LUNG CANCER TREATMENT REGIMENS (Part 1 of 7)

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 healthcare 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 only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes 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.

Non-Small Cell Lung Cancer (NSCLC)

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

Chemotherapy Regimens For Neoadjuvant and Adjuvant Therapy[1]

REGIMEN	DOSING
Cisplatin + vinorelbine[2-4]	**Days 1 and 8:** Cisplatin 50mg/m² IV **plus** **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 **plus** **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 **plus** **Days 1 + 8:** Vinorelbine 25–30mg/m². Repeat every 3 weeks for 4 cycles.
Cisplatin + etoposide[3]	**Day 1:** Cisplatin 100mg/m² IV **plus** **Days 1–3:** Etoposide 100mg/m² IV. Repeat cycle every 4 weeks for 4 cycles.
Cisplatin + vinblastine[3]	**Days 1, 22, 43, 64:** Cisplatin 80mg/m² IV. **Days 1, 8, 15, 22, 29, and then every 2 weeks after day 43:** Vinblastine 4 mg/m². Repeat every 3 weeks for 4 cycles.
Cisplatin + gemcitabine[5]	**Day 1:** Cisplatin 75mg/m² IV **plus** **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[7,8]	**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=6 IV. Repeat cycle every 3 weeks for 4 cycles.
Concurrent Chemotherapy/Radiotherapy (RT)[1]	
Cisplatin + etoposide[10,†] **(preferred regimen)**	**Days 1, 8, 29 and 36:** Cisplatin 50mg/m² IV **plus** **Days 1–5 and 29–33:** Etoposide 50mg/m² IV **plus** Concurrent thoracic radiotherapy 1.8Gy/day for 5 days/week (total dose, 61Gy).
Cisplatin + vinblastine (preferred regimen)[11]	**Days 1 and 29:** Cisplatin 100mg/m² IV **plus** **Days 1, 8, 15, 22 and 29:** Vinblastine 5mg/m² IV with concurrent thoracic radiotherapy (total dose, 60Gy).
Carboplatin + pemetrexed (nonsquamous)[12]	**Day 1:** Carboplatin AUC 5 IV **plus** **Day 1:** Pemetrexed 500 mg/m² IV with concurrent thoracic radiotherapy. Repeat every 3 weeks for 4 cycles.
Cisplatin + pemetrexed (nonsquamous)[7,8]	**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.
Sequential Chemotherapy/ Radiotherapy (RT)[1]	
Cisplatin + vinblastine[11]	**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[13]	**Day 1:** Paclitaxel 200mg/m² IV over 3 hours + carboplatin AUC=6 IV over 1 hour. Repeat every 3 weeks for 2 cycles; **followed by** thoracic radiotherapy 63Gy beginning on Day 42.

continued

LUNG CANCER TREATMENT REGIMENS (Part 2 of 7)

Non-Small Cell Lung Cancer (NSCLC) (continued)

Concurrent Chemotherapy/ Radiotherapy (RT) Followed by Chemotherapy[1]

REGIMEN	DOSING
Paclitaxel + carboplatin[13]	**Day 1 (weekly):** Paclitaxel 45–50mg/m² IV and carboplatin AUC=2 IV. Concurrent thoracic radiotherapy; **followed by** two additional cycles of paclitaxel 200mg/m² IV and carboplatin AUC=6 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** two additional cycles of cisplatin 50mg/m² IV and etoposide 50mg/m² IV.

Systemic Therapy for Advanced Disease[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.

Principals 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.

Principles of Third-Line Therapy[1]

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

Continuation After Disease Progression[1]

- With the exception of targeted agents (erlotinib, gefitinib, afatinib, crizotinib, ceritinib) in patients with EGFR-sensitizing mutations or ALK rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations. (refer to discussion section of NCCN Guidelines for Non-Small Cell Lung Cancer v.5.2015)

Systemic Treatment Options for Patients with NSCLC[1,‡]

