

Therapy for Stage IV Non–Small Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline, Version 2025.1

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ABSTRACT

Living guidelines are developed for selected topic areas with rapidly evolving evidence that drives frequent change in recommended clinical practice. Living guidelines are updated on a regular schedule by a standing expert panel that systematically reviews the health literature on a continuous basis, as described in the [ASCO Guidelines Methodology Manual](#). ASCO Living Guidelines follow the [ASCO Conflict of Interest Policy Implementation for Clinical Practice Guidelines](#). Living Guidelines and updates are not intended to substitute for independent professional judgment of the treating clinician and do not account for individual variation among patients. See appendix for disclaimers and other important information ([Appendix 1](#) and [Appendix 2](#)). Updates are published regularly and can be found at <https://ascopubs.org/nsclc-non-da-living-guideline>.

ACCOMPANYING CONTENT

 Listen to the podcast by Brittany Harvey and Dr Lyudmila Bazhenova at <https://ascopubs.org/doi/therapy-stage-iv-nsclc-without-driver-alterations-asco-living-guideline-update-2025-1>

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 Appendix

 Data Supplement

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BACKGROUND

In 2022, ASCO launched living clinical practice guidelines for systemic therapy for patients with stage IV non–small cell lung cancer (NSCLC) with¹ and without² driver alterations. Both have been updated recently.^{3–13} Based on routine literature searches (up to March 10, 2025), this version of the stage IV NSCLC without driver alterations living guidelines reviews new evidence to assess whether recommendations are up to date.

Refer to Appendix [Table A1](#) for the full list of recommendations and Appendix [Figures A1](#) and [A2](#) for the updated

algorithms. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) and the Data Supplement provide additional information.

RESULTS

The guideline Expert Panel (Appendix [Table A2](#)) reviewed new evidence from three studies^{14–16} that met the systematic review inclusion criteria (Appendix [Tables A3–A6](#)) and drafted and approved the updated recommendations. Evidence supporting unchanged recommendations is reviewed in previous publications of this guideline.^{7–9,11,13}

UPDATED RECOMMENDATIONS

First-Line Treatment Options for Patients With Good Performance Status, Any Histology, and Any PD-L1 Expression

Recommendations 1.5, 2.0, 2.6, 3.4, 3.8, 4.3

Clinicians may offer nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy (Evidence quality: Moderate; Strength of recommendation: Weak).

Evidence review and clinical interpretation.

NIPPON, JCOG2007,¹⁵ is a randomized, open-label phase III study conducted in 48 centers across Japan. Patients with stage III or IV NSCLC not amenable to curative-intent therapy, Eastern Cooperative Oncology Group performance status (PS) 0–1, whose tumors did not harbor any actionable mutations were randomly assigned in 1:1 fashion to receive platinum-doublet chemotherapy plus pembrolizumab or plus ipilimumab and nivolumab. Tumor PD-L1 positivity was not required. In the pembrolizumab group, patients received histology-specific carboplatin-doublet chemotherapy and pembrolizumab for four cycles followed by pembrolizumab maintenance; pemetrexed was also continued in the non-squamous histology. Patients in the nivolumab-ipilimumab group received nivolumab (360 mg once on day 1 of each 3-week cycle), ipilimumab (1 mg/kg once on day 1 of each 6-week cycle), and histology-specific carboplatin-doublet for two cycles followed by nivolumab-ipilimumab maintenance. Maintenance therapy in both arms was up to 2 years. Two hundred ninety-five patients were enrolled; 147 in the pembrolizumab group and 148 in the nivolumab-ipilimumab group. After a median follow-up of 15.3 months, there was no statistically significant difference in median overall survival (OS; 20.5 months in the pembrolizumab group v 23.7 months in the nivolumab-ipilimumab group; $P = .46$). The median progression-free survival (PFS) was 7.4 months in the pembrolizumab group versus 6.0 months in the nivolumab-ipilimumab group; the objective response rate was 65% versus 55%, respectively. Forty-one percent of patients in the pembrolizumab group versus 60% in the nivolumab-ipilimumab group had a nonhematologic grade ≥ 3 adverse events (AEs). Febrile neutropenia, maculopapular rash, adrenal insufficiency, and hyponatremia occurred with more than 5% frequency in the nivolumab-ipilimumab group compared to the pembrolizumab group. Finally, patients in the pembrolizumab group tended to have higher quality-of-life scores. This study is the first study to compare the CHECKMATE 9LA regimen against the KEYNOTE 189/KEYNOTE 407 regimens. While chemotherapy plus nivolumab-ipilimumab led to a numerically higher OS compared to chemotherapy plus pembrolizumab, the difference was not statistically significant. Additionally, a high number of treatment-related deaths occurred in the nivolumab-ipilimumab treated patients ($n = 11/148$, 7% v $n = 3/144$, 2%

