Non-Small Cell Lung Cancer

Overall management of Non-Small Cell Lung Cancer from diagnosis through recurrence is described in the full NCCN Guidelines® for Non-Small Cell Lung Cancer. Reproduced with permission from the NCCN Guidelines for Non-Small Cell Lung Cancer V5.2018. © 2018 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN 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.
HISTOLOGIC SUBTYPE

- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

Squamous cell carcinoma

TESTING

- Molecular testing
  - EGFR mutation testing
  - ALK testing
  - ROS1 testing
  - BRAF testing
  - Testing should be conducted as part of broad molecular profiling
  - PD-L1 testing

TESTING RESULTS

- Sensitizing EGFR mutation positive (see NSCL-18)
  - ALK positive (see NSCL-21)
  - ROS1 positive (see NSCL-24)
  - BRAF V600E positive (see NSCL-25)
  - PD-L1 positive and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-26)
  - EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1 <50% or unknown (see NSCL-27)

- ALK positive (see NSCL-21)
- ROS1 positive (see NSCL-24)
- BRAF V600E positive (see NSCL-25)
- PD-L1 positive and EGFR, ALK, ROS1, BRAF negative or unknown (see NSCL-26)
- EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1 <50% or unknown (see NSCL-28)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
SENSITIZING EGFR MUTATION POSITIVE

EGFR mutation discovered prior to first-line chemotherapy

Sensitizing EGFR mutation positive

EGFR mutation discovered during first-line chemotherapy

FIRST-LINE THERAPY

Erlotinib (category 1) or Afatinib (category 1) or Gefitinib (category 1) or Osimertinib (category 1)

Progression

See Subsequent Therapy (NSCL-19)

See Subsequent Therapy (NSCL-20)

Complete planned chemotherapy, including maintenance therapy, or interrupt, followed by erlotinib or afatinib or gefitinib or osimertinib

Progression

See Subsequent Therapy (NSCL-19)

See Subsequent Therapy (NSCL-20)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

hhSee Principles of Molecular and Biomarker Analysis (NSCL-G).
mmSee Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
nnFor performance status 0-4.
**SENSITIZING EGFR MUTATION POSITIVE**

**Asymptomatic**
- Progression on erlotinib, afatinib, gefitinib
- T790M testing

**Symptomatic**
- Brain
- Systemic
- Isolated lesion
- Multiple lesions

**SUBSEQUENT THERAPY**

- **Progression**
  - Consider local therapy
  - Osimertinib (if T790M+)
  - Continue erlotinib or afatinib or gefitinib

- **Progression**
  - Consider local therapy
  - Osimertinib (if T790M+)
  - Continue erlotinib or afatinib or gefitinib
  - See NCCN Guidelines for CNS Cancers

- **Progression**
  - Consider local therapy
  - Continue erlotinib or afatinib or gefitinib
  - See subsequent therapy for multiple lesions, noted below

- **Progression**
  - T790M+
  - Osimertinib (category 1)
  - See Initial cytotoxic therapy options

- **Progression**
  - T790M-
  - See Subsequent Therapy (NSCL-20)

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
**SENSITIZING EGFR MUTATION POSITIVE**

- **Asymptomatic**
  - Progression on osimertinib
  - Consider local therapy
  - Continue osimertinib

- **Symptomatic**
  - Brain
    - Isolated lesion
    - Consider local therapy
    - Continue osimertinib
  - Systemic
    - Multiple lesions
    - Consider local therapy
    - Continue osimertinib
    - See Initial cytotoxic therapy options
      - Adenocarcinoma (NSCL-27)
      - Squamous cell carcinoma (NSCL-28)

**SUBSEQUENT THERAPY**

- Progression
  - See subsequent therapy for multiple lesions, noted below

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
PD-L1 EXPRESSION POSITIVE

FIRST-LINE THERAPY

SUBSEQUENT THERAPY

PD-L1 expression positive (≥50%) and EGFR, ALK, ROS1, BRAF negative or unknown → Pembrolizumab (category 1) → Progression → See Initial cytotoxic therapy options for Adenocarcinoma (NSCL-27) or Squamous cell carcinoma (NSCL-28)

---

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

---

See Principles of Molecular and Biomarker Analysis (NSCL-G).

