single trials
- Inconsistent and insufficient data to compare QoL across studies
- The role of immunotherapy for patients with performance status 2
- Due to the emerging science, insufficient information on predictive patient factors
- The role of TMB
- The role of Teff
- Insufficient data on combination checkpoint inhibitors or **any other combinations of** immune checkpoint inhibitors with chemotherapy other than those recommended in the first-line setting

Therefore, the Expert Panel suggests that investigators fill these gaps and that future research should include more patient-reported outcomes and generate more information on predictive patient factors.

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/guidelines/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.

RELATED ASCO GUIDELINES

- Palliative Care in the Global Setting[5] (http://ascopubs.org/doi/10.1200/JGO.18.00026)
- Integration of Palliative Care into Standard Oncology Practice[29] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[3] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors[4] (http://ascopubs.org/doi/10.1200/JCO.2017.77.6385)
- Molecular Testing for the Selection of Patients with Lung Cancer for Treatment with Targeted Tyrosine Kinase Inhibitors Guideline Endorsement[2] (http://ascopubs.org/doi/10.1200/JCO.2017.76.7293)

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EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO)/Ontario Health (Cancer Care Ontario) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data 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/lung-cancer-guidelines.

EQUAL CONTRIBUTION

N.H.H. and G.M. were Expert Panel co-chairs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update Expert Panel Membership

Name and designation	Affiliation/Institution	Role/Area of Expertise
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Tanyanika Phillips, MD	City of Hope, City of Duarte, CA	PGIN representative
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Joan H. Schiller, MD, FASCO	Inova Schar Cancer Institute, Falls Church, VA	Medical oncology
Bryan J. Schneider, MD	University of Michigan Health System, Ann Arbor, MI	Medical oncology
Navneet Singh, MD, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Medical oncology
David R. Spigel, MD	Sarah Cannon Research Institute, Nashville, TN	Medical oncology
Joan Tashbar	Circle of Hope for Cancer Research, St Cloud, FL	Patient representative
Janis O. Stabler	VA	Patient representative
Sarah Temin, MSPH	ASCO, Alexandria, VA	ASCO practice guidelines staff (health research methods)

Abbreviations: OH (CCO), Ontario Health (Cancer Care Ontario); PGIN, Practice Guidelines Implementation Network.

TABLE A2. PD-L1 TPS Definition

Definition	Level, %
High	≥ 50
Low positive	≥ 1 to 49
Negative	< 1
	0
	Unknown

Abbreviations: PD-L1, programmed death ligand 1; TPS, tumor proportion score.