### Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy

**Note:** All recommendations are Category 2A unless otherwise indicated.

**Chemotherapy Regimens Used With Radiation Therapy (RT)**

**Concurrent Chemotherapy/RT**

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</table>
| **Paclitaxel + carboplatin**<sup>3,4</sup> | Days 1 and 8: Cisplatin 50mg/m² IV  
Days 1, 8, 15 and 22: Vinorelbine 25mg/m² IV.  
Repeat cycle every 4 weeks for 4 cycles.  
OR  
Day 1: Cisplatin 100mg/m² IV  
Days 1, 8, 15 and 22: Vinorelbine 30mg/m² IV.  
Repeat cycle every 4 weeks for 4 cycles.  
OR  
Day 1: Cisplatin 75–80mg/m²  
Days 1 and 8: Vinorelbine 25–30mg/m².  
Repeat every 3 weeks for 4 cycles. |
| **Cisplatin + etoposide**<sup>3</sup> | Day 1: Cisplatin 100mg/m² IV  
Days 1–3: Etoposide 100mg/m² IV.  
Repeat cycle every 4 weeks for 4 cycles. |
| **Cisplatin + gemcitabine**<sup>5</sup> | Day 1: Cisplatin 75mg/m² IV  
Days 1 and 8: Gemcitabine 1,250mg/m² IV.  
Repeat cycle every 3 weeks. |
| **Cisplatin + docetaxel**<sup>6</sup> | Day 1: Docetaxel 75mg/m² IV + cisplatin 75mg/m² IV.  
Repeat every 3 weeks for 4 cycles. |
| **Cisplatin + pemetrexed**<sup>7</sup> | Day 1: Cisplatin 75mg/m² IV + pemetrexed 500mg/m² IV.  
Repeat every 3 weeks for 4 cycles. |

**For patients with comorbidities or patients not able to tolerate cisplatin**

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<th>REGIMEN</th>
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</table>
| **Paclitaxel + carboplatin**<sup>9</sup> | Day 1: Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV.  
Repeat cycle every 3 weeks for 4 cycles. |

**Sequential Chemotherapy/RT (Adjuvant)**

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| **Paclitaxel + vinblastine**<sup>10</sup> | Days 1 and 29: Cisplatin 100mg/m² IV  
Days 1, 8, 15, 22 and 29: Vinblastine 5mg/m² IV with concurrent thoracic radiotherapy (total dose, 60Gy). |
| **Cisplatin + pemetrexed (nonsquamous)**<sup>11</sup> | Day 1: Cisplatin 75 mg/m² IV.  
Day 1: Pemetrexed 500 mg/m² IV with concurrent thoracic radiotherapy.  
Repeat every 3 weeks for 3 cycles. |
| **Paclitaxel + carboplatin**<sup>12</sup> | Paclitaxel 45mg/m² IV + carboplatin AUC 2mg • min/mL IV weekly with concurrent thoracic radiotherapy (total dose, 60Gy) given 5 days per week in 2Gy fractions. |
| **Paclitaxel + carboplatin**<sup>13</sup> | Day 1: Paclitaxel 200mg/m² IV over 3 hours + carboplatin AUC 6mg • min/mL IV over 1 hour.  
Repeat every 3 weeks for 2 cycles; **followed by** thoracic radiotherapy 63Gy beginning on Day 42. |
Concurrent Chemotherapy/RT Followed by Chemotherapy

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<tr>
<td>Paclitaxel + carboplatin</td>
<td>Day 1 (weekly): Paclitaxel 45–50mg/m² IV and carboplatin AUC 2mg • min/mL IV. Concurrent thoracic radiotherapy; followed by 2 additional cycles of paclitaxel 200mg/m² IV and carboplatin AUC 6mg • min/mL IV.</td>
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<tr>
<td>Cisplatin + etoposide</td>
<td>Days 1, 8, 29, and 36: Cisplatin 50mg/m² IV. Days 1–5, 29–33: Etoposide 50mg/m² IV with concurrent thoracic radiotherapy; followed by 2 additional cycles of cisplatin 50mg/m² IV and etoposide 50mg/m² IV.</td>
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Systemic Therapy for Advanced & Metastatic Disease