See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
ADENOCARCINOMA, LARGE CELL, NSCLC NOS

INITIAL CYTOTOXIC THERAPY

PS 0-2 ➔ Systemic therapy

Response or stable disease ➔ Tumor response evaluation

PS 0-2 ➔ Progression

Systemic immune checkpoint inhibitors (preferred)
Nivolumab (category 1) or pembrolizumab (category 1) or atezolizumab (category 1)

or Other systemic therapy:
Docetaxel or pemetrexed or gemcitabine or ramucirumab + docetaxel

Progression

Best supportive care
See NCCN Guidelines for Palliative Care

PS 3-4 ➔ Best supportive care
See NCCN Guidelines for Palliative Care

Response or stable disease ➔ Tumor response evaluation

4–6 cycles (total)

Continuation maintenance
• Bevacizumab (category 1)
• Pemetrexed (category 1)
• Atezolizumab and/or bevacizumab
• Gemcitabine (category 2B)

Switch maintenance
• Pemetrexed

or Close observation

Progression, see Subsequent therapy, above

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Visit NCCN.org to view the complete library of NCCN Guidelines.
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

ADVANCED DISEASE:
- 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, 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.
- Platinum combinations have generated a plateau in overall response rate (≈ 25%–35%), time to progression (4–6 mo), median survival (8–10 mo), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients.

Initial Cytotoxic Therapy
- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to 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 2 cycles, then every 2–4 cycles with CT of known sites of disease with or without contrast or when clinically indicated.

Maintenance Therapy
- Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4–6 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 4–6 cycles of initial therapy.
- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

See Initial Cytotoxic Therapy Options for Adenocarcinoma, Large cell, NSCLC NOS on NSCL-J (2 of 4)

See Initial Cytotoxic Therapy Options for Squamous Cell Carcinoma on NSCL-J (3 of 4)
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE*,**

**Initial Cytotoxic Therapy Options**

**Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)**
- Bevacizumab/carboplatin/paclitaxel (category 1)\(^1,†,‡,#\)
- Bevacizumab/carboplatin/pemetrexed\(^2,†,‡,#\)
- Bevacizumab/cisplatin/pemetrexed\(^3,†,‡,#\)
- Carboplatin/alumnum-bound paclitaxel (category 1)\(^4\)
- Carboplatin/docetaxel (category 1)\(^5\)
- Carboplatin/etoposide (category 1)\(^6,7\)
- Carboplatin/gemcitabine (category 1)\(^8\)
- Carboplatin/paclitaxel (category 1)\(^9\)
- Carboplatin/pemetrexed (category 1)\(^10\)
- Cisplatin/docetaxel (category 1)\(^5\)
- Cisplatin/etoposide (category 1)\(^11\)
- Cisplatin/gemcitabine (category 1)\(^9,12\)
- Cisplatin/paclitaxel (category 1)\(^13\)
- Cisplatin/pemetrexed (category 1)\(^10\)
- Gemcitabine/docetaxel (category 1)\(^14\)
- Gemcitabine/vinorelbine (category 1)\(^15\)
- Pembrolizumab/carboplatin/pemetrexed (category 1)\(^16,17,¶\)
- Pembrolizumab/cisplatin/pemetrexed (category 1)\(^17,¶\)
- Atezolizumab/carboplatin/paclitaxel/bevacizumab (category 1)\(^18\)

**Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)**
- Albumin-bound paclitaxel\(^19\)
- Carboplatin/albumin-bound paclitaxel\(^20,21\)
- Carboplatin/docetaxel\(^5\)
- Carboplatin/etoposide\(^6,7\)
- Carboplatin/gemcitabine\(^8\)
- Carboplatin/paclitaxel\(^9\)
- Carboplatin/pemetrexed\(^10\)
- Docetaxel\(^22,23\)
- Gemcitabine\(^24-26\)
- Gemcitabine/docetaxel\(^14\)
- Gemcitabine/vinorelbine\(^15\)
- Paclitaxel\(^27-29\)
- Pemetrexed\(^30\)

*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.
**Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.
†Bevacizumab should be given until progression.
‡Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
#Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.
¶If pembrolizumab not previously given.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE**

