### Clinical Question

Which patients with stage IV NSCLC should be treated with chemotherapy?

- **Recommendation:**
  - For patients with performance status (PS) 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 also may 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.

- **Evidence Rating:**
  - Type: Evidence-based; benefits outweigh harms
  - Evidence quality: High
  - Strength of recommendation: Strong

  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.

- **Evidence Rating:**
  - Type: Evidence-based; benefits outweigh harms
  - Evidence quality: High
  - Strength of recommendation: Strong

### First-Line Therapy

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

- **Treatment options include:**
  - For patients with high PDL-1 expression (TPS ≥ 50%), single-agent pembrolizumab should be used in the absence of contraindications to immune checkpoint therapy.

- **Evidence Rating:**
  - 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.
<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Recommendation</th>
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</table>
| For patients with low PDL-1 expression (TPS < 50%), clinicians should offer      | standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update                                                                                                                     | Type: Evidence-based, benefits outweigh harms  
  Evidence quality: High  
  Strength of recommendation: Strong                                                                 |
| or nonplatinum 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                                                                 |
| Cisplatin-based combinations                                                      | • cisplatin/docetaxel                                                                                                                                             | Type: Evidence-based; benefits outweigh harms  
  Evidence quality: High  
  Strength of recommendation: Strong                                                                 |
| • cisplatin/paclitaxel                                                           |                                                                                                                                                                    |                                                                                                          |
| • cisplatin/pemetrexed                                                          |                                                                                                                                                                    |                                                                                                          |
| • cisplatin/vinorelbine                                                         |                                                                                                                                                                    |                                                                                                          |
| Carboplatin-based combinations                                                   | • carboplatin/nab albumin-bound paclitaxel                                                                                                                         | Type: Evidence-based; benefits outweigh harms  
  Evidence quality: High  
  Strength of recommendation: Strong                                                                 |
| • carboplatin/paclitaxel                                                        |                                                                                                                                                                    |                                                                                                          |
| • carboplatin/pemetrexed                                                        |                                                                                                                                                                    |                                                                                                          |
| • carboplatin/docetaxel                                                         |                                                                                                                                                                    |                                                                                                          |
| Nonplatinum Doublets                                                            |                                                                                                                                                                    |                                                                                                          |
| What is the most effective first-line therapy for patients with stage IV NSCLC   | 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: Weak                                                                 |

**EGFR/ALK/ROS1 status, non-squamous cell carcinoma and no contraindications to bevacizumab?**
### Clinical Question

What is the most effective first-line therapy for patients with stage IV NSCLC with PS 2, non-squamous cell carcinoma, and negative or unknown tumor *EGFR*-sensitizing mutation and *ALK* or *ROS1* gene rearrangement status?

**Recommendation**

There is insufficient evidence to recommend bevacizumab in combination with pemetrexed plus carboplatin for patients who do not have contraindications to bevacizumab.

**Evidence Rating**

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

What is the most effective first-line therapy for patients with stage IV NSCLC with squamous cell carcinoma, negative or unknown tumor *EGFR*-sensitizing mutation, *ALK* or *ROS1* gene rearrangement status, and PS 0-1 (or possibly PS 2)?

**Recommendation**

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.

**Evidence Rating**

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

For patients with high PDL-1 expression (TPS ≥ 50%), single-agent pembrolizumab should be used in the absence of contraindications to immune checkpoint therapy.

**Evidence Rating**

- 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.

**Evidence Rating**

- Type: Evidence-based, benefits outweigh harms
- Evidence quality: High
- Strength of recommendation: Strong

For patients with low (TPS < 50%) or unknown PDL-1 expression, clinicians should offer standard chemotherapy with platinum-based two drug combinations as outlined in the 2015 update or nonplatinum based two drug therapy as outlined in the 2015 update for patients not deemed candidates for platinum-based therapy.