Principles of Therapy
- The drug regimen with the highest likelihood of benefit, with toxicity deemed acceptable to both the physician and the patient, should be given as initial therapy for advanced lung cancer.
- Stage, weight loss, performance status (PS), and gender predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.
- Histology of NSCLC is important in the selection of systemic therapy.
- New agent/platinum combinations have generated a plateau in overall response rate (25%–35%), time to progression (4–6 months), median survival (8–10 months), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients.
- unfit patients of any age (PS 3–4) do not benefit from cytotoxic treatment, except erlotinib for those who are epidermal growth factor receptor (EGFR) mutation-positive.

First-line Systemic Therapy Options

Principles of Therapy
- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology compared with cisplatin/gemcitabine.
- There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
- Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival.
- Single-agent therapy may be appropriate in select patients.
- Response assessment after 1–2 cycles, then every 2–4 cycles.

Adenocarcinoma, Large Cell, NSCLC NOS (PS 0–1)

Bevacizumab + carboplatin + paclitaxel (Category 1)
- Day 1: Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks for 6 cycles.
- Day 1: Bevacizumab 15mg/kg IV every 3 weeks until disease progression.

Bevacizumab + carboplatin + pemetrexed
- Day 1: Pemetrexed 500mg/m² IV + carboplatin AUC 6mg • min/mL IV + bevacizumab 15mg/kg IV. Repeat cycle every 3 weeks for up to 4 cycles, followed by:
  - Day 1: Pemetrexed 500mg/m² IV + bevacizumab 15mg/kg IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.

Bevacizumab + cisplatin + pemetrexed
- Day 1: Bevacizumab 7.5mg/kg IV + cisplatin 75mg/m² IV + pemetrexed 500mg/m² IV. Repeat cycle every 3 weeks for 4 cycles, followed by:
  - Day 1: Bevacizumab 7.5mg/kg IV + pemetrexed 500mg/m² IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.

Carboplatin + albumin-bound paclitaxel (Category 1)
- Day 1: Carboplatin AUC 6mg • min/mL IV
  - Days 1, 8, and 15: Nab-paclitaxel 100mg/m² IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.

Carboplatin + docetaxel (Category 1)
- Day 1: Docetaxel 75mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.

OR
First Course
- Day 1: Carboplatin AUC 4mg • min/mL IV
  - Days 1–14: Etoposide 50mg orally twice daily

Second Course
- Day 1: Carboplatin AUC 5mg • min/mL IV
  - Days 1–14: Etoposide 50mg orally twice daily

Third Course
- Day 1: Carboplatin AUC 5mg • min/mL IV
  - Days 1–21: Etoposide 50mg orally twice daily. Patients achieving a complete or partial response should receive an additional 3 courses at the same doses given in the third course.
# Non-Small Cell Lung Cancer Treatment Regimens (Part 3 of 9)

## Systemic Therapy for Advanced & Metastatic Disease

### Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1) (continued)