*Initial Cytotoxic Therapy Options*

**Squamous Cell Carcinoma (PS 0-1)**
- Carboplatin/albumin-bound paclitaxel (category 1)\(^4\)
- Carboplatin/docetaxel (category 1)\(^5\)
- Carboplatin/gemcitabine (category 1)\(^8\)
- Carboplatin/paclitaxel (category 1)\(^9\)
- Cisplatin/docetaxel (category 1)\(^5\)
- Cisplatin/etoposide (category 1)\(^11\)
- Cisplatin/gemcitabine (category 1)\(^9,12\)
- Cisplatin/paclitaxel (category 1)\(^13\)
- Gemcitabine/docetaxel (category 1)\(^14\)
- Gemcitabine/vinorelbine (category 1)\(^15\)
- Pembrolizumab/carboplatin/paclitaxel\(^31\)

**Squamous Cell Carcinoma (PS 2)**
- Albumin-bound paclitaxel\(^19\)
- Carboplatin/albumin-bound paclitaxel\(^20,21\)
- Carboplatin/docetaxel\(^5\)
- Carboplatin/etoposide\(^6,7\)
- Carboplatin/gemcitabine\(^8\)
- Carboplatin/paclitaxel\(^9\)
- Docetaxel\(^22,23\)
- Gemcitabine\(^24-26\)
- Gemcitabine/docetaxel\(^14\)
- Gemcitabine/vinorelbine\(^15\)
- Paclitaxel\(^27-29\)

---

*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.

**Carboplatin-based regimens are often used for patients with comorbidities or those who cannot tolerate cisplatin.

§Cisplatin/gemcitabine/necitumumab in the first-line setting and afatinib in the second-line setting are not used at NCCN Member Institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

---

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

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
Non-Small Cell Lung Cancer  |  NCCN Guidelines®  |  Version 5.2018

Provided by AstraZeneca:

TAGRISSO

INDICATIONS
TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

TAGRISSO is indicated for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test.

IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTC) interval prolongation occurred in 1.4% of the 1142 TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTC > 500 msec, and 3.6% of patients had an increase from baseline QTC > 60 msec. No QTC-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QT syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTC interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 6 weeks after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

IRESSA

INDICATION
IRESSA is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of IRESSA have not been established in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution mutations.

IMPORTANT SAFETY INFORMATION

- There are no contraindications for IRESSA
- Interstitial Lung Disease (ILD) or ILD-like reactions (eg, lung infiltration, pneumonitis, acute respiratory distress syndrome, or pulmonary fibrosis) occurred in 1.3% of 2462 IRESSA patients; of these, 0.7% were Grade ≥3 and 3 cases were fatal. Withhold IRESSA and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms such as dyspnea, cough and fever. Permanently discontinue IRESSA if ILD is confirmed
- In patients who received IRESSA, 11.4% of patients had increased alanine aminotransferase (ALT), 7.9% of patients had increased aspartate aminotransferase (AST), and 2.7% of patients had increased bilirubin. Grade ≥3 liver test abnormalities occurred in 5.1% ALT, 3.0% AST, and 0.7% bilirubin of patients. The incidence of fatal hepatotoxicity was 0.04%. Obtain periodic liver function testing. Withhold IRESSA in patients with worsening liver function and discontinue in patients with severe hepatic impairment
- Gastrointestinal perforation occurred in three (0.1%) of 2462 IRESSA patients. Permanently discontinue IRESSA in patients who develop gastrointestinal perforation
- Grade ≥3 diarrhea occurred in 3% of 2462 IRESSA patients. Withhold IRESSA for severe or persistent (up to 14 days) diarrhea
- Ocular disorders [keratitis (0.1%), corneal erosion and aberrant eyelash growth (0.2%), conjunctivitis, blepharitis and dry eye (5.7%)] occurred in 2462 IRESSA patients. The incidence of Grade 3 ocular disorders was 0.1%. Interrupt or discontinue IRESSA for severe or worsening ocular disorders

(continued on next page)
The National Comprehensive Cancer Network® (NCCN®) appreciates that supporting companies recognize NCCN’s need for autonomy in the development of the content of NCCN resources. All NCCN Guidelines are produced completely independently. NCCN Guidelines are not intended to promote any specific therapeutic modality. The distribution of this flashcard is supported by AstraZeneca.