

Therapy for Stage IV Non–Small Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline, Version 2024.3

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DOI <https://doi.org/10.1200/JCO-24-02786>

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 [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 <http://sites.libsyn.com/115284/therapy-for-stage-iv-nsclc-without-driver-alterations-asco-living-guideline-update-20243-part-1>

 Article, April 10, 2024 issue on p. **e23**

 Appendix

 Data Supplement

Accepted January 13, 2025
Published February 27, 2025

Evidence-Based Medicine
Committee approval: December 16, 2024

J Clin Oncol 43:e17-e30
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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.^{3–12} On the basis of routine literature searches (up to September 16, 2024), this version of the stage IV NSCLC without driver alterations living guidelines reviews new evidence to assess if recommendations are up to date.

Refer to Appendix [Table A1](#) (online only) for the full list of recommendations and Appendix [Figure A1](#) for the updated

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

RESULTS

The guideline Expert Panel (Appendix [Table A2](#)) reviewed new evidence from three studies^{13–15} that met the systematic review inclusion criteria (Appendix [Tables A3–A6](#)) and reviewed and approved the updated recommendations. Evidence supporting unchanged recommendations is reviewed in previous publications of this guideline.^{7–9,11}

UPDATED RECOMMENDATIONS

Second-Line and Subsequent Treatment Options for Patients With Good Performance Status

Recommendation 5.3

Clinicians may offer trastuzumab deruxtecan for patients with human epidermal growth factor receptor 2 (HER2)-overexpressing NSCLC defined as HER2 immunohistochemistry (IHC) 3+ (by gastric scoring). (Evidence quality: Very Low; Strength of recommendation: Weak).

Evidence review and clinical interpretation. HER2 overexpression, defined as HER2 protein expression of 2+ or 3+ as measured by IHC utilizing the gastroesophageal (GEA) definition, occurs in 8%-23% of patients with NSCLC. DESTINY-Lung01 was a multicenter open-label, two-cohort, phase II trial evaluating the antitumor activity and safety of trastuzumab deruxtecan (HER2 antibody drug-conjugate [ADC]) in patients with previously treated or refractory unresectable or metastatic nonsquamous NSCLC with HER2 overexpression as determined by the GEA scoring system.¹⁴ Patients enrolled in cohort 1 were treated with trastuzumab deruxtecan 6.4 mg/kg once every 3 weeks (n = 49) v 5.4 mg/kg once every 3 weeks in cohort 1A (n = 41). With a median follow-up of 12 months for cohort 1 and 10.6 months for cohort 1A, the median treatment durations were 4.1 months and 5.5 months, respectively. The confirmed objective response rates (ORRs) were 26.5% for cohort 1 and 34.1% for cohort 1A, with median durations of response of 5.8 months and 6.2 months, respectively. Patients with HER2 IHC 3+ expression in cohort 1A had an ORR of 53% (n = 9/17, 95% CI, 27.8% to 77%), and median duration of response was 6.9 months (range, 4.0, 11.7+). The most common adverse events (AEs; ≥20% patients) were nausea, fatigue, decreased appetite, constipation, vomiting, diarrhea, weight loss, anemia and alopecia. Also, drug-related serious AEs were reported in 20% of patients in cohort 1 versus 7% in cohort 1A. The most common severe (grade ≥3) AEs were neutropenia (24%) in cohort 1 and none in cohort 1A, and fatigue (10% v 7%, respectively). Pneumonitis occurred in 8% and 2% patients in cohort 1 and cohort 1A, respectively. With the safety and efficacy data taken together, trastuzumab deruxtecan 5.4 mg/kg once every 3 weeks was US Food and Drug Administration (FDA)-approved for patients with previously treated advanced tumors, including NSCLC in April 2024. A phase Ib trial for patients with metastatic, previously treated NSCLC with HER2 overexpression assessing trastuzumab deruxtecan 5.4 mg/kg once every 3 weeks is ongoing. Preliminary data presented at the 2024 International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC; n = 36) demonstrated encouraging tumor activity with an ORR of 44.4%, median progression-free survival (PFS) of 8.2 months, and median overall survival (OS) for 17.1 months. It is very important to highlight that 52.8% of patients in this study received prior

epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and differential responses were observed in patients who received prior EGFR TKI (ORR, 68.4%; n = 19) versus patients without prior EGFR TKI (ORR, 17.6%; n = 17). This raises the question of generalizability of these data to patients with HER2 overexpression and NSCLC without activating EGFR mutations or other actionable genomic alterations (AGA).

