NON-SMALL CELL LUNG CANCER TREATMENT REGIMENS (Part 1 of 9)

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced health care team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data become available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy[1]

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

REGIMEN	DOSING
Cisplatin + vinorelbine[2-4]	**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[3]	**Day 1:** Cisplatin 100mg/m² IV **Days 1–3:** Etoposide 100mg/m² IV. Repeat cycle every 4 weeks for 4 cycles.
Cisplatin + gemcitabine[5]	**Day 1:** Cisplatin 75mg/m² IV **Days 1 and 8:** Gemcitabine 1,250mg/m² IV. Repeat cycle every 3 weeks.
Cisplatin + docetaxel[6]	**Day 1:** Docetaxel 75mg/m² IV + cisplatin 75mg/m² IV. Repeat every 3 weeks for 4 cycles.
Cisplatin + pemetrexed[7]	**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[1]	
Paclitaxel + carboplatin[9]	**Day 1:** Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks for 4 cycles.

Chemotherapy Regimens Used With Radiation Therapy (RT)[1]

Concurrent Chemotherapy/RT[1ab]	
Cisplatin + etoposide[9,10]	**Days 1, 8, 29 and 36:** Cisplatin 50mg/m² IV **Days 1–5 and 29–33:** Etoposide 50mg/m² IV Concurrent thoracic radiotherapy 1.8Gy/day for 5 days/week (total dose, 61Gy).
Cisplatin + vinblastine[10]	**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).
Carboplatin + pemetrexed (nonsquamous)[11]	**Day 1:** Carboplatin AUC 5mg • min/mL IV **Day 1:** Pemetrexed 500 mg/m² IV with concurrent thoracic radiotherapy. Repeat every 3 weeks for 4 cycles.
Cisplatin + pemetrexed (nonsquamous)[12]	**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[13]	Paclitaxel 45mg/m² IV + carboplatin AUC 2mg • min/mL IV weekly with concurrent thoracic radiotherapy (total dose, 60Gy) given 5 days per weeks in 2Gy fractions.
Sequential Chemotherapy/RT (Adjuvant)[1]	
Cisplatin + vinblastine[10]	**Days 1 and 29:** Cisplatin 100mg/m² IV. **Days 1, 8, 15, 22 and 29:** Vinblastine 5mg/m² IV; followed by thoracic radiotherapy with 60Gy in 30 fractions beginning on Day 50.
Paclitaxel + carboplatin[14]	**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.

continued

NON-SMALL CELL LUNG CANCER TREATMENT REGIMENS (Part 2 of 9)

Chemotherapy Regimens Used With Radiation Therapy (RT)[1] (continued)

Concurrent Chemotherapy/RT Followed by Chemotherapy[1]

REGIMEN	DOSING
Paclitaxel + carboplatin[14]	**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.
Cisplatin + etoposide[10]	**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.

Systemic Therapy for Advanced & Metastatic Disease[1]

Principles of Therapy[1]

- 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[1]

Principles of Therapy[1]

- 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)[1]

Bevacizumab + carboplatin + paclitaxel (Category 1)[15]	**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[16]	**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[17]	**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)[18]	**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)[19c]	**Day 1:** Docetaxel 75mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
Carboplatin + etoposide (Category 1)[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/mLIV Days 1–14: Etoposide 50mg orally twice daily **Third Course** Day 1: Carboplatin AUC 5mg • min/mLIV 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.

continued

Systemic Therapy for Advanced & Metastatic Disease[1] (continued)

First-line Systemic Therapy Options[1] (continued)

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

REGIMEN	DOSING
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)[23c]	**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)[19c]	**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)[23,27]	**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)[28c]	**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)[30c]	**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.
Carboplatin + docetaxel[19c]	**Day 1:** Docetaxel 75mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
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.

continued

Systemic Therapy for Advanced & Metastatic Disease[1] (continued)

First-line Systemic Therapy Options[1] (continued)

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)[1] (continued)