**Evidence Rating**

- Type: Evidence-based, benefits outweigh harms
- Evidence quality: Intermediate
- Strength of recommendation: Weak
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<tr>
<td><strong>SYSTEMIC THERAPY FOR STAGE IV NON-SMALL CELL LUNG CANCER:</strong>&lt;br&gt;<strong>AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE UPDATE</strong></td>
<td><strong>For patients with stage IV squamous NSCLC receiving cisplatin and gemcitabine, the panel recommends neither for nor against the addition of necitumumab to chemotherapy.</strong></td>
<td><strong>Evidence Rating</strong>&lt;br&gt;Type: Evidence-based; benefits outweigh harms&lt;br&gt;Evidence quality: Intermediate&lt;br&gt;Strength of recommendation: Weak</td>
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<tr>
<td><strong>Cisplatin-based combinations</strong>&lt;br&gt;• cisplatin/docetaxel&lt;br&gt;• cisplatin/gemcitabine&lt;br&gt;• cisplatin/paclitaxel&lt;br&gt;• cisplatin/vinorelbine</td>
<td><strong>Chemotherapy</strong>&lt;br&gt;Type: Evidence-based, benefits outweigh harms&lt;br&gt;Evidence quality: Intermediate&lt;br&gt;Strength of recommendation: Weak</td>
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<td><strong>Carboplatin-based combinations</strong>&lt;br&gt;• carboplatin/gemcitabine&lt;br&gt;• carboplatin/paclitaxel&lt;br&gt;• carboplatin/nab albumin-bound paclitaxel&lt;br&gt;• carboplatin/docetaxel</td>
<td><strong>Palliative care</strong>&lt;br&gt;Type: Evidence-based, benefits outweigh harms&lt;br&gt;Evidence quality: Intermediate&lt;br&gt;Strength of recommendation: Strong</td>
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<td><strong>Nonplatinum Doublets</strong></td>
<td><strong>In the context of shared decision making, combination chemotherapy, single-agent therapy, or palliative therapy alone may be used for patients with stage IV NSCLC with negative or unknown <em>EGFR/ALK</em> status, SCC, and PS 2.</strong></td>
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<tr>
<td>What is the most effective first therapy for patients with stage IV NSCLC with negative or unknown <em>EGFR/ALK</em> status, SCC, and PS 2?</td>
<td><strong>What is the most effective first-line therapy for patients with stage IV NSCLC and a sensitizing <em>EGFR</em> mutation, first-line options are:</strong></td>
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<td>NSCLC with a tumor <em>EGFR-</em> sensitizing mutation and PS 0-2?</td>
<td>afatinib</td>
<td>Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong</td>
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<tr>
<td></td>
<td>erlotinib</td>
<td>Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong</td>
</tr>
<tr>
<td></td>
<td>gefitinib</td>
<td>Type: Evidence-based; benefits outweigh harms Evidence quality: High Strength of recommendation: Strong</td>
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</table>

**Second-Line therapy**

What is the most effective first-line therapy for patients with stage IV NSCLC with a tumor *EGFR-* sensitizing mutation and PS 0-2?

- Squamous and non-squamous and negative/unknown *EGFR* mutation, *ALK* or *ROS1* gene rearrangement
- 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 PDL-1 expression (TPS ≥ 1%, 22C3 assay), in the absence of contraindications to immune checkpoint therapy
- For patients with negative or unknown tumor PDL-1 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
- There are insufficient data to recommend combination checkpoint inhibitors or immune checkpoint inhibitors with chemotherapy in the second-line setting
### Clinical Question

**SYSTEMIC THERAPY FOR STAGE IV NON-SMALL CELL LUNG CANCER:**

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY CLINICAL PRACTICE GUIDELINE UPDATE**