Additional Notable Trials Reviewed

HARMONi-2

Data from the phase III HARMONi-2 study on the bispecific antibody (PD-1 and vascular endothelial growth factor) ivonescimab compared with PD-1 inhibitor pembrolizumab as a first-line treatment for 398 patients with PD-L1-positive advanced NSCLC in 55 centers in China was presented at the 2024 IASLC WCLC. The Expert Panel awaits the peer-reviewed publication of this study findings.

TROPION-Lung01

The TROPION-Lung01 open-label phase III trial enrolled patients with relapsed or recurrent stage IIIB-C or IV NSCLC with and without AGA. Patients without AGA must have received prior platinum-based chemotherapy and anti-PD-(L)1 therapy.¹³ Patients were randomly assigned to receive ADC datopotamab deruxtecan 6 mg/kg (n = 299) or docetaxel 75 mg/m² (n = 305) once every 3 weeks. The primary end points were PFS and OS, with a preplanned outcomes analysis by pathologic subtype. Datopotamab deruxtecan improved median PFS compared to docetaxel (4.4 months v 3.7 months; hazard ratio [HR], 0.75 [95% CI, 0.62 to 0.91]; P = .004) but not OS (datopotamab deruxtecan 12.9 months v docetaxel 11.8 months; HR, 0.94 [95% CI, 0.78 to 1.14], P = .530). PFS benefit was more pronounced in the nonsquamous histology (5.5 months v 3.6 months; HR, 0.63 [95% CI, 0.51 to 0.790]) and not observed in the squamous group (2.8 months v 3.9 months; HR, 1.41 [95% CI, 0.95 to 2.08]). Subgroup analyses in patients with nonsquamous NSCLC and those with AGA showed trends for better OS with datopotamab deruxtecan. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 42.1% of patients with docetaxel and 25.6% with datopotamab deruxtecan. Interstitial lung disease, a TRAE of special interest with deruxtecan-containing ADC,¹⁶ occurred in 8.8% of patients with datopotamab deruxtecan and 4.1% with docetaxel. Though these results appear promising, the panel felt the strength of the evidence based on this unplanned subgroup analyses was insufficient to make a recommendation at this time.

There are no validated biomarkers for datopotamab deruxtecan use in NSCLC. TROP2 expression by IHC was not associated with response.¹⁷ An exploratory biomarker, TROP2 normalized membrane ratio, as measured by quantitative continuous scoring is promising, but cannot be

recommended at the time of publication of this guideline due to lack of validation.

LUNAR Study

Tumor Treating Fields (TTFields) are electric fields administered via a portable device that disrupts multiple intracellular processes responsible for cancer cell proliferation. The LUNAR study was a randomized, open-label, phase III trial for patients with metastatic NSCLC whose disease progressed on platinum-based therapy, but were not required to have checkpoint inhibitors (the current standard of care).¹⁵ Participants were randomly assigned 1:1 to either TTFields plus standard therapy (n = 137) or standard therapy alone (n = 139). Standard therapy consisted of the investigator's choice of an immune checkpoint inhibitor or docetaxel. TTFields therapy (150 kHz) was administered continuously to the thoracic area, with a recommendation to maintain an average device usage of 18 hours per day. The primary end point of the study was OS in an intention-to-treat population. The addition of TTFields therapy improved median OS over standard therapy alone post platinum chemotherapy (13.2 months v 9.9 months; HR, 0.74 [95% CI, 0.56 to 0.98]; *P* = .035). In preplanned subset analysis, a more pronounced benefit was observed in patients treated with immunotherapy (HR, 0.63 [95% CI, 0.41 to 0.96]; *P* = .030), while outcomes were similar in patients receiving docetaxel with or without TTFields (HR, 0.81 [95% CI, 0.55 to 1.19]; *P* = .28). A key limitation of this study is that only 32% of patients received prior immunotherapy (per current guideline recommendations), and the majority of these were treated in the docetaxel arm. Fourteen percent of patients discontinued the device due to device-related toxicity. All-cause AEs were numerically higher in the TTFields arm (97%) compared to the standard-of-care arm (91%), but there was no

significant difference in the rate of grade 3 AEs (59% v 56%, respectively).