in the pembrolizumab-treated patients), and patient accrual was terminated early. Of note, treatment-related deaths were reported to occur in 2% of patients in CHECKMATE-9LA which was similar to the chemotherapy control arm.¹⁷ Chemotherapy plus nivolumab-ipilimumab was associated with numerically shorter PFS and quality-of-life scores, and an increased rate of high-grade AEs. At time of publication, subgroup analysis did not reveal any specific population that benefited from combination nivolumab-ipilimumab compared to pembrolizumab including in patients with squamous histology (hazard ratio, [HR] 1.02 [95% CI, 0.47 to 2.21]) or patients with PD-L1-negative tumors (HR, 1.44 [95% CI, 0.82 to 2.50]). The high rate of treatment-related deaths in the nivolumab-ipilimumab-chemotherapy treated patients with good PS and organ function raises concern for optimal patient selection for this regimen in a broader cohort of patients, although OS data are not fully mature, and the study power is limited by early termination.

HARMONi-2. This a randomized, double-blind, phase III study conducted in China of the anti-PD-1 and vascular endothelial growth factor (VEGF) bispecific antibody, ivonescimab compared to pembrolizumab in patients with PD-L1-positive ($>1\%$), *EGFR* or *ALK*-negative metastatic or advanced NSCLC.¹⁶ The study included 398 patients randomly assigned to ivonescimab ($n = 198$ patients) or pembrolizumab ($n = 200$), with a primary endpoint of PFS in intention-to-treat (ITT) population assessed by independent review committee (IRC). Block randomization was utilized for 1:1 ratio with stratification factors including disease stage (stage IIIB–C v IV), histology, and PD-L1 tumor proportion score ($\geq 50\%$ v $1\%–49\%$). Baseline demographics were relatively balanced between arms although the pembrolizumab arm had slightly more patients aged 65 or over (58% v 51%). The primary endpoint of study was reached with a median PFS of 11.1 months (95% CI, 7.3 to not estimable) with ivonescimab versus 5.8 months (95% CI, 5.0 to 8.2) with pembrolizumab (HR, 0.51 [95% CI, 0.38 to 0.69]; one-sided $P < .0001$) as assessed by IRC. PFS benefit was seen for ivonescimab across most subgroups including by histology and PD-L1 expression. Grade 3 or higher treatment-related AEs were higher in patients treated with ivonescimab (29%) compared to pembrolizumab (16%) including anticipated VEGF inhibition-related AEs, though rates of immune-related AEs (irAEs) were similar (30% v 28%) overall, with numerically lower rates of serious irAEs for ivonescimab (6% v 11%). Although these data are promising, limitations considered include the lack of data from a global cohort; whether PFS benefit will translate to an OS benefit and whether this will outweigh increased toxicity from the regimen, and the shorter than expected PFS for pembrolizumab treated patients including both PD-L1 high (compared to KEYNOTE-024), and PD-L1 positive (compared to KEYNOTE-042) cohorts.^{18,19} In light of these limitations, the use of ivonescimab is not recommended

currently, but will be re-evaluated when new data are published.

Second-Line and Subsequent Treatment Options for Patients With Good PS

Recommendation 5.1

Clinicians should offer docetaxel with or without ramucirumab if the patient has already received platinum-based chemotherapy (Evidence quality: Low; Strength of recommendation: Strong).

Evidence review and clinical interpretation.