<table>
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<tr>
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<th>Evidence Quality</th>
<th>Strength of Recommendation</th>
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</table>
| 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 | Type: Evidence-based, benefits outweigh harms  
Evidence quality: High  
Strength of recommendation: Strong |  |
| or nonplatinum based two-drug therapy if platinum contraindicated as outlined in the 2015 update | Type: Informal consensus; benefits outweigh harms  
Evidence quality: Low  
Strength of recommendation: Strong | 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 | Type: Evidence-based, benefits outweigh harms  
Evidence quality: Intermediate  
Strength of recommendation: Moderate |  |
| Non-squamous only:                                                                 |                                                                                                                                                                                                 | Type: Evidence-based; benefits outweigh harms  
Evidence quality: High  
Strength of recommendation: Strong |  |
| Patients with non-squamous cell carcinoma who have not previously received pemetrexed-based first-line or maintenance therapy should be offered pemetrexed second-line | Type: Evidence-based; benefits outweigh harms  
Evidence quality: High  
Strength of recommendation: Strong | Type: Evidence-based; benefits outweigh harms  
Evidence quality: High  
Strength of recommendation: Strong |  |
| 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? | For patients with stage IV NSCLC with a sensitizing EGFR mutation and progression following first-line therapy with an EGFR tyrosine kinase inhibitor (TKI) with the presence of the T790M resistance mutation, clinicians should recommend osimertinib  
Type: Evidence-based; benefits outweigh harms  
Evidence quality: High  
Strength of Recommendation: Strong | 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 | Type: Informal consensus; benefits outweigh harms  
Evidence quality: Low  
Strength of recommendation: Strong |  |
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<tr>
<td><strong>ROS1 rearrangement – What is the most effective second-line therapy for patients with ROS1 rearrangement?</strong></td>
<td>Patients who have not received prior crizotinib. If patients have ROS1 rearrangement and have not received crizotinib in the first-line, single-agent crizotinib may be offered as second-line therapy.</td>
<td>Type: Informal consensus; benefits outweigh harms. Evidence quality: Low. Strength of recommendation: Moderate.</td>
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<td>Patients who received prior crizotinib. If patients have ROS1 rearrangement and have received crizotinib in the first-line, then they may be offered platinum-based therapy in the second-line with or without bevacizumab.</td>
<td>Type: Informal consensus; benefits outweigh harms. Evidence quality: Insufficient. Strength of recommendation: Moderate.</td>
</tr>
<tr>
<td><strong>What is the most effective therapy for patients with stage IV NSCLC and BRAF mutations who have received prior chemotherapy?</strong></td>
<td>Clinicians may offer atezolizumab, nivolumab, or pembrolizumab (if PDL-1 TPS &gt;1%) with BRAF unless the patient received immune checkpoint therapy in the first-line setting.</td>
<td>Type: Informal consensus; benefits outweigh harms. Evidence quality: Insufficient. Strength of recommendation: Weak.</td>
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<td>If patients with BRAF mutations received immunotherapy in second-line, clinicians may offer patients dabrafenib alone or in combination with trametinib in third-line</td>
<td>Type: Informal consensus; benefits outweigh harms. Evidence quality: Insufficient. Strength of recommendation: Moderate.</td>
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</table>

**Third-Line Therapy**

<table>
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<tr>
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<tr>
<td><strong>What is the most effective third-line therapy for patients with stage IV NSCLC with non-squamous cell carcinoma, negative or unknown tumor EGFR-sensitizing mutation/ALK or ROS1 gene rearrangement status and PS 0-1 or possibly PS 2?</strong></td>
<td>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.</td>
<td>Type: Informal consensus; benefits outweigh harms. Evidence quality: Low. Strength of recommendation: Strong.</td>
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<tr>
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| What is the most effective third-line therapy for patients with tumor EGFR-sensitizing mutation positive status who have had prior platinum-based chemotherapy and EGFR TKI? | 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  
Evidence quality: Insufficient  
Strength of recommendation: Weak |
| Fourth-Line Therapy                                                              |                                                                                |                                                                                 |
| Is there a role for cytotoxic therapy for patients who have received three prior regimens and good PS? | 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. |                                                                                 |