TTFields gained regulatory approval from the FDA in October 2024 for patients with metastatic NSCLC who are receiving PD-(L)1 inhibitors or docetaxel and have experienced progression during or after treatment with a platinum-based chemotherapy regimen. While the subset analysis of this study should be interpreted with caution, the most significant benefit was seen in the immunotherapy-naïve second-line population. In countries such as the United States, this patient population is rare, as immunotherapy is firmly established as first-line treatment. Given the potential lifestyle implications of wearing a device for 18 hours per day, the lack of evidence in the immunotherapy-pretreated population, and the absence of data in the first-line setting for immunotherapy-naïve patients, there are insufficient data to definitively recommend the addition of TTFields to systemic therapy for most patients. Additional clinical studies are needed to recommend this device's use in the immunotherapy-naïve first-line setting and in the chemo-immunotherapy pretreated setting. Additional studies to promote external generalizability of the use of TTFields in patients with advanced NSCLC are also needed if this novel technology is to be widely adopted.

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/living-guidelines. Patient information is available at www.cancer.org.

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EDITOR'S NOTE

This ASCO Living Clinical Practice Guideline provides recommendations, with review and analysis of the relevant literature for each recommendation. Additional information, including links to patient information at www.cancer.org, is available at www.asco.org/living-guidelines.

EQUAL CONTRIBUTION

N.B.L. and L.B. were Expert Panel Coauthors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO-24-02786>.

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ACKNOWLEDGMENT

The authors would like to thank Drs Tanyanika Philips and Estelamari Rodríguez and the ASCO Evidence-Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline update.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No other potential conflicts of interest were reported.

APPENDIX 1. GUIDELINE DISCLAIMER

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

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TABLE A1. All Recommendations

Clinical Question	Recommendations	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 performance status and the following biomarkers?			
Nonsquamous cell carcinoma			
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
Squamous cell carcinoma			
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	Recommendations	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 squamous cell carcinoma 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 performance status?			
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 PS, Eastern Cooperative Oncology Group performance status; 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 Non–Small Cell Lung Cancer Living Guideline Expert Panel Membership

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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
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Narjust Florez, MD	Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA	Medical Oncology
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Balazs Halmos, MD	Montefiore Einstein Comprehensive Center for Cancer Care, Bronx, NY	Medical Oncology
Sara Kuruville, MD (Ontario Health representative)	London Health Sciences Center, London, ON, Canada	Medical Oncology
Narinder Malhotra, MD	Medicus Healthcare Solutions, Windham, NH	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, MBChB	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 Center, 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, No.	Median Age, Years	Patient Characteristics				Disease Characteristics		
				Sex, %		Smokers, %	Race or Ethnicity, %	History of Brain Me- tastasis, %	ECOG PS, %	Other Characteris- tics, %
				Male	Female					
Phase III RCTs										
Ahn et al ¹³ 2024 TROPION-Lung01 Open-label phase III	Datopotamab deruxtecan v Docetaxel	299 305	63 64	61 69	39 31	79 82	Asian: 40 White: 41 American Indian or Alaska Native: 0.3 Black: 2 Others/missing: 17 Asian: 39 White: 41 American Indian or Alaska Native: 0 Black: 1.3 Others/missing 18	26 30	0: 30 1: 70 0: 31 1: 69	PD-L1 expression <1%: 34.8 ≥1%: 52.8 Unknown/ missing: 3.7 Not done: 8.7 <1%: 38.0 ≥1%: 48.2 Unknown/ missing: 3.0 Not done: 10.8
Smit et al ¹⁴ 2024 DESTINY-Lung01 Single-arm, phase II trial	Trastuzumab deruxtecan Cohort 1 (6.4 mg/kg once every 3 weeks) Cohort 1A (5.4 mg/kg once every 3 weeks)	49 41	63 62	61 54	39 46	67 78	Asian: 27 White: 63 American Indian or Alaska Native: 0 Black: 8 Others/missing: 2 Asian: 10 White: 76 American Indian or Alaska Native: 2 Black: 5 Others/missing 7	35 29	0: 29 1: 71 0: 12 1: 88	HER2 status IHC 3+: 20 IHC 2+: 80 IHC 3+: 41 IHC 2+: 59
Leal et al ¹⁵ 2024 LUNAR	TTFields therapy with standard therapy group v Standard therapy group	137 139	63 65	66 63	34 37	85 84	Asian: 12 White: 81 American Indian or Alaska Native: 0 Black: 2 Others/missing: 4 Asian: 9 White: 80 American Indian or Alaska Native: 0 Black: 2 Others/missing 8	0 1	0: 28 1: 68 2: 4 0: 29 1: 68 2: 3	Histology type Nonsquamous: 58 Squamous: 42 Nonsquamous: 55 Squamous: 45