DUBLIN-3 is a phase III, single-blind, randomized controlled trial of docetaxel (75 mg/m² given once on day 1 of 21 days cycle) and plinabulin (30 mg/m² given once on day 1 and day 8) or placebo as second- or third-line treatment for patients with *EGFR* wild-type NSCLC with disease progression after platinum-based doublet chemotherapy.¹⁴ Plinabulin is a small-molecule tubulin binder that prevents polymerization of tubulin and appears to impact dendritic cell maturation and T-cell activation. In total, 559 patients were enrolled and randomly assigned to either plinabulin with docetaxel (n = 278) or placebo with docetaxel (n = 281). The primary end point was OS in the ITT population, which was 10.5 months (95% CI, 9.34 to 11.87) in plinabulin arm

compared to 9.4 months (95% CI, 8.38 to 10.68) in the placebo arm (stratified HR, 0.82 [95% CI, 0.68 to 0.99]). Only one in five patients enrolled had prior PD-1 or PD-L1 therapy, and in these patients, there was no statistically significant improvement in OS for plinabulin over placebo. Subgroup analyses demonstrated improved OS in patients with nonsquamous histology and in patients treated in second line. Patients in the plinabulin arm had lower rates of neutropenia but higher rates of serious treatment-emergent AEs overall (33.1% v 42%). Limitations considered include single blinding, the relatively low number of patients who received prior treatment with first-line immune checkpoint inhibitor reflecting current standard-of-care practices, and the modest OS benefit. Thus, this trial does not change current guideline recommendations.

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

Additional information including a supplement, clinical tools, and resources can be found at www.asco.org/thoracic-cancer-guidelines. Patient information is available at www.cancer.org.

each recommendation. Additional information, including links to patient information at www.cancer.org, is available at www.asco.org/thoracic-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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EDITOR'S NOTE

This ASCO Living Clinical Practice Guideline provides recommendations, with review and analysis of the relevant literature for

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

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TABLE A1. All Recommendations

Clinical Question	Recommendation	Evidence Quality	Strength of Recommendation
NOTE: For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored based on discussion of efficacy and toxicity with each patient. The following recommendations (strong or weak/conditional) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible.			
Clinical question 1: What are the most effective first-line treatment options for patients with good PS and the following biomarkers?			
Non-SCC			
PD-L1 expression TPS ≥50%	1.1. Clinicians should offer single-agent pembrolizumab or cemiplimab or atezolizumab	High	Strong
	1.2. Clinicians may offer pembrolizumab + carboplatin + pemetrexed or cemiplimab + carboplatin + pemetrexed	Moderate	Weak
	1.3. Clinicians may offer atezolizumab + carboplatin + nab-paclitaxel with or without bevacizumab (in the absence of contraindications to bevacizumab)	Moderate	Weak
	1.4. Clinicians may offer nivolumab and ipilimumab	Moderate	Weak
	1.5. Clinicians may offer nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Moderate	Weak
	1.6. Clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Moderate	Weak
PD-L1 expression, TPS 1%-49%	1.7. Clinicians should offer pembrolizumab + carboplatin + pemetrexed or cemiplimab + carboplatin + pemetrexed	Moderate	Strong
	1.8. Clinicians may offer atezolizumab + carboplatin + (nab)-paclitaxel ± bevacizumab in the absence of contraindications to bevacizumab	Moderate	Weak
	1.9. Clinicians may offer nivolumab and ipilimumab	Moderate	Weak
	2.0. Clinicians may offer nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Moderate	Weak
	2.1. Clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Moderate	Weak
	2.2. For patients who are ineligible for or decline the combination of doublet platinum ± anti-PD-(L)1, clinicians may offer monotherapy with anti-PD-1	Moderate	Weak
Unknown or negative PD-L1 expression, TPS <1%	2.3. Clinicians may offer pembrolizumab + carboplatin + pemetrexed or cemiplimab + carboplatin + pemetrexed	Moderate	Weak
	2.4. Clinicians may offer atezolizumab + carboplatin + (nab)-paclitaxel ± bevacizumab in the absence of contraindications to bevacizumab	Moderate	Weak
	2.5. Clinicians may offer nivolumab and ipilimumab	Moderate	Weak
	2.6. Clinicians may offer nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Moderate	Weak
	2.7. Clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Moderate	Weak
SCC			
PD-L1 expression, TPS ≥50%	3.1. Clinicians should offer single-agent pembrolizumab or cemiplimab or atezolizumab	High	Strong
	3.2. Clinicians may offer pembrolizumab + carboplatin + paclitaxel (or nab-paclitaxel) or cemiplimab + carboplatin + paclitaxel	Moderate	Weak
	3.3. Clinicians may offer nivolumab and ipilimumab	Moderate	Weak
	3.4. Clinicians may offer nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Moderate	Weak
	3.5. Clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Moderate	Weak