- **Cisplatin**[14–21]
- **Carboplatin**[17,18–23]
- **Paclitaxel**[14,17,18,20–23]
- **Docetaxel**[5,6,19,23,24]
- **Vinorelbine**[6,20,21]
- **Gemcitabine**[5,16,18–20,24]
- **Etoposide**[17]
- **Irinotecan**[20]
- **Vinblastine**
- **Mitomycin**
- **Ifosfamide**[23]
- **Pemetrexed**[7,8]
- **Erlotinib**[25]
- **Bevacizumab**[26]
- **Cetuximab**[27]
- **Albumin-bound paclitaxel**[28–30§]
- **Crizotinib**[31]
- **Afatinib**[32]
- **Ceritinib**[33]
- **Ramucirumab**[34]
- **Nivolumab**[35]

continued

LUNG CANCER TREATMENT REGIMENS (Part 3 of 7)

Non-Small Cell Lung Cancer (NSCLC) (continued)

First-Line Systemic Therapy for Advanced Disease[1]

REGIMEN	DOSING
Bevacizumab carboplatin + paclitaxel[26,36]	**Day 1:** Paclitaxel 200mg/m² IV **Day 1:** Carboplatin AUC=6 IV. Repeat every 3 weeks for 6 cycles. **Day 1:** Bevacizumab 15mg/kg IV every 3 weeks until disease progression.
Cetuximab + cisplatin + vinorelbine[27]‖	**Day 1:** Cetuximab 400mg/m² IV + cisplatin 80mg/m² IV, **plus** **Days 1 and 8:** Vinorelbine 25mg/m² IV, **plus** **Day 8:** Cetuximab 250mg/m² IV once weekly. Repeat every 3 weeks for 6 cycles.
Erlotinib[37,38]¶	**Day 1:** Erlotinib 150mg PO once daily; following 4 cycles of platinum-based chemotherapy.
Cisplatin + paclitaxel‖[19]	**Day 1:** Paclitaxel 135mg/m² IV over 24 hours **Day 2:** Cisplatin 75mg/m² IV. Repeat cycle every 3 weeks.
Cisplatin + gemcitabine[19]	**Day 1:** Cisplatin 100mg/m² IV **Days 1, 8 and 15:** Gemcitabine 1,000mg/m² IV. Repeat cycle every 4 weeks.
Cisplatin + docetaxel[6]	**Day 1:** Cisplatin 75mg/m² IV + docetaxel 75mg/m² IV. Repeat cycle every 3 weeks.
Cisplatin + vinorelbine[6]	**Day 1:** Cisplatin 100mg/m² IV **Days 1, 8, 15 and 22:** Vinorelbine 25mg/m² IV over 10 minutes. Repeat cycle every 4 weeks.
Carboplatin + paclitaxel[19]	**Day 1:** Carboplatin AUC=5–6 IV **Day 1:** Paclitaxel 225mg/m² IV over 3 hours. Repeat cycle every 3 weeks.
Pemetrexed + cisplatin[24,39]	**Day 1:** Pemetrexed 500mg/m² IV + cisplatin 75mg/m² IV. Repeat cycle every 3 weeks.
Crizotinib[40]#	Crizotinib 250mg PO twice daily.**
Afatinib[32]¶	Afatinib 40mg PO once daily.

Principals of First-Line Therapy[1]

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in patients with PS 0–1 with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
- Cetuximab + vinorelbine/cisplatin is an option for patients with PS 0–1 (category 2B).
- Erlotinib is recommended as a first-line therapy in patients with sensitizing EGFR mutations and should not be given as first-line therapy to patients negative for these EGFR mutations or with unknown EGFR status.
- Afatinib is indicated for select patients with sensitizing EGFR mutations.
- Crizotinib is indicated for select patients with ALK rearrangements.
- 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 or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, or albumin-bound paclitaxel.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (e.g., gemcitabine/docetaxel, gemcitabine/vinorelbine).
- Response assessment after 1–2 cycles, then every 2–4 cycles.

