Systemic Therapy for Stage IV Non-Small Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update
Introduction

• The purpose of this guideline update is to revise the 2011 American Society of Clinical Oncology (ASCO) guideline on the systemic treatment of patients with stage IV non–small-cell lung cancer (NSCLC).

• This update includes 73 phase III randomized controlled trials on systemic therapy.

• The current guideline update reviews and analyzes new and updated evidence, including data regarding afatinib, ceritinib, crizotinib, erlotinib, continuation maintenance, and switch maintenance.

• This guideline does not specifically address the histologic classification or molecular pathology of NSCLC.
The ASCO Clinical Practice Guidelines Committee (CPGC) guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an update panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology and data supplements can be found at:

www.asco.org/guidelines/nsclc
Clinical Questions

What systemic therapy treatment options should be offered to patients with stage IV NSCLC, depending on the subtype of the patient’s cancer?

Subquestions:
• What are the most effective first- and second-line therapies?
• What is the role of maintenance (both switch and continuation) therapy?
• What other clinical characteristics, besides the specified histologic/molecular subgroups, should impact drug selection?
• Is there a role for third-line therapy or beyond?
Target Population and Audience

**Target Population:** Patients with Stage IV NSCLC.

**Target Audience:** This Clinical Practice Guideline Update is targeted to health care providers (including primary care physicians, medical oncologists, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team), patients, and their caregivers in North America and beyond.
Summary of Guideline Recommendations

CLINICAL QUESTION A1
Which patients with stage IV NSCLC should be treated with chemotherapy?

Recommendation A1
(a) For patients with performance status (PS) of 0 or 1, 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 also may be used to treat selected patients with PS 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)

(b) Because there is no cure for patients with stage IV NSCLC, early concomitant assistance of palliative care 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)

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Summary of Guideline Recommendations

CLINICAL QUESTION A2
What is the most effective first-line therapy for patients with stage IV NSCLC with nonsquamous cell carcinoma, negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0-1 or possibly PS 2?

Recommendation A2
For patients who have the characteristics described in Clinical Question A2 and who have nonsquamous histology, the following options are acceptable:

- cisplatin-based combinations (type: evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - cisplatin/docetaxel cisplatin/paclitaxel*
  - cisplatin/pemetrexed*
  - cisplatin/vinorelbine*

- carboplatin-based combinations (type: evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - carboplatin/nab albumin-bound paclitaxel*
  - carboplatin/paclitaxel*
  - carboplatin/pemetrexed
  - carboplatin/docetaxel

- nonplatinum doublets (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: weak)

*US FDA–approved combinations; source: cancer.gov
Summary of Guideline Recommendations

CLINICAL QUESTION A2.a
What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown EGFR/ALK status, non-squamous cell carcinoma (NSCC), and no contraindications to bevacizumab?

Recommendation A2.a.1
For patients receiving carboplatin/paclitaxel, the Update Committee recommends the addition of bevacizumab, 15 mg/kg every 3 weeks, except for patients with SCC histologic type, clinically significant hemoptysis, inadequate organ function, Eastern Cooperative Oncology Group PS greater than 1, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Bevacizumab may be continued, as tolerated, until disease progression (no change since 2011). (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate)

Recommendation A2.a.2
There is insufficient evidence to recommend (for or against) pemetrexed in combination with bevacizumab/carboplatin for patients who do not have contraindications to bevacizumab.

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Summary of Guideline Recommendations

CLINICAL QUESTION A2.b
What is the most effective first-line therapy for patients with stage IV NSCLC with PS 2, NSCC, and negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status?

Recommendation A2.b
In the context of shared decision-making, combination therapy, single-agent chemotherapy, 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)

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CLINICAL QUESTION A3
What is the most effective first-line therapy for patients with stage IV NSCLC with squamous cell carcinoma (SCC), negative or unknown EGFR-sensitizing mutation and ALK gene rearrangement status, and PS 0-1 or possibly PS 2?

Recommendation A3
Patients with the characteristics listed in Clinical Question A3 and with SCC histology should be offered the following options:

- cisplatin-based combinations (type: evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - cisplatin/docetaxel
  - cisplatin/gemcitabine*
  - cisplatin/paclitaxel*
  - cisplatin/vinorelbine*

- carboplatin-based combinations (type: evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong)
  - carboplatin/gemcitabine
  - carboplatin/paclitaxel*
  - carboplatin/nab albumin-bound paclitaxel*

- nonplatinum doublets (type: evidence-based, benefits outweigh harms; evidence quality: low; strength of recommendation: weak)

*US FDA–approved combinations; source: cancer.gov
Summary of Guideline Recommendations

CLINICAL QUESTION A3.a
What is the most effective first 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 chemotherapy, 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)
Summary of Guideline Recommendations

CLINICAL QUESTION A4
What is the most effective first-line therapy for patients with stage IV NSCLC with an EGFR-sensitizing mutation and PS 0-1 or possibly PS 2?