(continued on following page)

TABLE A1. All Recommendations (continued)

Clinical Question	Recommendation	Evidence Quality	Strength of Recommendation
PD-L1 expression, TPS 1%-49%	3.6. Clinicians should offer pembrolizumab + carboplatin + paclitaxel (or nab-paclitaxel) or cemiplimab + carboplatin + paclitaxel	Moderate	Strong
	3.7. Clinicians may offer nivolumab and ipilimumab	Moderate	Weak
	3.8. Clinicians may offer nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Moderate	Weak
	3.9. Clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Moderate	Weak
	4.0. For patients who are ineligible for or decline the combination of doublet platinum ± anti-PD-(L)1, clinicians may offer single-agent anti-PD-1	Moderate	Weak
Unknown or negative PD-L1 expression, TPS <1%	4.1. Clinicians should offer pembrolizumab + carboplatin + paclitaxel (or nab-paclitaxel) or cemiplimab + carboplatin + paclitaxel	Moderate	Weak
	4.2. Clinicians may offer nivolumab and ipilimumab	Moderate	Weak
	4.3. Clinicians may offer nivolumab and ipilimumab plus two cycles of platinum-based chemotherapy	Moderate	Weak
	4.4. Clinicians may offer durvalumab and tremelimumab plus platinum-based chemotherapy	Moderate	Weak
Patients with unspecified histology			
	4.5. Patients with advanced lung cancer should be referred to interdisciplinary palliative care teams (consultation) that provide inpatient and outpatient care early in the course of disease, alongside active treatment of their cancer	High	Strong
	4.6. For patients who are not candidates for immune checkpoint inhibitor therapy, clinicians should offer platinum--doublet combination therapy for patients with preserved PS	High	Strong
	4.7. Clinicians may offer nonplatinum therapy combinations for patients who have contraindications to platinum therapy	Moderate	Weak
Patients with contraindications to bevacizumab	4.8. Bevacizumab should be avoided for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, ECOG PS >1, clinically significant cardiovascular disease, or medically uncontrolled hypertension	High	Strong
	4.9. Maintenance bevacizumab given with pemetrexed has no survival advantage and significant increased toxicity compared to maintenance pemetrexed or bevacizumab alone	Moderate	Weak
Clinical question 2: What are the most effective second-line and subsequent treatment options for patients with good PS?			
Patients previously treated with immune checkpoint therapy without chemotherapy	5.0. Clinicians should offer platinum doublet chemotherapy	Low	Strong
Patients previously treated with chemotherapy and immune checkpoint therapy	5.1. Clinicians should offer docetaxel with or without ramucirumab if the patient has already received platinum-based chemotherapy	Low	Strong
	5.2. Clinicians may offer pemetrexed or gemcitabine if the patient has already received platinum-based chemotherapy	Low	Weak
	5.3. Clinicians may offer trastuzumab deruxtecan for patients with HER2-overexpressing NSCLC defined as HER2 IHC 3+ (by gastric scoring)	Very low	Weak

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score.