Subsequent Second-Line Systemic Therapy for Advanced Disease[1]

Docetaxel[23]	**Day 1:** Docetaxel 75mg/m² IV. Repeat cycle every 3 weeks.
Pemetrexed[7]	**Day 1:** Pemetrexed 500mg/m² IV. Repeat cycle every 3 weeks.
Erlotinib[25]	Erlotinib 150mg PO once daily.
Ceritinib[33]#	Ceritinib 750mg PO once daily.
Ramucirumab + docetaxel[34]	**Day 1:** Ramucirumab 10mg/kg IV + docetaxel 75mg/m² IV. Repeat cycle every 3 weeks.
Afatinib[32]¶	Afatinib 40mg PO once daily.
Nivolumab[35]	Nivolumab 3mg/kg IV over 60 minutes every 2 weeks.

continued

LUNG CANCER TREATMENT REGIMENS (Part 4 of 7)

Non-Small Cell Lung Cancer (NSCLC) (continued)

Subsequent Systemic Therapy for Advanced Disease[1] (continued)

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.
  - 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.
  - Afatinib is indicated for select patients with sensitizing EGFR mutations.
  - Ceritinib is indicated for patients with ALK rearrangements who have disease progression on or are intolerant to crizotinib.
- If not already given, options for patients with PS 0–2 include docetaxel, pemetrexed (nonsquamous), erlotinib, or gemcitabine (category 2B for all options).

Continuation After Disease Progression[1]

- With the exception of targeted agents (erlotinib, gefitinib, afatinib, crizotinib) in patients with EGFR-sensitizing mutations or ALK rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations (refer to discussion section of NCCN Guidelines for Non-Small Cell Lung Cancer v.5.2015).

Small Cell Lung Cancer (SCLC)

Chemotherapy as Primary or Adjuvant Therapy‡‡

Limited Stage (maximum of 4–6 cycles)[1]

REGIMEN	DOSING
Cisplatin + etoposide[41–43§§]	**Day 1:** Cisplatin 60mg/m² IV **plus** **Days 1–3:** Etoposide 120mg/m² IV. Repeat cycle every 3 weeks for at least 4 cycles. **OR** **Day 1:** Cisplatin 80mg/m² IV **plus** **Days 1–3:** Etoposide 100mg/m² IV. Repeat every 4 weeks for 4–6 cycles.
Carboplatin + etoposide[44]	**Day 1:** Carboplatin AUC=5–6 IV **plus** **Days 1–3:** Etoposide 100mg/m² IV. Repeat every 3 weeks for 4–6 cycles.

Extensive Stage (maximum of 4–6 cycles)[1]

Cisplatin + etoposide[45–47]	**Day 1:** Cisplatin 75–80mg/m² IV **Days 1–3:** Etoposide 80–100mg/m² IV. Repeat every 3 weeks for 4–6 cycles. **OR** **Days 1–3:** Cisplatin 25mg/m² IV + etoposide 100mg/m² IV. Repeat cycle every 3 weeks for 4-6 cycles.
Cisplatin + irinotecan[41,48,49]	**Day 1:** Cisplatin 60mg/m² IV **Days 1, 8 and 15:** Irinotecan 60mg/m² IV. Repeat cycle every 4 weeks for 4 cycles. **OR** **Day 1 and 8:** Cisplatin 30mg/m² IV **Day 1 and 8:** Irinotecan 65mg/m² IV. Repeat every 3 weeks for 4–6 cycles.
Carboplatin + irinotecan[50]	**Day 1:** Carboplatin AUC=5 IV **plus** **Days 1, 8 and 15:** Irinotecan 50mg/m² IV. Repeat cycle every 4 weeks for 4–6 cycles.
Carboplatin + etoposide[51]	**Day 1:** Carboplatin AUC=5–6 IV. **Days 1–3:** Etoposide 100mg/m² IV. Repeat every 4 weeks for 4–6 cycles.