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

TABLE A4. Patients With Pretreated Advanced/Metastatic Non–Small Cell Lung Cancer: Dato-DXd Versus Docetaxel

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Docetaxel	Dato-DXd		
PFS	HR: 0.75 (95% CI, 0.62 to 0.91) On the basis of data from 604 participants in one study Follow-up 10.9 months	715 per 1,000 Difference: 105 fewer per 1,000 (95% CI, 174 fewer to 34 fewer)	610 per 1,000	Low ^a	Datopotamab deruxtecan probably improves PFS
PFS (non-SCC)	HR: 0.63 (95% CI, 0.51 to 0.79) On the basis of data from 468 participants in one study Follow-up 10.9 months	726 per 1,000 Difference: 168 fewer per 1,000 (95% CI, 243 fewer to 86 fewer)	558 per 1,000	Low ^a	Datopotamab deruxtecan probably improves PFS in non-SCC
OS	HR: 0.94 (95% CI, 0.78 to 1.14) On the basis of data from 604 participants in one study Follow-up 23.1 months	715 per 1,000 Difference: 22 fewer per 1,000 (95% CI, 91 fewer to 46 more)	693 per 1,000	Low ^a	Datopotamab deruxtecan probably has little or no difference in OS
Safety	On the basis of data from 587 participants in one study Follow-up 23.1 months	Grade ≥ 3 TRAEs occurred at rates of 25.6% and 42.1%, serious TRAEs at 11.1% and 12.8%, dose reductions at 20.2% and 29.7%, and treatment discontinuations at 8.1% and 12.1% for Dato-DXd and docetaxel, respectively. No late-onset toxicities were observed for Dato-DXd. Three patients (1.0%) treated with Dato-DXd, and two (0.7%) with docetaxel had investigator-assessed TRAEs associated with death		Low ^a	Median treatment durations were 4.2 months (range, 0.7-27.2) with Dato-DXd and 2.8 months (range, 0.7-25.3) with docetaxel. The incidence of any-grade TRAEs was similar in both groups (87.5% and 86.9%, respectively)

Abbreviations: Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SCC, squamous cell carcinoma; TRAEs, treatment-related adverse events.

^aImprecision: serious. Only data from one study. On the basis of subgroup analysis.

TABLE A5. Previously Treated Patients With HER2-Overexpressing or HER2 (ERBB2)-Mutant Unresectable or Metastatic Non–Small Cell Lung Cancer: Trastuzumab Deruxtecan 6.4 mg/kg once every 3 weeks (cohort 1) and Trastuzumab Deruxtecan 5.4 mg/kg once every 3 weeks (cohort 1A)