TABLE A2. Stage IV NSCLC Living Guideline Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Cochairs		
Lyudmila Bazhenova, MD	University of California, San Diego, San Diego, CA	Medical Oncology
Natasha B. Leighl, MD	Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada	Medical Oncology
Dwight H. Owen, MD, MS	Ohio State University, Columbus, OH	Medical Oncology
Jyoti Patel, MD	Northwestern University, Chicago, IL	Medical Oncology
Panel members		
Fawzi Abu Rous, MD	Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI	Medical Oncology
Amith Ahluwalia, MD	Confluence Health Wenatchee Valley Hospital and Clinics, Wenatchee, WA	Medical Oncology
Krishna Alluri, MD	Texas Oncology, San Antonio, TX	Medical Oncology
Ibrahim Hanna Azar, MD	IHA Hematology Oncology Consultants, Ypsilanti, MI	Medical Oncology
Greg Durm, MD	Indiana University Health, Indianapolis, IN	Medical Oncology
Jill Feldman, MA	EGFR Resisters patient advocacy group, Deerfield, IL	Patient Research Advocate
Narjust Florez, MD	Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	Medical Oncology
Janet Freeman-Daily, MSc, Engr	The ROS1ders, Seattle, WA	Patient Research Advocate
Naoki Furuya, MD, PhD	St Marianna University School of Medicine, Kawasaki, Japan	Medical Oncology
Shirish Gadgeel, MD	Henry Ford Cancer Institute/Henry Ford Health System, Detroit, MI	Medical Oncology
Balazs Halmos, MD	Montefiore Einstein Comprehensive Center for Cancer Care, Bronx, NY	Medical Oncology
Sara Kuruvilla, MD (Ontario Health representative)	London Health Sciences Centre, London, ON, Canada	Medical Oncology
Narinder Malhotra, MD	Yolanda G. Barco Cancer Institute, Meadville, PA	Medical Oncology
Kristen Ashley Marrone, MD	John Hopkins Medical Center, Baltimore, MD	Medical Oncology
Deebye Raj Mishra, MD	BP Koirala Institute of Health Sciences, Kathmandu, Nepal	Pulmonology
Michael Mullane, MD	Aurora Cancer Care, Mount Pleasant, WI	Medical Oncology
Jarushka Naidoo, MBBCh	Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD	Medical Oncology
Bruna Pellini, MD	Moffitt Cancer Center, Tampa, FL	Medical Oncology
Carolyn J. Presley, MD, MHS	Ohio State University, Comprehensive Cancer Center and The James Cancer Hospital/Solove Research Institute, Columbus, OH	Medical Oncology Geriatric Oncology
Sonam Puri, MD	Moffitt Cancer Center, Tampa, FL	Medical Oncology
Angel Qin, MD	University of Michigan Health System, Ann Arbor, MI	Medical Oncology
Joshua Reuss, MD	Georgetown University, Washington, DC	Medical Oncology
Logan Roof, MD	Ohio State University, Columbus, OH	Medical Oncology
Erin L. Schenk, MD, PhD	University of Colorado Anschutz Medical Center, Aurora, CO	Medical Oncology
Lecia Sequist, MD, MPH	Massachusetts General Hospital, Boston, MA	Medical Oncology
Navneet Singh, MD, DM	Postgraduate Institute of Medical Education and Research, Chandigarh, India	Medical Oncology
Eric K. Singhi, MD	University of Texas MD Anderson Cancer Center, Houston, TX	Medical Oncology
Ana I. Velazquez, MD, MSc	University of California, San Francisco, CA	Medical Oncology
Yubao Wang, MD, PhD	Lovelace Cancer Care, Albuquerque, NM	Medical Oncology
Paul Wheatley Price, MD, MBChB	The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada	Medical Oncology
Nofisat Ismaila, MD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A3. Characteristics of Studies Identified in the Literature Search Since Last Update