Recommendation A4
If patients have stage IV NSCLC and a sensitizing EGFR mutation, one of the following is recommended, first-line

• afatinib
• erlotinib
• gefitinib

• Each are evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong
Summary of Guideline Recommendations

CLINICAL QUESTION A5
What is the most effective first-line therapy for patients with stage IV NSCLC with ALK gene rearrangement and PS 0-1 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).

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Summary of Guideline Recommendations

CLINICAL QUESTION A6
What is the most effective first-line therapy for patients with stage IV NSCLC with \( \text{ROS1} \) rearrangement, no \( \text{ALK} \) gene rearrangement, negative/unknown \( \text{EGFR} \)-sensitizing mutation status, and PS 0-1 or possibly PS 2?

**Recommendation A6**
If patients have stage IV NSCLC with \( \text{ROS1} \) 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)
Summary of Guideline Recommendations

CLINICAL QUESTION A7
What is the most effective first-line therapy for patients with stage IV NSCLC with negative or unknown \textit{EGFR/ALK} status and large cell neuroendocrine carcinoma?

\textbf{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
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)
Summary of Guideline Recommendations

CLINICAL QUESTION A9
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. (For the addition of pemetrexed (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: moderate))
Summary of Guideline Recommendations

CLINICAL QUESTION B1
What is the most effective second-line therapy for patients with stage IV NSCLC with negative or unknown EGFR/ALK status and NSCC?

Recommendation B1
For patients with advanced NSCLC, NSCC, negative or unknown EGFR/ALK status, and adequate PS when the disease has progressed during or after first-line platinum-based therapy, docetaxel, erlotinib, gefitinib, or pemetrexed are acceptable as second-line therapy (type: evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

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Summary of Guideline Recommendations

CLINICAL QUESTION B2
What is the most effective second-line therapy for patients with stage IV NSCLC with negative or unknown $EGFR/ALK$ status and SCC?

Recommendation B2
For patients with advanced NSCLC, SCC, negative or unknown $EGFR/ALK$ status, and adequate PS when the disease has progressed during or after first-line, platinum-based therapy, docetaxel, erlotinib, or gefitinib are acceptable as second-line therapy (type: evidence-based; benefits outweigh harms; evidence quality: high; strength of recommendation: strong)

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CLINICAL QUESTION B3.a

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 TKI and experienced disease progression?

Recommendation B3.a

For patients with a sensitizing EGFR mutation(s) who did not respond to a first-line EGFR TKI, combination cytotoxic chemotherapy is recommended (Recommendation A2), following the first-line recommendations for patients with NSCC. (type: informal consensus; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong)
CLINICAL QUESTION B3.b
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 TKI and experienced disease progression after an initial response?

Recommendation B3.b
Patients who received an EGFR TKI in the first-line setting, had an initial response, and subsequently experienced disease progression, may be switched to chemotherapy or another EGFR TKI as second-line therapy (type: informal consensus; balance of benefits and harms; evidence quality: low; strength of recommendation: weak)
CLINICAL QUESTION B4
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 tumor(s) have ALK rearrangements and who received crizotinib in the first-line 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
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 (no change).
This recommendation has not changed. As stated in Recommendation A8, age alone is not a contraindication to chemotherapy for NSCLC.
CLINICAL QUESTION C
Is there a role for third-line therapy or beyond in the treatment of stage IV NSCLC?

Recommendation C1
When disease progresses on or after second-line chemotherapy, treatment with erlotinib may be recommended as third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib (no change).

Recommendation C2
Data are not sufficient to make a recommendation for or against using cytotoxic drugs as third-line therapy; patients should consider experimental treatment, clinical trials, and continued best supportive (palliative) care (no change from previous recommendations).
Health Disparities

• Disparities in race, sex, socioeconomic status, level of education, residence, and insurance status, among other factors, continue to be associated with outcomes such as mortality, incidence, stage at diagnosis, and timely receipt of recommended treatment, for patients with NSCLC.

• Racial, ethnic, and socioeconomic disparities in health care contribute significantly to health disparities in the United States.

• Patients with cancer who are members of racial/ethnic minorities can suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, be more likely to be uninsured, and face a greater risk of receiving poor-quality care than other Americans.

• Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to vulnerable populations.

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Multiple Chronic Conditions

The five most commonly encountered chronic conditions in patients with lung cancer irrespective of age include:

- Hypertension
- Chronic Obstructive Pulmonary Disease (COPD)
- Hyperlipidemia
- Ischemic Heart Disease
- Anemia

- Each of those is reported with a frequency greater than 50% in patients age 65 years or older
- Patients with MCCs are a complex and heterogeneous population, which makes it difficult to account for all of the possible permutations involved in developing specific recommendations for care.
- Clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

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Discussion

The following topics are discussed at greater length within the guideline:

• Inclusion of palliative care in the treatment plan
• Patient-clinician communication
• The importance of clinical trials
• Future directions of research into systemic treatment
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/guidelines/nsclc

Patient information is available at www.cancer.net
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Abbreviation: PGIN, Practice Guidelines Implementation Network
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