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Trastuzumab Deruxtecan 5.4 mg/kg once every 3 weeks	Trastuzumab Deruxtecan 6.4 mg/kg once every 3 weeks		
ORR	On the basis of data from 90 participants in one study Follow-up 12 months	The confirmed ORR by independent central review was 26.5% (95% CI, 15.0 to 41.1; 13 of 49, all partial responses) in cohort 1 and 34.1% (95% CI, 20.1 to 50.6; 14 of 41; two complete responses and 12 partial responses) in cohort 1A		Very low ^a	Responses were observed in patients with HER2 IHC 3+ or 2+ status tumors, regardless of the presence of stable CNS metastases at baseline and in patients with previous anti-PD-1 and anti-PD-L1 therapy. Antitumour activity was also observed in patients with and without HER2 amplification
Safety	On the basis of data from 90 participants in one study Follow-up 12 months	The most common treatment-emergent AEs of grade 3 or worse were neutropenia (12 [24%] of 49 in cohort 1, none in cohort 1A), pneumonia (six [12%] and two [5%], respectively), fatigue (six [12%] and three [7%], respectively), and disease progression (six [12%] and four [10%], respectively)		Very low ^a	The safety profile of trastuzumab deruxtecan was generally manageable and favored the 5.4 mg/kg once every 3 weeks dose
PFS	On the basis of data from 90 participants in one study Follow-up 12 months	The median PFS per independent central review was 5.7 months (95% CI, 2.8 to 7.2) in cohort 1 and 6.7 months (95% CI, 4.2 to 8.4) in cohort 1A		Very low ^a	In cohort 1, 31 (63%) patients had PFS events (24 [49%] progressive disease, seven [14%] deaths), and in cohort 1A, 29 (71%) patients had PFS events (17 [41%] progressive disease, 12 [29%] deaths)
OS	On the basis of data from 90 participants in one study Follow-up 12 months	The median OS was 12.4 months (95% CI, 7.8 to 17.2) in cohort 1 and 11.2 months (95% CI, 8.4 to NE) in cohort 1A		Very low ^a	In cohort 1, 39 (80%) patients died, and in cohort 1A, 23 (56%) patients died

Abbreviations: AEs, adverse events; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

^aImprecision: serious; only data from one study.

TABLE A6. Previously Treated Patients With Metastatic Non–Small Cell Lung Cancer: TTFields Therapy With Standard Therapy Versus Standard Therapy

Outcome	Study Results and Measurements	Absolute Effect Estimates		Quality of Evidence	Summary
		Standard Therapy	TTFields Therapy with Standard Therapy		
OS	HR: 0.74 (95% CI, 0.56 to 0.98) On the basis of data from 276 participants in one study Follow-up 10.6 months	784 per 1,000	678 per 1,000 Difference: 106 fewer per 1,000 (95% CI, 208 fewer to 7 fewer)	Low ^a	TTFields therapy with standard therapy may improve OS
PFS	HR: 0.85 (95% CI, 0.67 to 1.11) On the basis of data from 276 participants in one study Follow-up 10.6 months	849 per 1,000	799 per 1,000 Difference: 50 fewer per 1,000 (95% CI, 131 fewer to 28 more)	Low ^a	TTFields therapy with standard therapy might have little or no difference in PFS
Safety	On the basis of data from 267 participants in one study Follow-up 10.6 months	Serious AEs of any cause were reported in 70 (53%) of 133 patients receiving TTFields therapy plus standard therapy and 51 (38%) of 134 patients receiving standard therapy alone. The most frequent grade 3-4 AEs were leukopenia (37 [14%] of 267), pneumonia (28 [10%]), and anemia (21 [8%]). TTFields therapy-related AEs were reported in 95 (71%) of 133 patients; these were mostly (81 [85%]) grade 1-2 skin and subcutaneous tissue disorders		Low ^a	270 (98%) of 276 patients discontinued the study, mostly because of progression or death (167 [61%] of 276). At data cutoff, 92 deaths had occurred in the group of 137 patients assigned to TTFields therapy and standard therapy, and 109 deaths had occurred in the 139 patients assigned to standard therapy alone

Abbreviations: AEs, adverse events; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTFields, Tumor Treating Fields.

^aRisk of bias: serious. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; imprecision: serious. Only data from one study.