Subsequent Chemotherapy

Relapse <2–3 months, PS 0–2[1]

Paclitaxel[18,52]	**Day 1:** Paclitaxel 175mg/m² IV over 3 hours **plus** **Day 1:** Cisplatin 80mg/m² IV. Repeat every 3 weeks for at least 2 cycles. **OR** **Day 1:** Paclitaxel 80mg/m² IV over 1 hour. Repeat every week for 6 weeks, followed by a 2-week break.

continued

Small Cell Lung Cancer (SCLC) (continued)

Subsequent Chemotherapy (continued)

Relapse <2–3 months, PS 0–2[1] (continued)

REGIMEN	DOSING
Docetaxel[53]	**Day 1:** Docetaxel 100mg/m² IV over 1 hour. Repeat every 21 days.
Topotecan[54–57]	**Days 1–5:** Topotecan 1.5mg/m² IV once daily over 30 minutes. Repeat every 3 weeks. **OR** **Days 1–5:** Topotecan 2.3mg/m² PO once daily. Repeat every 3 weeks.
Irinotecan[58]	**Day 1:** Irinotecan 100mg/m² IV over 90 minutes. Repeat every week.
Temozolomide[59]	**Day 1–21:** Temozolomide 75mg/m² PO for a 4-week cycle.
Gemcitabine[60,61]	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m² IV for a 4-week cycle.
Ifosfamide[62]	**Day 1:** Ifosfamide/mesna 5,000mg/m² IV. Repeat every 3 weeks.
Relapse > 2–3 months up to 6 months[1]	
Topotecan (Category 1) [54–57]	**Days 1–5:** Topotecan 1.5mg/m² IV once daily over 30 minutes. Repeat every 3 weeks. **OR** **Days 1–5:** Topotecan 2.3mg/m² PO once daily. Repeat every 3 weeks.
Paclitaxel[18,52]	**Day 1:** Paclitaxel 175mg/m² IV over 3 hours **plus** **Day 1:** Cisplatin 80mg/m². Repeat every 3 weeks for at least ² cycles. **OR** **Day 1:** Paclitaxel 80mg/m² IV over 1 hour. Repeat every week for 6 weeks, followed by a 2-week break.
Docetaxel[53]	**Day 1:** Docetaxel 100 mg/m² IV over 1 hour. Repeat every 21 days.
Irinotecan[58]	**Day 1:** Irinotecan 100mg/m² IV over 90 minutes. Repeat every week.
Gemcitabine[60,61]	**Days 1, 8, and 15:** Gemcitabine 1,000mg/m² IV for a 4-week cycle.
Vinorelbine[63,64]	**Day 1:** Vinorelbine 25–30mg/m² IV. Repeat every week
Etoposide (PO)[65,66]	**Day 1–21:** Etoposide 50mg/m² PO.
Temozolomide[59]	**Day 1–21:** Temozolomide 75mg/m² PO for a 4-week cycle.
Cyclophosphamide + doxorubicin + vincristine (CAV)[54]	**Day 1:** Cyclophosphamide 1,000 mg/m² IV **plus** **Day 1:** Doxorubicin 45mg/m² IV **plus** **Day 1:** Vincristine 2mg IV. Repeat every 21 days.
Relapse> 6 months[1]	
• **Original regimen**[67,68||||]	

* For adenocarcinoma, large cell carcinoma, and NSCLC NOS without specific histologic subtype.

† This regimen can be used as neoadjuvant chemoradiotherapy. Cisplatin and etoposide is the preferred regimen. If weekly carboplatin and paclitaxel is used because the patient is not able to tolerate concurrent full-dose cisplatin and radiotherapy, the treating physician should consider 2 cycles of full-dose platinum therapy after local treatment is completed

‡ Most are used in combination, while others are used as monotherapy (e.g., maintenance or second-line therapy).

§ 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 (dexamethasone, H2 blockers, H1 blockers) are contraindicated.

|| Indicated in advanced NSCLC.

¶ Indicated for EGFR mutation–positive patients and may be considered as an option for patients who test positive for an EGFR mutation.

Indicated for ALK-positive patients.

** May reduce to 200mg twice daily not tolerated or toxicity occurs. If further reduction is needed, reduce to 250mg once daily.

†† The regimens included are representative of the more commonly used regimens for small cell lung cancer. Other regimens may be acceptable.

‡‡ The use of rnyeloid growth factors is not recommended during concurrent chemotherapy plus radiotherapy.

§§ During chemotherapy + radiotherapy, cisplatin/etoposide is recommended (Category 1).

|||| Consider dose reductions versus growth factors in the poor performance status patient.

continued

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