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| **Carboplatin + gemcitabine** *(Category 1)*[^22] | Day 1: Carboplatin AUC 5mg • min/mL IV  
Days 1, 8, and 15: Gemcitabine 1,000mg/m² IV  
Repeat cycle every 4 weeks for 4 cycles. |
| **Carboplatin + paclitaxel** *(Category 1)*[^23] | Day 1: Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV.  
Repeat every 3 weeks until disease progression or unacceptable toxicity. |
| **Carboplatin + pemetrexed** *(Category 1)*[^24] | Day 1: Pemetrexed 500mg/m² IV + carboplatin AUC 6mg • min/mL IV.  
Repeat cycle every 3 weeks for up to 6 cycles. |
| **Carboplatin + vinorelbine** *(Category 1)*[^25] | Day 1: Carboplatin AUC 6mg • min/mL IV  
Days 1 and 8: Vinorelbine 30mg/m² IV  
Day 9: Pegfilgrastim 6mg SC.  
Repeat cycle every 3 weeks for 4 cycles. |
| **Cisplatin + docetaxel** *(Category 1)*[^16] | Day 1: Cisplatin 75mg/m² IV + docetaxel 75mg/m² IV.  
Repeat cycle every 3 weeks. |
| **Cisplatin + etoposide** *(Category 1)*[^26] | Day 1: Cisplatin 100mg/m² IV  
Days 1–3: Etoposide 100mg/m² IV.  
Repeat cycle every 3 weeks for up to 6 cycles. |
| **Cisplatin + gemcitabine** *(Category 1)*[^20,27] | Day 1: Cisplatin 80mg/m² IV  
Days 1 and 8: Gemcitabine 1,000mg/m² IV.  
Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.  
OR Day 1: Cisplatin 75mg/m² IV  
Days 1 and 8: Gemcitabine 1,250mg/m² IV.  
Repeat cycle every 3 weeks for up to 6 cycles. |
| **Cisplatin + paclitaxel** *(Category 1)*[^28] | Day 1: Paclitaxel 135mg/m² IV over 24 hours  
Day 2: Cisplatin 75mg/m² IV.  
Repeat cycle every 3 weeks. |
| **Cisplatin + pemetrexed** *(Category 1)*[^27] | Day 1: Pemetrexed 500mg/m² IV + cisplatin 75mg/m² IV.  
Repeat cycle every 3 weeks. |
| **Cisplatin + vinorelbine** *(Category 1)*[^19,23,29] | Day 1: Cisplatin 100mg/m² IV  
Days 1, 8, 15 and 22: Vinorelbine 25mg/m² IV over 10 minutes.  
Repeat cycle every 4 weeks. |
| **Gemcitabine + docetaxel** *(Category 1)*[^30] | Days 1 and 8: Gemcitabine 1,000mg/m² IV  
Day 8: Docetaxel 85mg/m² IV.  
Repeat cycle every 3 weeks for 8 cycles. |
| **Gemcitabine + vinorelbine** *(Category 1)*[^31] | Days 1 and 8: Vinorelbine 25mg/m² IV + gemcitabine 1,000mg/m² IV.  
Repeat cycle every 3 weeks. |
| **Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)**[^1] | **Albumin-bound paclitaxel**[^32] | Day 1: Albumin-bound paclitaxel 260mg/m² IV.  
Repeat cycle every 3 weeks. |
| **Carboplatin + albumin-bound paclitaxel**[^33,34] | Day 1: Carboplatin AUC 6mg • min/mL IV  
Days 1, 8, and 15: Albumin-bound paclitaxel 100mg/m² IV.  
Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.  
**OR**  
**First Course**  
Day 1: Carboplatin AUC 4mg • min/mL IV  
Days 1–14: Etoposide 50mg orally twice daily  
**Second Course**  
Day 1: Carboplatin AUC 5mg • min/mL IV  
Days 1–14: Etoposide 50mg orally twice daily  
**Third Course**  
Day 1: Carboplatin AUC 5mg • min/mL IV  
Days 1–21: Etoposide 50mg orally twice daily.  
Patients achieving a complete or partial response should receive an additional 3 courses at the same doses given in the third course. |
| **Carboplatin + etoposide**[^20,21] | Day 1: Carboplatin 325mg/m² IV  
Days 1, 2, and 3: Etoposide 100mg/m² IV.  
Repeat cycle every 3 to 4 weeks until disease progression or unacceptable toxicity.  
**OR**  
**First Course**  
Day 1: Carboplatin AUC 4mg • min/mL IV  
Days 1–14: Etoposide 50mg orally twice daily  
**Second Course**  
Day 1: Carboplatin AUC 5mg • min/mL IV  
Days 1–14: Etoposide 50mg orally twice daily  
**Third Course**  
Day 1: Carboplatin AUC 5mg • min/mL IV  
Days 1–21: Etoposide 50mg orally twice daily.  
Patients achieving a complete or partial response should receive an additional 3 courses at the same doses given in the third course. |
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<tbody>
<tr>
<td><strong>Carboplatin + gemcitabine</strong>&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Day 1: Carboplatin AUC 5mg • min/mL IV Days 1, 8, and 15: Gemcitabine 1,000mg/m² IV Repeat cycle every 4 weeks for 4 cycles.</td>
</tr>
<tr>
<td><strong>Carboplatin + paclitaxel</strong>&lt;sup&gt;23c&lt;/sup&gt;</td>
<td>Day 1: Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat every 3 weeks until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Carboplatin + pemetrexed</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Day 1: Pemetrexed 500mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks for up to 6 cycles.</td>
</tr>
<tr>
<td><strong>Carboplatin + vinorelbine</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Day 1: Carboplatin AUC 6mg • min/mL IV Days 1 and 8: Vinorelbine 30mg/m² IV Day 9: Pegfilgrastim 6mg SC. Repeat cycle every 3 weeks for 4 cycles.</td>
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<tr>
<td><strong>Docetaxel</strong>&lt;sup&gt;35,36c&lt;/sup&gt;</td>
<td>Day 1: Docetaxel 75mg/m² IV over 1 hour. Repeat cycle every 3 weeks.</td>
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<tr>
<td><strong>Etoposide</strong>&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Days 1–21: Etoposide 50mg/m² orally daily. Repeat cycle every 4 to 5 weeks.</td>
</tr>
<tr>
<td><strong>Gemcitabine</strong>&lt;sup&gt;38-40&lt;/sup&gt;</td>
<td>Days 1 and 8: Gemcitabine 1,250mg/m² IV. Repeat cycle every 3 weeks.</td>
</tr>
<tr>
<td><strong>Gemcitabine + docetaxel</strong>&lt;sup&gt;30c&lt;/sup&gt;</td>
<td>Days 1 and 8: Gemcitabine 1,000mg/m² IV Day 8: Docetaxel 85mg/m² IV. Repeat cycle every 3 weeks for 8 cycles.</td>
</tr>
<tr>
<td><strong>Gemcitabine + vinorelbine</strong>&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Days 1 and 8: Vinorelbine 25mg/m² IV + gemcitabine 1,000mg/m² IV. Repeat cycle every 3 weeks.</td>
</tr>
<tr>
<td><strong>Irinotecan</strong>&lt;sup&gt;41,42&lt;/sup&gt;</td>
<td>Day 1: Irinotecan 300mg/m² IV. Repeat cycle every 3 weeks.</td>
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<tr>
<td><strong>Paclitaxel</strong>&lt;sup&gt;43-45&lt;/sup&gt;</td>
<td>Days 1, 8, and 15: Paclitaxel 80mg/m² IV. Repeat cycle every 4 weeks for up to 4 courses.</td>
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<tr>
<td><strong>Pemetrexed</strong>&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Day 1: Pemetrexed 500mg/m² IV. Repeat cycle every 3 weeks.</td>
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<tr>
<td><strong>Vinorelbine</strong>&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Days 1, 8, and 15: Vinorelbine 30mg/m² IV. Repeat cycle every 3 weeks.</td>
</tr>
<tr>
<td><strong>Squamous Cell Carcinoma (PS 0-1)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Day 1: Carboplatin AUC 6mg • min/mL IV Days 1, 8, and 15: Albumin-bound paclitaxel 100mg/m² IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Carboplatin + docetaxel (Category 1)</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Day 1: Docetaxel 75mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Carboplatin + etoposide (Category 1)</strong>&lt;sup&gt;20,21&lt;/sup&gt;</td>
<td>Day 1: Carboplatin 325mg/m² IV Days 1, 2, and 3: Etoposide 100mg/m² IV. Repeat cycle every 3 to 4 weeks until disease progression or unacceptable toxicity. <strong>OR</strong> <strong>First Course</strong> Day 1: Carboplatin AUC 4mg • min/mL IV Days 1–14: Etoposide 50mg orally twice daily <strong>Second Course</strong> Day 1: Carboplatin AUC 5mg • min/mL IV Days 1–14: Etoposide 50mg orally twice daily <strong>Third Course</strong> Day 1: Carboplatin AUC 5mg • min/mL IV Days 1–21: Etoposide 50mg orally twice daily. Patients achieving a complete or partial response should receive an additional 3 courses at the same doses given in the third course.</td>
</tr>
<tr>
<td><strong>Carboplatin + gemcitabine (Category 1)</strong>&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Day 1: Carboplatin AUC 5mg • min/mL IV Days 1, 8, and 15: Gemcitabine 1,000mg/m² IV Repeat cycle every 4 weeks for 4 cycles.</td>
</tr>
<tr>
<td><strong>Carboplatin + paclitaxel (Category 1)</strong>&lt;sup&gt;23c&lt;/sup&gt;</td>
<td>Day 1: Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat every 3 weeks until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Carboplatin + vinorelbine (Category 1)</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Day 1: Carboplatin AUC 6mg • min/mL IV Days 1 and 8: Vinorelbine 30mg/m² IV Day 9: Pegfilgrastim 6mg SC. Repeat cycle every 3 weeks for 4 cycles.</td>
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### Squamous Cell Carcinoma (PS 0-1)