REGIMEN	DOSING
Carboplatin + gemcitabine[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[23c]	**Day 1:** Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat every 3 weeks until disease progression or unacceptable toxicity.
Carboplatin + pemetrexed[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[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.
Docetaxel[35,36c]	**Day 1:** Docetaxel 75mg/m² IV over 1 hour. Repeat cycle every 3 weeks.
Etoposide[37]	**Days 1–21:** Etoposide 50mg/m² orally daily. Repeat cycle every 4 to 5 weeks.
Gemcitabine[38-40]	**Days 1 and 8:** Gemcitabine 1,250mg/m² IV. Repeat cycle every 3 weeks.
Gemcitabine + docetaxel[30c]	**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[31]	**Days 1 and 8:** Vinorelbine 25mg/m² IV + gemcitabine 1,000mg/m² IV. Repeat cycle every 3 weeks.
Irinotecan[41,42]	**Day 1:** Irinotecan 300mg/m² IV. Repeat cycle every 3 weeks.
Paclitaxel[43-45]	**Days 1, 8, and 15:** Paclitaxel 80mg/m² IV. Repeat cycle every 4 weeks for up to 4 cycles.
Pemetrexed[46]	**Day 1:** Pemetrexed 500mg/m² IV. Repeat cycle every 3 weeks.
Vinorelbine[35]	**Days 1, 8, and 15:** Vinorelbine 30mg/m² IV. Repeat cycle every 3 weeks.
Squamous Cell Carcinoma (PS 0-1)[1]	
Carboplatin + albumin-bound paclitaxel (Category 1)[18]	**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.
Carboplatin + docetaxel (Category 1)[19]	**Day 1:** Docetaxel 75mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
Carboplatin + etoposide (Category 1)[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.
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)[23c]	**Day 1:** Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat every 3 weeks until disease progression or unacceptable toxicity.
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.

continued

Systemic Therapy for Advanced & Metastatic Disease[1] (continued)

First-line Systemic Therapy Options[1] (continued)

Squamous Cell Carcinoma (PS 0-1)[1] (continued)

REGIMEN	DOSING
Cisplatin + docetaxel (Category 1)[19]	**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)[23,27]	**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)[28c]	**Day 1:** Paclitaxel 135mg/m² IV over 24 hours **Day 2:** 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.
Cisplatin + gemcitabine + necitumumab (Category 3)[47]	**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.
Gemcitabine + docetaxel (Category 1)[30c]	**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.
Squamous Cell Carcinoma (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.
Carboplatin + docetaxel[19c]	**Day 1:** Docetaxel 75mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
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.
Carboplatin + gemcitabine[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[23c]	**Day 1:** Paclitaxel 200mg/m² IV + carboplatin AUC 6mg • min/mL IV. Repeat every 3 weeks until disease progression or unacceptable toxicity.
Carboplatin + vinorelbine[24]	**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.

continued

Systemic Therapy for Advanced & Metastatic Disease[1] (continued)

First-line Systemic Therapy Options[1] (continued)

Squamous Cell Carcinoma (PS 2)[1] (continued)

REGIMEN	DOSING
Cisplatin + gemcitabine + necitumumab (Category 3)[47]	**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.
Docetaxel[35,36c]	**Day 1:** Docetaxel 75mg/m² IV over 1 hour. Repeat cycle every 3 weeks.
Etoposide[37]	**Days 1–21:** Etoposide 50mg/m² orally daily. Repeat cycle every 4 to 5 weeks.
Gemcitabine[38-40]	**Days 1 and 8:** Gemcitabine 1,250mg/m² IV. Repeat cycle every 3 weeks.
Gemcitabine + docetaxel[30c]	**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[31]	**Days 1 and 8:** Vinorelbine 25mg/m² IV + gemcitabine 1,000mg/m² IV. Repeat cycle every 3 weeks.
Irinotecan[41,42]	**Day 1:** Irinotecan 300mg/m² IV. Repeat cycle every 3 weeks.
Paclitaxel[43-45]	**Days 1, 8, and 15:** Paclitaxel 80mg/m² IV. Repeat cycle every 4 weeks for up to 4 cycles.
Vinorelbine[35]	**Days 1, 8, and 15:** Vinorelbine 30mg/m² IV. Repeat cycle every 3 weeks.