Author Year Reference	Interventions and Comparisons	Patients Randomly Assigned, No.	Median Age, Years	Patient Characteristic				Disease Characteristic		
				Sex, %		Smokers, %	Race or Ethnicity, %	History of Brain Metastasis, %	ECOG PS, %	Other Characteristic, %
				Male	Female					
Phase III RCTs										
Shiraishi et al ¹⁵ 2024 JCOG2007 Open-label phase III	Platinum-doublet-pembrolizumab v Platinum-doublet nivolumab + ipilimumab	147 148	68 68	79 81	21 19	88 89	NR	13 20	0: 45 1: 55 0: 47 1: 53	PD-L1 expression <1%: 41 1%-49%: 32 ≥50: 17 Unknown: 10 <1%: 39 1%-49%: 33 ≥50: 16 Unknown: 12
Xiong et al ¹⁶ 2025 HARMONi-2 Double-blind, phase III study in China	Ivonescimab v Pembrolizumab	198 200	65 66	83 85	17 16	Never: 20 Current: 20 Former: 61 Never: 19 Current: 21 Former: 60	Chinese: 100	17 20	0: 13 1: 87 0: 13 1: 87	1%-49%: 58 ≥50%: 42 ≥90%: 11 1%-49%: 58 ≥50%: 43 ≥90%: 9
Han et al ¹⁴ 2024 DUBLIN-3 Single-blind phase III	Docetaxel + plinabulin v Docetaxel + placebo	278 281	60 61	74 72	26 28	NR	NR	NR	0: 16 1: 80 2: 4 0: 14 1: 82 2: 3	Previous PD-1 or PD-L1 therapy received 20 18

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, not reported; PS, performance status; RCT, randomized controlled trial.

TABLE A4. Patients With Previously Untreated Advanced NSCLC: Pembrolizumab Versus Nivolumab + Ipilimumab

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Nivolumab + Ipilimumab	Pembrolizumab		
OS	Hazard ratio: 0.98 (95% CI, 0.72 to 1.34) Based on data from 147 participants in one study Follow-up 15.3 months	385 per 1,000 Difference: six fewer per 1,000 (95% CI, 90 fewer to 94 more)	379 per 1,000	Low Due to serious imprecision and serious indirectness ^a	Nivolumab + ipilimumab may have little or no difference on OS
Safety	Based on data from 295 participants in one study Follow-up 15.3 months	Nonhematologic adverse events of grade 3 or worse occurred in 87 (60%) of 146 patients in the nivolumab-ipilimumab group and 59 (41%) of 144 patients in the pembrolizumab group. The pembrolizumab group tended to have a better quality of life compared with the nivolumab-ipilimumab group		Low Due to serious indirectness and serious imprecision ^a	The safety and efficacy data suggest an unfavorable benefit-risk profile for nivolumab-ipilimumab combined with platinum-based chemotherapy relative to pembrolizumab

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival.

^aIndirectness: serious. Early termination of study because of the number of deaths from intervention; imprecision: serious. Only data from one study.

TABLE A5. Patients With Previously Untreated Locally Advanced or Metastatic PD-L1–Positive NSCLC Without Sensitizing EGFR Mutations: Ivonescimab Versus Pembrolizumab

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Pembrolizumab	Ivonescimab		
PFS	Hazard ratio: 0.51 (95% CI, 0.38 to 0.69) Based on data from 398 participants in one study Follow-up 8.7 months	560 per 1,000 Difference: 218 fewer per 1,000 (95% CI, 292 fewer to 128 fewer)	342 per 1,000	Moderate Due to serious imprecision ^a	Ivonescimab probably improves PFS
Safety	Based on data from 398 participants in one study Follow-up 8.7 months	Grade 3 or higher treatment-related AEs occurred in 58 (29%) patients with ivonescimab and 31 (16%) patients with pembrolizumab. Immune-related AEs of grade 3 or higher were observed in 14 (7%) of 197 patients on ivonescimab and 16 (8%) of 199 patients on pembrolizumab. Ivonescimab demonstrated a manageable safety profile in patients with both squamous and nonsquamous non-small cell lung cancers. In patients with squamous cell carcinoma, grade 3 or higher treatment-related AEs were comparable between the two groups		Moderate Due to serious imprecision ^a	Ivonescimab probably improves safety slightly

Abbreviations: AEs, adverse events; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

^aImprecision: serious. Only data from one study.