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<tr>
<td><strong>Cisplatin + docetaxel (Category 1)</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Day 1: Cisplatin 75mg/m² IV + docetaxel 75mg/m² IV. Repeat cycle every 3 weeks.</td>
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<tr>
<td><strong>Cisplatin + etoposide (Category 1)</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Day 1: Cisplatin 100mg/m² IV Days 1–3: Etoposide 100mg/m² IV. Repeat cycle every 3 weeks for up to 6 cycles.</td>
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<tr>
<td><strong>Cisplatin + gemcitabine (Category 1)</strong>&lt;sup&gt;21,27&lt;/sup&gt;</td>
<td>Day 1: Cisplatin 80mg/m² IV Days 1 and 8: Gemcitabine 1,000mg/m² IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity. OR Day 1: Cisplatin 75mg/m² IV Days 1 and 8: Gemcitabine 1,250mg/m² IV. Repeat cycle every 3 weeks for up to 6 cycles.</td>
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<tr>
<td><strong>Cisplatin + paclitaxel (Category 1)</strong>&lt;sup&gt;28c&lt;/sup&gt;</td>
<td>Day 1: Paclitaxel 135mg/m² IV over 24 hours Day 2: Cisplatin 75mg/m² IV. Repeat cycle every 3 weeks.</td>
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<tr>
<td><strong>Cisplatin + gemcitabine + necitumumab (Category 3)</strong>&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Day 1: Cisplatin 75mg/m² IV over 120 minutes Days 1 and 8: Gemcitabine 1,250mg/m² IV over 30 minutes + necitumumab 800mg IV over a minimum of 50 minutes. Repeat cycle every 3 weeks for up to 6 cycles. Patients free of disease progression should continue single-agent necitumumab on the same treatment schedule until disease progression or unacceptable toxicity.</td>
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<tr>
<td><strong>Gemcitabine + docetaxel (Category 1)</strong>&lt;sup&gt;30c&lt;/sup&gt;</td>
<td>Days 1 and 8: Gemcitabine 1,000mg/m² IV Day 8: Docetaxel 85mg/m² IV. Repeat cycle every 3 weeks for 8 cycles.</td>
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<tr>
<td><strong>Gemcitabine + vinorelbine (Category 1)</strong>&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Days 1 and 8: Vinorelbine 25mg/m² IV + gemcitabine 1,000mg/m² IV. Repeat cycle every 3 weeks.</td>
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<tr>
<td><strong>Cisplatin + etoposide</strong>&lt;sup&gt;20,21&lt;/sup&gt;</td>
<td>Day 1: Carboplatin AUC 6mg • min/mL IV Days 1, 2, and 3: Etoposide 100mg/m² IV. Repeat cycle every 3 to 4 weeks until disease progression or unacceptable toxicity. OR First Course Day 1: Carboplatin AUC 4mg • min/mL IV Days 1–14: Etoposide 50mg orally twice daily Second Course Day 1: Carboplatin AUC 5mg • min/mL IV Days 1–14: Etoposide 50mg orally twice daily Third Course Day 1: Carboplatin AUC 5mg • min/mL IV Days 1–21: Etoposide 50mg orally twice daily. Patients achieving a complete or partial response should receive an additional 3 courses at the same doses given in the third course.</td>
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<tr>
<td><strong>Carboplatin + paclitaxel</strong>&lt;sup&gt;23c&lt;/sup&gt;</td>
<td>Day 1: Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat every 3 weeks until disease progression or unacceptable toxicity.</td>
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<tr>
<td><strong>Carboplatin + vinorelbine</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Day 1: Carboplatin AUC 5mg • min/mL IV Days 1 and 8: Vinorelbine 30mg/m² IV Day 9: Pegfilgrastim 6mg SC. Repeat cycle every 3 weeks for 4 cycles.</td>
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**First-line Systemic Therapy Options**