Principles of Maintenance Therapy[1]

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[1]

Principles of Subsequent Therapy[1]

- 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).

continued

NON-SMALL CELL LUNG CANCER TREATMENT REGIMENS (Part 7 of 9)

Systemic Therapy for Advanced & Metastatic Disease[1] (continued)

Subsequent Therapy for Advanced & Metastatic Disease[1] (continued)

REGIMEN	DOSING
Nivolumab (Category 1)[48,49]	**Day 1:** Nivolumab 240mg IV over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
Pembrolizumab (Category 1)[50d]	**Day 1:** Pembrolizumab 2mg/kg IV. Repeat cycle every 3 weeks until disease progression or unacceptable toxicity.
Docetaxel[35,36]	**Day 1:** Docetaxel 75mg/m^2 IV over 1 hour. Repeat cycle every 3 weeks.
Pemetrexed[46]	**Day 1:** Pemetrexed 500mg/m^2 IV. Repeat cycle every 3 weeks.
Gemcitabine[38-40]	**Days 1 and 8:** Gemcitabine 1,250mg/m^2 IV. Repeat cycle every 3 weeks.
Ramucirumab + docetaxel[51]	**Day 1:** Ramucirumab 10mg/kg IV + docetaxel 75mg/m^2 IV. Repeat cycle every 3 weeks.

First-line Targeted Therapy for Advanced & Metastatic Disease[1]

Sensitizing *EGFR* Mutation Positive[1]

Erlotinib (Category 1)[52]	Erlotinib 150mg orally once daily until disease progression or unacceptable toxicity.
Afatinib (Category 1)[53]	Afatinib 40mg orally once daily until disease progression or unacceptable toxicity.
Gefitinib (Category 1)[54]	Gefitinib 250mg orally once daily until disease progression or unacceptable toxicity.

ALK Positive[1]

Crizotinib (Category 1)[55]	Crizotinib 250mg orally twice daily until disease progression or unacceptable toxicity.

Subsequent Targeted Therapy for Advanced & Metastatic Disease[1]

Sensitizing *EGFR* Mutation Positive[1]

Osimertinib[56]	Osimertinib 80mg orally once daily until disease progression or unacceptable toxicity.
Erlotinib[52]	Erlotinib 150mg orally once daily until disease progression or unacceptable toxicity.
Afatinib[53]	Afatinib 40mg orally once daily until disease progression or unacceptable toxicity.
Gefitinib[54]	Gefitinib 250mg orally once daily until disease progression or unacceptable toxicity.

ALK Positive[1]

Crizotinib[55]	Crizotinib 250mg orally twice daily until disease progression or unacceptable toxicity.
Ceritinib[57]	Ceritinib 750mg orally once daily until disease progression or unacceptable toxicity.
Alectinib[58]	Alectinib 600mg orally twice daily until disease progression or unacceptable toxicity.

[a] Regimens can be used as neoadjuvant/preoperative/induction chemradiotherapy.

[b] Regimens can be used as adjuvant or definitive concurrent chemotherapy/RT.

[c] Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) are contraindicated.

[d] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.

References

1. Referenced with permission from NCCN Clinical Practice Guidelines in Oncology™ Non-Small Cell Lung Cancer. v 4.2016. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 15, 2016.
2. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. *N Engl J Med.* 2005;352:2589–2597.
3. Arriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *N Engl J Med.* 2004;350:351–360.
4. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol.* 2006;7:719–727.
5. Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol.* 2012;30:3516–3524.
6. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol.* 2003;21:3016–3024.
7. Kreuter M, Vansteenkiste J, Fishcer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. *Ann Oncol.* 2013;24:986–992.
8. Strauss GM, Herndon III JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol.* 2008;26:5043–5051.
9. Albain KS, Crowley JJ, Turrisi AT III, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group Phase II Study, SWOG 9019. *J Clin Oncol.* 2002;20:3454–3460.