TABLE A6. Patients With Advanced or Metastatic *EGFR* Wild-Type NSCLC Whose Disease Progressed After First-Line Platinum-Based Therapy: Docetaxel + Plinabulin Versus Docetaxel + Placebo

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Docetaxel + Placebo	Docetaxel + Plinabulin		
OS	Hazard ratio: 0.82 (95% CI, 0.68 to 0.99) Based on data from 559 participants in one study Follow-up 30.6 months	818 per 1,000 Difference: 65 fewer per 1,000 (95% CI, 132 fewer to 3 fewer)	753 per 1,000	Moderate Due to serious imprecision ^a	Docetaxel + plinabulin probably improves OS
Safety	Based on data from 559 participants in one study Follow-up 30.6 months	Grade 3 or 4 GI disorders occurred more frequently in the plinabulin group than in the placebo group, with the most frequent being diarrhea (24 [9%] of 274 patients v three [1%] of 278) and vomiting (six [2%] v one [<1%]), as did transient grade 3 hypertension (50 [18%] v eight [3%]). Treatment-emergent death was reported in 12 patients (4%) in the plinabulin group and 10 patients (4%) in the placebo group		Moderate Due to serious imprecision ^a	All AEs were manageable with dose adjustments or supportive care. The proportion of patients with grade 5 SAEs leading to death was similar in both groups (12 patients [4%] in the plinabulin group v 10 [4%] in the control group)

Abbreviations: AE, adverse event; NSCLC, non–small cell lung cancer; OS, overall survival; SAE, serious adverse event.

^aImprecision: serious. Only data from one study.