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| **Cisplatin + gemcitabine + necitumumab (Category 3)**<sup>47</sup> | Day 1: Cisplatin 75mg/m<sup>2</sup> IV over 120 minutes  
Days 1 and 8: Gemcitabine 1,250mg/m<sup>2</sup> IV over 30 minutes + necitumumab 800mg IV over a minimum of 50 minutes.  
Repeat cycle every 3 weeks for up to 6 cycles. Patients free of disease progression should continue single-agent necitumumab on the same treatment schedule until disease progression or unacceptable toxicity. |
| **Docetaxel**<sup>35,36</sup> | Day 1: Docetaxel 75mg/m<sup>2</sup> IV over 1 hour.  
Repeat cycle every 3 weeks. |
| **Etoposide**<sup>37</sup> | Days 1–21: Etoposide 50mg/m<sup>2</sup> orally daily.  
Repeat cycle every 4 to 5 weeks. |
| **Gemcitabine**<sup>38-40</sup> | Days 1 and 8: Gemcitabine 1,250mg/m<sup>2</sup> IV.  
Repeat cycle every 3 weeks. |
| **Gemcitabine + docetaxel**<sup>30</sup> | Days 1 and 8: Gemcitabine 1,000mg/m<sup>2</sup> IV  
Day 8: Docetaxel 85mg/m<sup>2</sup> IV.  
Repeat cycle every 3 weeks for 8 cycles. |
| **Gemcitabine + vinorelbine**<sup>31</sup> | Days 1 and 8: Vinorelbine 25mg/m<sup>2</sup> IV + gemcitabine 1,000mg/m<sup>2</sup> IV.  
Repeat cycle every 3 weeks. |
| **Irinotecan**<sup>41,42</sup> | Day 1: Irinotecan 300mg/m<sup>2</sup> IV.  
Repeat cycle every 3 weeks. |
| **Paclitaxel**<sup>43-45</sup> | Days 1, 8, and 15: Paclitaxel 80mg/m<sup>2</sup> IV.  
Repeat cycle every 4 weeks for up to 4 cycles. |
| **Vinorelbine**<sup>35</sup> | Days 1, 8, and 15: Vinorelbine 30mg/m<sup>2</sup> IV.  
Repeat cycle every 3 weeks. |