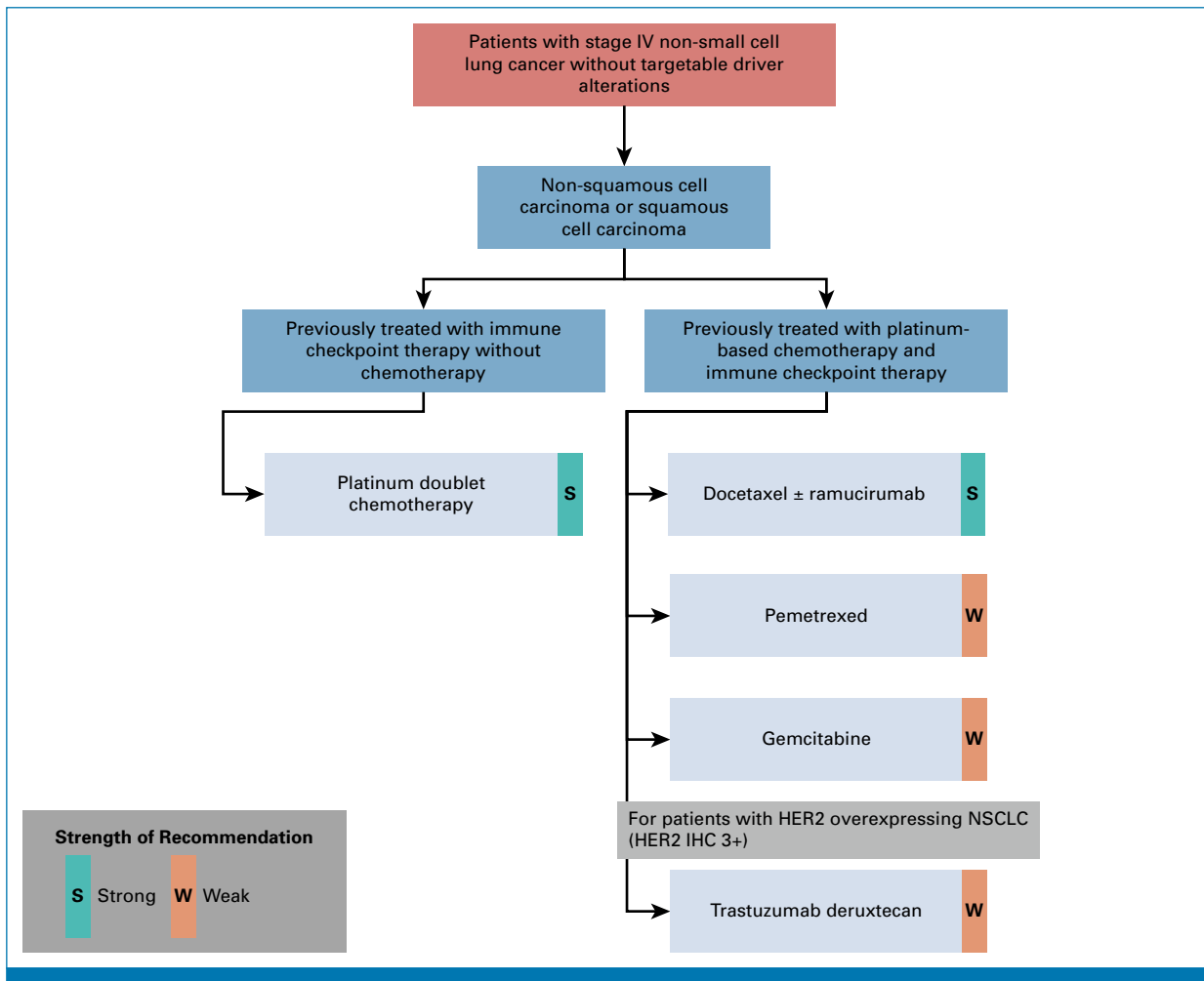


FIG A1. Second-line and subsequent treatment options for patients with stage IV non-small cell lung cancer without driver alterations. For recommendations with multiple treatment options of the same evidence quality and strength of recommendation, the decision of which agent to offer should be tailored on the basis of discussion of efficacy and toxicity with each patient. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.