continued

References

10. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst.* 2011;103:1452–1460.
11. Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol.* 2011;29: 3120–3125.
12. Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a e systematic review of completed and ongoing studies. *Lung Cancer.* 2015;87:232–240.
13. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol.* 2015;16:187–199.
14. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol.* 2005;23:5883–5891.
15. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med.* 2006;355:2542–2550.
16. Patel JD, Socinski MA, Garon EB, et al. Pointbreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small cell lung cancer. *J Clin Oncol.* 2013;31:4349–4357.
17. Barlesi F, Scherpereel A, Rittmeywr A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small cell lung cancer: AVAPERL. *J Clin Oncol.* 2013;31: 3004–3011.
18. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol*. 2012:30:2055–2062.
19. Fossella F, Periera JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol.* 2003; 21(16):3016–3024.
20. Klastersky J, Sculier JP, Lacroix H, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. *J Clin Oncol.* 1990;8:1556–1562.
21. Frasci G, Comella P, Panza N, eta l. Carboplatin-oral etoposide personalized dosing in elderly non-small cell lung cancer patients. Gruppo Oncologico Cooperativo Sud-Italia. *Eur J Cancer.* 1998;34:1710–1714.
22. Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and ciplatin in patients with advanced non-small cell lung carcinoma. *Cancer*. 2003;98:542–553.
23. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non- small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol*. 2007;18:317–323.
24. Scagliotti GV, Kortsik C, Dark GG, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. *Clin Cancer Res*. 2005;11:690–696.
25. Riedel RF, Andrews C, Garst J, et al. A phase II trial of carboplatin/vinorelbine with pegfilgrastim support for the treatment of patients with advanced non-small cell lung cancer. *J Thorac Oncol.* 2007;2:520–526.
26. Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol.* 1999;17:12–18.
27. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage NSCLC. *J Clin Oncol.* 2008;26:3543–3551.
28. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med.* 2002;346:92–98.
29. Kelly K, Crowley J, Bunn PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small cell lung cancer: A Southwest Oncology Group trial. *J Clin Oncol.* 2001;19:3210–3218.
30. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. *Ann Oncol.* 2005;16:602–610.
31. Tan EH, Szczesna A, Krzakowski M, et al. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer.* 2005;49:233–240.
32. Green M, Manikhas G, Orlov S, et al. Abraxane®, a novel Cremophor® -free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol*. 2006;17:1263–1268.
33. Rizvi N, Riely G, Azzoli, C, et al. Phase I/II Trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non–small-cell lung cancer. *J Clin Oncol.* 2008;26:639–643.
34. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol*. 2012:30:2055–2062.
35. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum- containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*. 2000;18:2354–2362.
36. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small cell lung cancer. *J Clin Oncol.* 2009;27:591–598.
37. Waits TM, Johnson DH, Hainsworth JD, et al. Prolonged administration of oral etoposide in non-small cell lung cancer: a phase II trial. *J Clin Oncol.* 1992;292–296.
38. Zatloukal P, Kanitz E, Magyar P, et al Gemcitabine in locally advanced and metastatic non-small cell lung cancer: the Central European phase II study. *Lung Cancer.* 1998;22: 243–250.
39. Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single agent gemcitabine in the treatment of locally advanced or metastatic non-small cell lung cancer: the Swedish Lung Cancer Study group. *J Clin Oncol.* 2005;23:8380–8288.
40. Perol M, Chouaid C, Perol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin- gemcitabine induction chemotherapy in advanced non-small cell lung cancer. *J Clin Oncol.* 2012;30:3516–3524.
41. Georgoulias V, Kouroussis C, Agelidou A, et al. Irinotecan plus gemcitabine vs irinotecan for the second-line treatment of patients with advanced non-small cell lung cancer pretreated with docetaxel and cisplatin: a multicentre, randomised, phase II study. *Br J Cancer.* 2004;91:482–488.

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References (continued)

42. Fukuoka M, Niitani H, Suzuki A, et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small cell lung cancer. *J Clin Oncol.* 1992;10: 16–20.
43. Lilenbaum RC, Herndon JE, List MA, et al. Single-agent versus combination chemotherapy in advanced non-small cell lung cancer: the cancer and leukemia group B (study 9730). *J Clin Oncol.* 2005;23:190–196.
44. Ceresoli GL, Gregorc V, Cordio S, et al. Phase II study of weekly paclitaxel as second-line therapy in patients with advanced non-small cell lung cancer. *Lung Cancer.* 2004;44:231–239.
45. Yasuda K, Igishi T, Kawasaki Y, et al. Phase II study of weekly paclitaxel in patients with non-small cell lung cancer who have failed previous treatments. *Oncology*. 2004;66:347–352.
46. Hanna NH, Sheperd FA, Fossella FV, et al. Randomized phase III study of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. *J Clin Oncol.* 2004;22:1589–1597.
47. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. *Lancet Oncol.* 2015;16:763–774.
48. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med.* 2015;373:1627–1639.
49. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
50. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small- cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2015.
51. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665–673.
52. Tarceva [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2016.
53. Gilotrif [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2016.
54. Iressa [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2015.
55. Xalkori [prescribing information]. New York, NY: Pfizer Inc.; 2016.
56. Tagrisso [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2016.
57. Zykadia [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; 2016.
58. Alecensa [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2016.

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