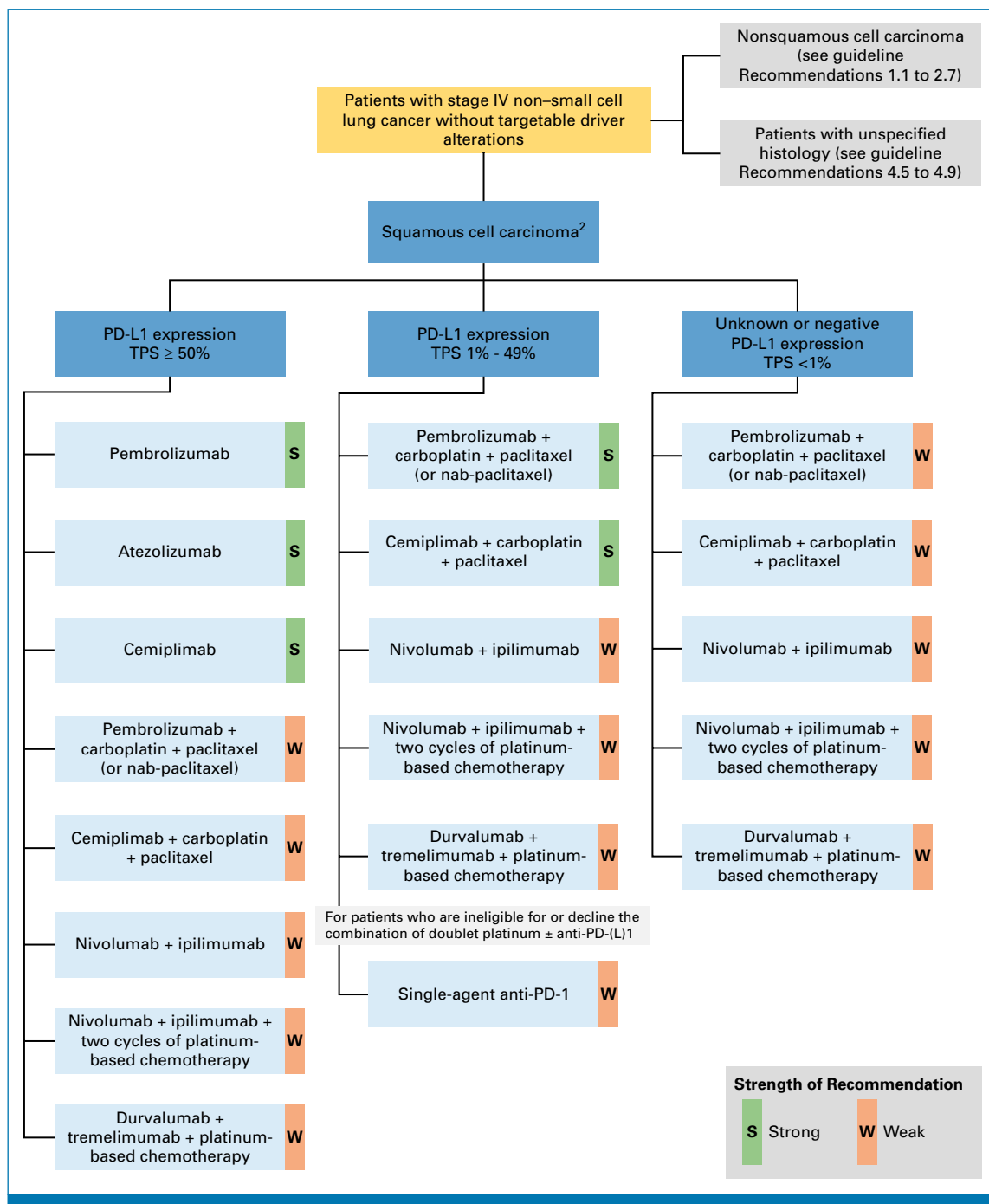


FIG A1. First-line treatment options for patients with stage IV NSCLC without driver alterations and SCC. For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored based on discussion of efficacy and toxicity with each patient. nab, nanoparticle albumin-bound; NSCLC, non-small cell lung cancer; PS, performance status; SCC, squamous cell carcinoma; TPS, tumor proportion score.

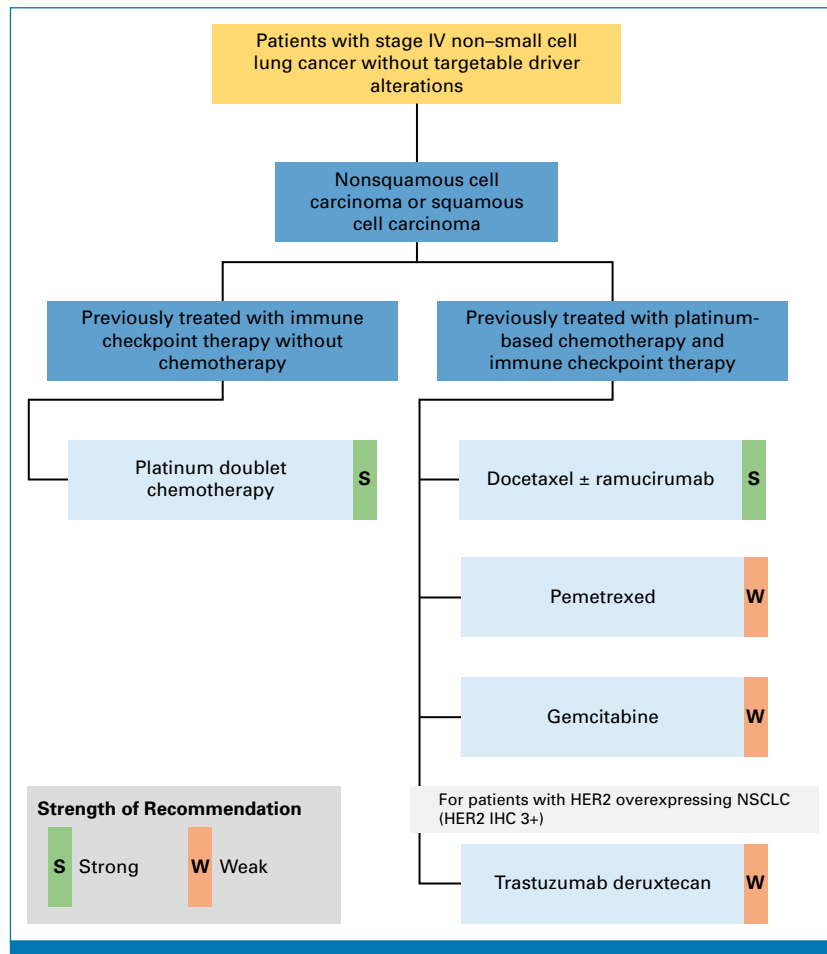


FIG A2. Second-line and subsequent treatment options for patients with stage IV NSCLC without driver alterations. For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored based on discussion of efficacy and toxicity with each patient. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma.