Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

# General

## Guideline Title

Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update.

## Bibliographic Source(s)

Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis PM, Giaccone G, Hesketh PJ, Jaiyesimi I, Leighl NB, Riely GJ, Schiller JH, Schneider BJ, Smith TJ, Tashbar J, Biermann WA, Masters G. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017 Oct 20;35(30):3484-515. [45 references] PubMed

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, Brahmer JR, Ellis PM, Gajra A, Rackear N, Schiller JH, Smith TJ, Strawn JR, Trent D, Johnson DH. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol. 2015 Oct 20;33(30):3488-515.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

| Assessment | Standard of Trustworthiness |
|---|---|
| YES | Disclosure of Guideline Funding Source |
| | Disclosure and Management of Financial Conflict of Interests |

| | |
|---|---|
| | Guideline Development Group Composition |
| YES | Multidisciplinary Group |
| YES | Methodologist Involvement |
| | Patient and Public Perspectives |
| | Use of a Systematic Review of Evidence |
| | Search Strategy |
| | Study Selection |
| | Synthesis of Evidence |
| | Evidence Foundations for and Rating Strength of Recommendations |
| | Grading the Quality or Strength of Evidence |
| | Benefits and Harms of Recommendations |
| | Evidence Summary Supporting Recommendations |
| | Rating the Strength of Recommendations |
| | Specific and Unambiguous Articulation of Recommendations |
| | External Review |
| | Updating |

# Recommendations

## Major Recommendations

Definitions for the rating of evidence (High, Intermediate, Low, Insufficient); types of recommendations (Evidence Based, Formal Consensus, Informal Consensus, No Recommendation); and strength of recommendations (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

2017 Recommendations

Clinical Question A2. First-Line Treatment

Clinical Question A2.a. Non–Squamous Cell Carcinoma (NSCC) and Negative or Unknown *EGFR* or *ALK/ROS1*. What is the most effective first-line therapy for patients with NSCC and negative or unknown tumor epidermal growth factor receptor (*EGFR*)-sensitizing mutation, aplastic lymphoma kinase (*ALK*) or proto-oncogene receptor kinase (*ROS1*) gene rearrangement status, and with performance status (PS) of 0 or 1 (or possibly PS of 2)?

*Recommendation A2.a*: Treatment options include:

For patients with high programmed death ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥50%), single-agent pembrolizumab should be used in the absence of contraindications to immune checkpoint therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
There are insufficient data to recommend other checkpoint inhibitors or to recommend combination checkpoint inhibitors or immune checkpoint therapy with chemotherapy in the first-line setting at the time of this update.
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 (see the "Availability of Companion Documents" field) (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong) or non–platinum-based two-drug therapy as outlined in the 2015 update for patients not deemed candidates for platinum-based therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak).

Clinical Question A3. Squamous Cell Carcinoma (SCC). What is the most effective first-line therapy for patients with stage IV non-small-cell lung cancer (NSCLC) with SCC, negative or unknown tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement status, and PS of 0 or 1 (or possibly PS of 2)?

*Recommendation A3*: Treatment options include:

For patients with high PD-L1 expression (TPS ≥50%), single-agent pembrolizumab should be used in the absence of contraindications to immune checkpoint therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
There are insufficient data to recommend other checkpoint inhibitors or to recommend combination checkpoint inhibitors or immune checkpoint inhibitors with chemotherapy in the first-line setting.
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) or 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).
For patients with stage IV squamous NSCLC receiving cisplatin and gemcitabine, the Panel neither recommends for nor recommends against the addition of necitumumab to chemotherapy (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak).

<u>Clinical Question B. Second-Line Treatment</u>

Clinical Question B1. What is the most effective second-line therapy for patients with negative or unknown tumor *EGFR*-sensitizing mutation, *ALK* gene rearrangement status, or *ROS1* gene rearrangement status and PS of 0 or 1 (or possibly PS of 2)?

Clinical Question B1.a. Negative/Unknown *EGFR/ALK/ROS1*. What is the most effective therapy for patients with non–squamous cell carcinoma who have received one prior chemotherapy regimen?

*Recommendation B1*: Squamous and non-squamous and negative or unknown *EGFR* mutation, *ALK* gene rearrangement status, or *ROS1* gene rearrangement status.

For patients who received first-line chemotherapy and have not received prior immune checkpoint inhibitor therapy, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab in patients with positive tumor PD-L1 expression (TPS ≥1%, 22C3 assay) in the absence of contraindications to immune checkpoint therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).
For patients with negative or unknown tumor PD-L1 expression (TPS <1%) who received first line-therapy chemotherapy, clinicians should use single-agent nivolumab or atezolizumab in the absence of contraindications to immune checkpoint therapy (Type: evidence-based, benefits outweigh harms;

Evidence quality: high; Strength of recommendation: strong).
There are insufficient data to recommend combination checkpoint inhibitors or immune checkpoint inhibitors with chemotherapy in the second-line setting.
For patients who received an immune checkpoint inhibitor as first-line therapy, clinicians should offer standard platinum-based chemotherapy, as outlined in the 2015 update (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong), or non–platinum-based, two-drug therapy if platinum is contraindicated, as outlined in the 2015 update (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).
For patients with contraindications to immune checkpoint inhibitor therapy after first-line chemotherapy, docetaxel is recommended as second-line therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).
Non-squamous only: Patients with non–squamous cell carcinoma who have not previously received pemetrexed-based first-line or maintenance therapy should be offered pemetrexed as second-line therapy (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Clinical Question B3.a. *EGFR* Positive. What is the most effective second-line therapy for patients with stage IV NSCLC with a sensitizing *EGFR* mutation who received a first-line EGFR tyrosine kinase inhibitor (TKI) and experienced disease progression?

*Recommendation B3.a*: For patients with stage IV NSCLC with a sensitizing *EGFR* mutation and disease progression after first-line therapy with an EGFR-TKI and the presence of the T790M resistance mutation, clinicians should recommend osimertinib (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong). If the T790M mutation is not present, clinicians may offer treatment with a platinum doublet (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

*Recommendation B3.b*: Patients who received an EGFR-TKI in the first-line setting, had an initial response, and subsequently experienced slow or minimal disease progression at isolated sites may continue EGFR-TKI with local therapy to the isolated sites (Type: informal consensus-based; Evidence quality: insufficient; Strength of recommendation: weak).

Clinical Question B6. *ROS1* Rearrangement. What is the most effective second-line therapy for patients with *ROS1* rearrangement?

*Recommendation B6.a. Patients who have not received prior crizotinib*: If patients have *ROS1* rearrangement and have not received crizotinib in the first-line setting, single-agent crizotinib may be offered as second-line therapy (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

*Recommendation B6.b. Patient who received prior crizotinib*: If patients have *ROS1* rearrangement and have received crizotinib in the first-line setting, then they may be offered platinum-based therapy in the second-line setting with or without bevacizumab (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Clinical Question B8. *BRAF* Mutations. What is the most effective therapy for patients with stage IV NSCLC and *BRAF* mutations who have received prior chemotherapy?

*Recommendation B8*: Clinicians may offer atezolizumab, nivolumab, or pembrolizumab (if PD-L1 TPS >1%) in patients with *BRAF* mutations unless the patient received immune checkpoint therapy in the first-line setting (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: weak). If patients with *BRAF* mutations received immunotherapy in the second-line, clinicians may offer patients dabrafenib alone or in combination with trametinib in the third-line (Type: informal consensus, benefits outweigh harms; Evidence quality: insufficient; Strength of recommendation: moderate).

Clinical Question C. Third-Line Treatment

Clinical Question C1. *EGFR* Negative. What is the most effective third-line therapy for patients with stage IV non-squamous NSCLC, negative or unknown tumor *EGFR*-sensitizing mutation or *ALK* or *ROS1* gene rearrangement status, and PS of 0 or 1 (or possibly PS of 2)?

*Recommendation C1*: For the majority of patients who received chemotherapy with or without bevacizumab and immune checkpoint therapy, clinicians should offer the options of single-agent pemetrexed or docetaxel in the third-line setting (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: strong).

Clinical Question C2. *EGFR* Positive. What is the most effective third-line therapy for patients with a tumor *EGFR*-sensitizing mutation who have received prior platinum-based chemotherapy and EGFR-TKI?

*Recommendation C2*: There are insufficient data to recommend immunotherapy in preference to chemotherapy (pemetrexed or docetaxel) for patients with *EGFR*-sensitizing mutations who have received at least one EGFR-TKI and subsequent platinum-based chemotherapy (Type: informal consensus based; Evidence quality: insufficient; Strength of recommendation: weak).

Clinical Question D. Fourth-Line Treatment

Clinical Question D1. Is there a role for cytotoxic therapy in patients who have received three prior regimens and who have a good PS?

*Recommendation D1*: Data are not sufficient to make a recommendation for or against using cytotoxic drugs as fourth-line therapy; patients should consider experimental treatment, clinical trials, and continued best supportive (palliative) care.

2015 Recommendations

Clinical Question A1. General

Clinical Question A1. Which patients with stage IV non-small-cell lung cancer should be treated with chemotherapy?

*Recommendation A1.a*: For patients with performance status of 0 or 1 *receiving chemotherapy*, a combination of two cytotoxic drugs is recommended. Platinum combinations are recommended over nonplatinum therapy; however, nonplatinum therapy combinations are recommended for patients who have contraindications to platinum therapy. Chemotherapy may also be used to treat selected patients with PS of 2 who desire aggressive treatment after a thorough discussion of the risks and benefits of such treatment (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

*Recommendation A1.b*: Because there is no cure for patients with stage IV NSCLC, early concomitant palliative care assistance has improved the survival and well being of patients and is therefore recommended (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question A2. First Line Treatment

Clinical Question A2. What is the most effective first-line therapy for patients with stage IV NSCLC with NSCC, negative or unknown *EGFR*-sensitizing mutation and *ALK* gene rearrangement status, and PS 0 to 1 or possibly PS 2?

*Recommendation A2*: Treatment options include:

- Cisplatin-based combinations
  - Cisplatin and docetaxel
  - Cisplatin and paclitaxel
  - Cisplatin and pemetrexed
  - Cisplatin and vinorelbine

- Carboplatin-based combinations
  - Carboplatin and nanoparticle albumin-bound (nab) paclitaxel
  - Carboplatin and paclitaxel (with or without bevacizumab; see 2015 recommendation A2.a.1)
  - Carboplatin and pemetrexed
  - Carboplatin and docetaxel
- Nonplatinum doublets

Clinical Question A2.a.1. NSCC and Negative or Unknown *EGFR* or *ALK/ROS1*. What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR*, *ALK*, or *ROS1* status, NSCC, and no contraindications to bevacizumab?

*Recommendation A2.a.1*: For patients receiving carboplatin plus paclitaxel, the Update Committee recommends the addition of bevacizumab 15 mg/kg once every 3 weeks, except for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, Eastern Cooperative Oncology Group PS >1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

*Recommendation A2.a.2*: There is insufficient evidence to recommend bevacizumab in combination with pemetrexed plus carboplatin for patients who do not have contraindications to bevacizumab. (Note: slight wording change from Recommendation A2.a.2. [2015])

Clinical Question A2.b. Non-squamous Cell Carcinoma and PS of 2. What is the most effective first-line therapy for patients with stage IV NSCLC with PS 2, NSCC, and negative or unknown tumor *EGFR*-sensitizing mutation and *ALK* or *ROS1* gene rearrangement status?

*Recommendation A2.b*: In the context of shared decision making, combination therapy, single-agent therapy, or palliative therapy alone may be used for patients in this population with PS 2 (Chemotherapy: Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak; Palliative care: Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Clinical Question A3. Squamous Cell Carcinoma. What is the most effective first-line therapy for patients with stage IV NSCLC with SCC, negative or unknown tumor *EGFR*-sensitizing mutation and *ALK* or *ROS1* gene rearrangement status, and PS of 0 or 1 (or possibly PS of 2)?

*Recommendation A3*:

- Cisplatin-based combinations
  - Cisplatin and docetaxel
  - Cisplatin plus paclitaxel
  - Cisplatin plus gemcitabine
  - Cisplatin plus vinorelbine
- Carboplatin-based combinations
  - Carboplatin and nab paclitaxel
  - Carboplatin and paclitaxel
  - Carboplatin and gemcitabine
  - Carboplatin and docetaxel
- Nonplatinum doublets

Clinical Question A3.a. Squamous Cell Carcinoma and PS of 2. What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status, SCC, and PS 2?

*Recommendation A3.a*: In the context of shared decision making, combination chemotherapy, single-agent therapy, or palliative therapy alone may be used for patients with the characteristics described in Clinical Question A3.a. (Chemotherapy: Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: weak; Palliative care: Type: evidence based, benefits

outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong.)

Clinical Question A4. *EGFR* Positive. What is the most effective first-line therapy for patients with stage IV NSCLC with a tumor *EGFR*-sensitizing mutation and PS of 0 to 2?

*Recommendation A4*: If patients have stage IV NSCLC and a sensitizing *EGFR* mutation, the following are first-line options:

> Afatinib (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)
> Erlotinib (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)
> Gefitinib (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong)

Clinical Question A5. What is the most effective first-line therapy for patients with stage IV NSCLC with *ALK* gene rearrangement and PS 0 to 1 or possibly PS 2?

*Recommendation A5*: If patients have stage IV NSCLC and *ALK* rearrangements, first-line crizotinib is recommended (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question A6. *ROS1* Positive. What is the most effective first-line therapy for patients with stage IV NSCLC with *ROS1* rearrangement, no *ALK* gene rearrangement, negative or unknown *EGFR*-sensitizing mutation status, and PS 0 to 1 or possibly PS 2?

*Recommendation A6*: If patients have stage IV NSCLC with *ROS1* rearrangement, single-agent crizotinib is recommended, because it has shown some results indicating improved response rate and duration of response (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Clinical Question A7. Large-cell Neuroendocrine Carcinoma. What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR/ALK* status and large-cell neuroendocrine carcinoma?

*Recommendation A7*: Patients with large-cell neuroendocrine carcinoma may receive the same treatment as other patients with NSCC or treatment with etoposide in platinum combinations (Type: informal consensus, benefits outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Clinical Question A8. Elderly. What is the best chemotherapy for treatment of the elderly with stage IV NSCLC?

*Recommendation A8*: Decisions on the selection of chemotherapy should not be made or altered based on age alone (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question A9. Maintenance. What is the optimal treatment for patients with stable disease or response after four cycles of cytotoxic chemotherapy?

*Recommendation A9*: In patients with stage IV NSCLC, first-line cytotoxic chemotherapy should be stopped at disease progression or after four cycles in patients whose disease is stable but not responding to treatment; two-drug cytotoxic combinations should be administered for no more than six cycles. For patients with stable disease or response after four cycles of a first-line pemetrexed-containing regimen, continuation maintenance treatment with pemetrexed is recommended. For patients with stable disease or response after four cycles of a regimen that did not include a pemetrexed-containing combination, alternative single-agent chemotherapy, such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients, or a break from cytotoxic chemotherapy with initiation of second-line chemotherapy at disease progression may be recommended (Addition of pemetrexed: Type: evidence based, benefits outweigh harms; Evidence quality: intermediate;

Strength of recommendation: moderate).

Clinical Question B. Second-Line Treatment

Clinical Question B2. What is the most effective therapy for patients with squamous cell carcinoma who have received one prior chemotherapy regimen?

*Recommendation B2*: For patients with advanced NSCLC, SCC, negative or unknown *EGFR/ALK* status, and adequate PS, when disease has progressed during or after first-line platinum-based therapy, docetaxel, erlotinib, or gefitinib is acceptable as second-line therapy.

Clinical Question B4. *ALK* Rearrangement. What is the most effective second-line therapy for patients with stage IV NSCLC with *ALK* rearrangement with progression after first-line crizotinib?

*Recommendation B4*: Patients whose tumors have *ALK* rearrangements and who received crizotinib in the first-line setting may be offered the option of chemotherapy (after first-line recommendations for patients with NSCC [see Recommendation A2]) or ceritinib in the second-line setting (Chemotherapy: Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong; Ceritinib: Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical Question B5. Elderly. What is the optimal second-line treatment for elderly patients with stage IV NSCLC?

*Recommendation B5*: The evidence does not support the selection of a specific second-line chemotherapy drug or combination based on age alone. This recommendation has not changed. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC.

Definitions

Guide for Rating Quality of Evidence

| Rating for Strength of Evidence | Definition |
|---|---|
| High | High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and that further research is very unlikely to change either the magnitude or direction of this net effect. |
| Intermediate | Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect. |
| Low | Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect. |
| Insufficient | Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic. |

Guide for Types of Recommendations

| Type of Recommendation | Definition |
|---|---|
| Evidence based | There was sufficient evidence from published studies to inform a recommendation to guide clinical practice. |
| Formal consensus | The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Expert Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and |

| Type of Recommendation | Definition |
|---|---|
| | reported in the Data Supplement (see the "Availability of Companion Documents" field). |
| Informal consensus | The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Expert Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Expert Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). |
| No recommendation | There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Expert Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation. |

Guide for Strength of Recommendations

| Rating for Strength of Recommendation | Definition |
|---|---|
| Strong | There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. |
| Moderate | There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. |
| Weak | There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. |

## Clinical Algorithm(s)

The following algorithms are available from the American Society of Clinical Oncology (ASCO) Web site:

Systemic therapy for stage IV non-small-cell lung non-squamous cell carcinoma

Systemic therapy for stage IV non-small-cell lung squamous cell carcinoma

# Scope

## Disease/Condition(s)

Stage IV non-small-cell lung cancer (NSCLC)

## Guideline Category

Management

Treatment

## Clinical Specialty

Internal Medicine

Medical Genetics

Oncology

## Intended Users

Advanced Practice Nurses

Nurses

Patients

Physician Assistants

Physicians

Social Workers

## Guideline Objective(s)

- To provide evidence-based recommendations updating the 2015 American Society of Clinical Oncology guideline on systemic therapy for patients with stage IV non-small-cell lung cancer (NSCLC)
- To address the following overarching clinical questions: For patients with stage IV NSCLC in certain histologic or molecular subgroups (including epidermal growth factor receptor [*EGFR*], *EGFR*-positive T790M, anaplastic lymphoma kinase [*ALK*], proto-oncogene receptor tyrosine kinase [*ROS1*], programmed death ligand 1/programmed cell death 1 [PD-L1/PD-1]), what is the most effective first-line therapy? What is the most effective second-line therapy? Is there a role for third-line or later therapy?

## Target Population

Patients with stage IV non-small-cell lung cancer (NSCLC)

## Interventions and Practices Considered

1. First-line chemotherapy
    - Cisplatin-based combinations (docetaxel, paclitaxel, pemetrexed, or vinorelbine)
    - Carboplatin-based combinations (albumin-bound [nab] paclitaxel, paclitaxel with or without bevacizumab, pemetrexed, or docetaxel)
    - Non-platinum doublets
    - Bevacizumab added to carboplatin-paclitaxel
    - Combination therapy, single-agent chemotherapy, or palliative therapy alone
    - Afatinib, erlotinib, or gefitinib as options in patients with a sensitizing epidermal growth factor receptor (*EGFR*) mutation
    - Crizotinib
    - Single-agent pembrolizumab
    - Standard chemotherapy with platinum-based two-drug combinations or non-platinum based two-

drug therapy
    - Etoposide in platinum combinations
    - Concomitant palliative care assistance
    - Maintentance treatment
2. Second-line chemotherapy
    - Single-agent nivolumab, pembrolizumab, or atezolizumab
    - Standard platinum-based chemotherapy or non–platinum-based two-drug therapy
    - Docetaxel
    - Pemetrexed
    - Osimertinib
    - Platinum doublet
    - Continued epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) with local therapy to the isolated sites
    - Single-agent crizoitnib
    - Platinum-based therapy with or without bevacizumab
    - Atezolizumab, nivolumab, or pembrolizumab in patient with *BRAF* mutations
    - Dabrafenib alone or in combination with trametinib in patients with *BRAF* mutations
3. Third-line chemotherapy: single-agent pemetrexed or docetaxel
4. Fourth-line therapy: experimental treatment, clinical trials, and continued best supportive (palliative) care

Note: The following were considered but not recommended:

- Other checkpoint inhibitors, combination checkpoint inhibitors, or immune checkpoint therapy with chemotherapy in the first-line setting
- Bevacizumab in combination with pemetrexed plus carboplatin for patients who do not have contraindications to bevacizumab
- Immunotherapy in preference to chemotherapy (pemetrexed or docetaxel) in patients with tumor EGFR-sensitizing mutation(s) who have received at least one first-line EGFR-TKI and prior platinum-based chemotherapy

## Major Outcomes Considered

- Therapeutic efficacy (overall survival [OS], progression-free survival [PFS], response rate [RR])
- Morbidity/quality of life (recurrence-free survival, event-free survival, all-cause mortality)

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review

American Society of Clinical Oncology (ASCO) guidelines are based on systematic reviews of the literature. A protocol for each systematic review defines parameters for a targeted literature search. Additional parameters include relevant study designs, literature sources, types of reports, and pre-specified inclusion and exclusion criteria for literature identified. The protocol for this guideline was reviewed and approved by the ASCO Clinical Practice Guidelines Committee's Thoracic Cancer Guideline Advisory Group (GAG).

The recommendations were developed by an Expert Panel with multidisciplinary representation using a systematic review (MEDLINE, February 2014 to December 2016) of phase II or III randomized controlled trials (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 non-small-cell lung cancer (NSCLC) (many trials also included patients with stage IIIB NSCLC)
Fully published presentations of English-language reports of phase II or III RCTs or meeting abstracts with fully available presentations
Minimal sample size of 20 patients for immune checkpoint therapy or targeted therapy studies (50 patients for chemotherapy)
Studies must have met enrollment targets
Used intent-to-treat analysis for primary and secondary outcomes
Independent determination of response
For non-RCTs used to support recommendations, results must have been consistent

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; or published in a non-English language.

Refer to the Data Supplement (see the "Availability of Companion Documents" field) for additional details on the literature search strategy, including search terms used.

## Number of Source Documents

A total of 10 randomized controlled trials (RCTs) found by the American Society of Clinical Oncology (ASCO) (in addition to five RCTs in Cancer Care Ontario's [CCO's] systematic review) met eligibility criteria and form the evidentiary basis for the guideline recommendations; the Panel also reviewed six nonrandomized studies.

Refer to the Data Supplement (see the "Availability of Companion Documents" field) for a Quality of Reporting of Meta-analyses (QUOROM) diagram detailing the literature search results.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Guide for Rating Quality of Evidence

| Rating for Strength of Evidence | Definition |
|---|---|
| High | High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect. |
| Intermediate | Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect. |
| Low | Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect. |
| Insufficient | Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic. |

Guide for Rating of Potential for Bias

| Rating of Potential for Bias | Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials |
|---|---|
| Low risk | No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts). |
| Intermediate | The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. |
| High risk | There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. |

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Data Extraction

Literature search results were reviewed and deemed appropriate for full text review by one American Society of Clinical Oncology (ASCO) staff reviewer in consultation with the Expert Panel Co-Chairs. Data were extracted by one staff reviewer and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary. Evidence tables are provided in the manuscript and/or in Data Supplements 1 and 2 (see the "Availability of Companion Documents" field).

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed (Tables 4 and 5 in the original guideline document). Study quality was formally assessed for 15 (one set combined in assessment) trials identified by American Society of Clinical Oncology (ASCO) in Table 5 in the original guideline document. Cancer Care Ontario (CCO) assessed five studies separately, with slightly different methods (Table 4 in the original guideline document). Design aspects related to the individual study quality were assessed by one ASCO reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, and funding sources, generally indicating a low to intermediate potential risk of bias for most of the identified evidence. Refer to the Methodology Supplement (see the "Availability of Companion Documents") for definitions of ratings for overall potential risk of bias.

## Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

## Description of Methods Used to Formulate the Recommendations

Guideline Update Development Process

The Expert Panel met via teleconference and webinar and corresponded through e-mail. On the basis of 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.

American Society of Clinical Oncology (ASCO) guidelines staff updated the literature search that was conducted to inform its recommendations on the systemic therapy of patients with stage IV NSCLC. MEDLINE was searched from February 2014 to December 2016. The updated search was restricted to articles published in English and to systematic reviews, meta-analyses, and randomized controlled trials. The updated search was guided by the signals approach, which is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. The ASCO Expert Panel and guidelines staff will work with the Steering Committee to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update.

The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support methodology and accompanying BRIDGE-Wiz software. Ratings 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 (see the "Rating Scheme for the Strength of the Recommendations" and "Rating Scheme for the Strength of the Evidence" fields). In some selected cases where evidence is lacking, but there was a high level of agreement among the Expert Panel, informal consensus is used (as noted with the recommendations).

Detailed information about the methods used to develop this guideline update is available in the Methodology Supplement (see the "Availability of Companion Documents" field), including an overview (e.g., panel composition, development process, and revision dates); literature search and data extraction; the recommendation development process (GLIDES and BRIDGE-Wiz); and quality assessment.

## Rating Scheme for the Strength of the Recommendations

Guide for Types of Recommendations

| Type of Recommendation | Definition |
|---|---|
| Evidence based | There was sufficient evidence from published studies to inform a recommendation to guide clinical practice. |
| Formal consensus | The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Expert Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field). |
| Informal consensus | The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Expert Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Expert Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). |
| No recommendation | There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Expert Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation. |

Guide for Strength of Recommendations

| Rating for Strength of Recommendation | Definition |
|---|---|
| Strong | There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. |
| Moderate | There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. |
| Weak | There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. |

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All American Society of Clinical Oncology (ASCO) guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication.

The CPGC approved this guideline on May 30, 2017.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate systemic treatment of patients with stage IV non–small-cell lung cancer

Refer to the "Literature review update and analysis" and "Clinical interpretation" sections of the original guideline document for a detailed discussion of the potential benefits of each recommendation.

## Potential Harms

See Table 3 in the original guideline document for information about adverse events.

Refer to the "Literature review update and analysis" and "Clinical interpretation" sections of the original guideline document for a detailed discussion of the potential harms of each recommendation.

# Contraindications

## Contraindications

The absolute contraindications to receiving immune checkpoint therapy are not well established. Likely contraindicated are patients who have received solid organ transplantations, but this is an evolving area of active investigation. The Panel concurred that patients who have received solid organ transplantations and patients with autoimmune disease that is clinically active or requires corticosteroids should not receive immune checkpoint therapy based on existing literature and the Panel's expert opinion. Reviewing literature on toxicity management for patients receiving immune checkpoint therapy outside of clinical trials was outside the scope of this guideline; however, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network are developing guidelines on the management of patients with immune-mediated adverse effects. The Panel wishes to highlight the importance of external generalizability to additional populations of patients with lung cancer not included in the clinical trials as an area of future study. Some contraindications may be relative; benefits of therapy may potentially outweigh harms; thus, clinicians will need to evaluate these patients on a case-by-case basis.

# Qualifying Statements

## Qualifying Statements

- The clinical practice guideline and other guidance published herein are provided by the American Society of Clinical Oncology (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating physician, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the

selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis, and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.
- Refer to the "Health Disparities," "Multiple Chronic Conditions" and "Limitations of the Research" sections in the original guideline document for additional qualifying information.

# Implementation of the Guideline

## Description of Implementation Strategy

Guideline Implementation

American Society of Clinical Oncology (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 *Journal of Clinical Oncology* (*JCO*) and *Journal of Oncology Practice*.

For additional information on the ASCO implementation strategy, please see the ASCO Web site .

## Implementation Tools

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

End of Life Care

Living with Illness

## IOM Domain

Effectiveness

# Identifying Information and Availability

## Bibliographic Source(s)

Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis PM, Giaccone G, Hesketh PJ, Jaiyesimi I, Leighl NB, Riely GJ, Schiller JH, Schneider BJ, Smith TJ, Tashbar J, Biermann WA, Masters G. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017 Oct 20;35(30):3484-515. [45 references] PubMed

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2017 Oct 20

## Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

## Source(s) of Funding

American Society of Clinical Oncology (ASCO)

## Guideline Committee

The American Society of Clinical Oncology Non-Small-Cell Lung Cancer Expert Panel

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# Financial Disclosures/Conflicts of Interest

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the American Society of Clinical Oncology (ASCO) Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/about-asco/legal/conflict-interest ). 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.

Authors' Disclosures of Potential Conflicts of Interest

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I=Immediate Family Member, Inst=My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to https://www.asco.org/about-asco/legal/conflict-interest or jco.ascopubs.org/site/ifc .

Nasser Hanna: Research Funding: Merck KGaA (Inst), Bristol-Myers Squibb (Inst)

David Johnson: Consulting or Advisory Role: Peloton Therapeutics, Genetech, Merck, Xcovery

Sarah Temin: No relationship to disclose

Sherman Baker Jr: Consulting or Advisory Role: Bristol-Myers Squibb

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Peter M. Ellis: Honoraria: Novartis, Pfizer; Consulting or Advisory Role: Pfizer; Other Relationship: Celgene, Mylan

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Thomas J. Smith: Employment: UpToDate; Patents, Royalties, Other Intellectual Property: UpToDate; Travel, Accommodations, Expenses: GEOMC

Joan Tashbar: No relationship to disclose

William A. Bierman: Stock or Other Ownership: Genomic Health

Gregory Masters: No relationship to disclose

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S Jr, Brahmer JR, Ellis PM, Gajra A, Rackear N, Schiller JH, Smith TJ, Strawn JR, Trent D, Johnson DH. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol. 2015 Oct 20;33(30):3488-515.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the Journal of Clinical Oncology Web site .

## Availability of Companion Documents

The following are available:

Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology; 2017. 18 p. Available from the Journal of Clinical Oncology Web site .

Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2017. 78 p. Available from the Journal of Clinical Oncology Web site .

Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2017. 30 p. Available in PDF and PowerPoint from the ASCO Web site.

Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. Summary of recommendations. Alexandria (VA): American Society of Clinical Oncology; 2017. 8 p. Available from the American Society of Clinical Oncology (ASCO) Web site .

Masters GA, Temin S, Azzoli CG, et al: Systemic therapy for stage IV non–small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015;33:3488-515. Available from the Journal of Clinical Oncology Web site .

## Patient Resources

The following is available:

Lung cancer—non–small cell. Patient information. [internet]. Alexandria (VA): American Society of Clinical Oncology; 2017. Available from the Cancer.Net Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC Status

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