**Principles of Maintenance Therapy**

Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4 to 6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4 to 6 cycles of initial therapy.

- **Continuation Maintenance:** Bevacizumab and cetuximab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
  - Continuation of bevacizumab after 4–6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).
  - Continuation of cetuximab after 4–6 cycles of cisplatin, vinorelbine, and cetuximab (category 1).
  - Continuation of pemetrexed after 4–6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (category 1).
  - Continuation of bevacizumab + pemetrexed after 4–6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma.
  - Continuation of gemcitabine after 4–6 cycles of platinum-doublet chemotherapy (category 2B).

- **Switch Maintenance:** Two studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4–6 cycles of therapy.
  - Initiation of pemetrexed after 4–6 cycles of first-line platinum-doublet chemotherapy for patients with histologies other than squamous cell carcinoma (category 2B).
  - Initiation of erlotinib after 4–6 cycles of first-line platinum-doublet chemotherapy (category 2B).
  - Initiation of docetaxel after 4–6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).

- Close surveillance of patients without therapy is a reasonable alternative to maintenance.

**Subsequent Therapy for Advanced & Metastatic Disease**

**Principles of Subsequent Therapy**

- In patients who have experienced disease progression either during or after first-line therapy, single-agent docetaxel, pemetrexed, or erlotinib are established second-line agents.
  - Nivolumab improves survival when compared with docetaxel.
  - Pembrolizumab improves overall survival in PD-L1 positive tumors when compared with docetaxel.
  - Docetaxel is superior to vinorelbine or ifosfamide.
  - Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
  - Ramucirumab + docetaxel improves survival when compared to docetaxel alone.
  - Erlotinib is superior to best supportive care.

- If not already given, options for patients with PS 0–2 include docetaxel, pemetrexed (nonsquamous), erlotinib, or gemcitabine (category 2B for all options).
Subsequent Therapy for Advanced & Metastatic Disease

**REGIMEN**

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<th>DOISING</th>
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</thead>
<tbody>
<tr>
<td><strong>Nivolumab (Category 1)</strong>&lt;sup&gt;48,49&lt;/sup&gt;</td>
<td>Day 1: Nivolumab 240mg IV over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Pembrolizumab (Category 1)</strong>&lt;sup&gt;38,40&lt;/sup&gt;</td>
<td>Day 1: Pembrolizumab 2mg/kg IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.</td>
</tr>
<tr>
<td><strong>Docetaxel</strong>&lt;sup&gt;35,36&lt;/sup&gt;</td>
<td>Day 1: Docetaxel 75mg/m² IV over 1 hour. Repeat cycle every 3 weeks.</td>
</tr>
<tr>
<td><strong>Pemetrexed</strong>&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Day 1: Pemetrexed 500mg/m² IV. Repeat cycle every 3 weeks.</td>
</tr>
<tr>
<td><strong>Gemcitabine</strong>&lt;sup&gt;38-40&lt;/sup&gt;</td>
<td>Days 1 and 8: Gemcitabine 1,250mg/m² IV. Repeat cycle every 3 weeks.</td>
</tr>
<tr>
<td><strong>Ramucirumab + docetaxel</strong>&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Day 1: Ramucirumab 10mg/kg IV + docetaxel 75mg/m² IV. Repeat cycle every 3 weeks.</td>
</tr>
</tbody>
</table>

First-line Targeted Therapy for Advanced & Metastatic Disease

**Sensitizing EGFR Mutation Positive**

- **Erlotinib (Category 1)**<sup>52</sup> | Erlotinib 150mg orally once daily until disease progression or unacceptable toxicity. |
- **Afatinib (Category 1)**<sup>53</sup> | Afatinib 40mg orally once daily until disease progression or unacceptable toxicity. |
- **Gefitinib (Category 1)**<sup>54</sup> | Gefitinib 250mg orally once daily until disease progression or unacceptable toxicity. |

**ALK Positive**

- **Crizotinib (Category 1)**<sup>55</sup> | Crizotinib 250mg orally twice daily until disease progression or unacceptable toxicity. |
- **Osimertinib**<sup>56</sup> | Osimertinib 80mg orally once daily until disease progression or unacceptable toxicity. |
- **Erlotinib**<sup>52</sup> | Erlotinib 150mg orally once daily until disease progression or unacceptable toxicity. |
- **Afatinib**<sup>53</sup> | Afatinib 40mg orally once daily until disease progression or unacceptable toxicity. |
- **Gefitinib**<sup>54</sup> | Gefitinib 250mg orally once daily until disease progression or unacceptable toxicity. |

**Subsequent Targeted Therapy for Advanced & Metastatic Disease**

**Sensitizing EGFR Mutation Positive**

- **Osimertinib**<sup>56</sup> | Osimertinib 80mg orally once daily until disease progression or unacceptable toxicity. |
- **Erlotinib**<sup>52</sup> | Erlotinib 150mg orally once daily until disease progression or unacceptable toxicity. |
- **Afatinib**<sup>53</sup> | Afatinib 40mg orally once daily until disease progression or unacceptable toxicity. |
- **Gefitinib**<sup>54</sup> | Gefitinib 250mg orally once daily until disease progression or unacceptable toxicity. |

**ALK Positive**

- **Crizotinib**<sup>55</sup> | Crizotinib 250mg orally twice daily until disease progression or unacceptable toxicity. |
- **Ceritinib**<sup>57</sup> | Ceritinib 750mg orally once daily until disease progression or unacceptable toxicity. |
- **Alectinib**<sup>58</sup> | Alectinib 600mg orally twice daily until disease progression or unacceptable toxicity. |

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**References**

References


References (continued)


