Overview

Lung cancer is the leading cause of cancer death in the United States. An estimated 226,200 new cases (116,500 in men and 109,700 in women) of lung and bronchial cancer will be diagnosed in 2012, and 160,300 deaths (87,700 in men and 72,600 in women) are estimated to occur from the disease. Only 15.9% of all patients are alive 5 years or more.
after lung cancer diagnosis (seer.cancer.gov/statfacts/html/lungb.html). Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; symptomatic patients are more likely to have chronic obstructive pulmonary disease.

These guidelines only include information about stage IV non–small cell lung cancer (NSCLC). The complete version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC is available on the NCCN Web site (NCCN.org).

Currently, most patients with NSCLC are diagnosed with advanced cancer at presentation. Symptoms of metastatic cancer include weight loss, bone pain, headaches, anemia, and paraneoplastic syndromes. A preliminary diagnosis of metastatic disease is established using symptoms, signs, and laboratory tests, and is aided by imaging (eg, PET/CT scan, MRI). Patients with widespread metastatic disease (stage IV) are usually candidates for systemic therapy (consisting of chemotherapy, targeted therapy, or a combination), clinical trials, and/or palliative treatment. The goal is to identify patients with metastatic disease before initiating aggressive treatment (eg, combined modality therapy), thus sparing these patients from unnecessary futile treatment. If metastatic disease is discovered during surgery, then extensive surgery is often aborted. Decisions regarding treatment should be based on multidisciplinary discussion.

**Risk Factors**

The primary risk factor for lung cancer is smoking tobacco, which accounts for more than 85% to 90% of cases.

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

### Pathologic Diagnosis of NSCLC

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**Non-small cell lung cancer (NSCLC)**

- Stage IV (M1a) (pleural or pericardial effusion)
- Solitary metastasis with resectable lung lesion
- Disseminated metastases

**Pathologic Diagnosis of NSCLC**

- **Initial Evaluation Clinical Stage**
  - Stage IV (M1b)
  - Workup as clinically indicated

**Pretreatment Evaluation**

- **Thoracentesis or pericardiocentesis ± thoracoscopy if thoracentesis indeterminate**
- **Mediastinoscopy**
- **Bronchoscopy**
- **Brain MRI**
- **PET/CT scan**

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\(^a\) See Principles of Pathologic Review (pages 1245–1247).

\(^b\) Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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NSCL-1, NSCL-10

**INITIAL TREATMENT**

- **Positive**
  - Local therapy if necessary (e.g., pleurodesis, ambulatory small catheter drainage, pericardial window) + treatment as for stage IV disease (page 1241)
  - Surgical resection, followed by WBRT (category 1) or stereotactic radiosurgery (SRS)
  - Surgical resection of lung lesion or SRS + WBRT (category 1 for one metastasis)
  - SRS alone

- **Brain**
  - Pathologic diagnosis by needle or resection
  - Local therapy for adrenal lesion (if lung lesion curable, based on T and N stage, category 2B)
  - See Systemic therapy (page 1241)

- **Adrenal**
  - Surgical resection of lung lesion or Stereotactic ablative radiotherapy (SABR) of lung lesion (category 2B)
  - See Systemic Therapy (page 1241)

- **Chemotherapy**
  - Surgical resection of lung lesion or Stereotactic ablative radiotherapy (SABR) of lung lesion (category 2B)
  - Chemotherapy

**PATHOLOGIC DIAGNOSIS OF NSCLC**

**INITIAL EVALUATION:**

- **Clinical Stage**
  - Non–small cell lung cancer (NSCLC)

- **See Principles of Pathologic Review (pages 1245–1247).**

- **Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.**

**PRETREATMENT EVALUATION:**

- **H&P (include performance status + weight loss)**
- **CT chest and upper abdomen, including adrenals**
- **CBC, platelets**
- **Chemistry profile**
- **Smoking cessation advice, counseling, and pharmacotherapy**

**STAGE IV (M1b):**

- Solitary metastasis with resectable lung lesion
- Disseminated metastases

**STAGE IV (M1a):**

- (pleural or pericardial effusion)
- Workup as clinically indicated

**Brain:**

- Surgical resection, followed by WBRT (category 1) or stereotactic radiosurgery (SRS)
- or
- SRS + WBRT (category 1 for one metastasis)
- or
- SRS alone

**Adrenal:**

- Pathologic diagnosis by needle or resection
- Local therapy for adrenal lesion (if lung lesion curable, based on T and N stage, category 2B)
- See Systemic therapy (page 1241)

**Chemotherapy:**

- Surgical resection of lung lesion or Stereotactic ablative radiotherapy (SABR) of lung lesion (category 2B)
- or
- Chemotherapy (category 2B)

**See Systemic Therapy (page 1241).**

**Table Notes:**

- Although most pleural effusions associated with lung cancer are from tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate the effusion is not related to the tumor, the effusion should be excluded as a staging element. Pericardial effusion is classified using the same criteria.
- See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Central Nervous System Cancers (to view the most recent version of these guidelines, visit NCCN.org).
- Patients with N2 disease have a poor prognosis and systemic therapy may be considered.
- See Principles of Surgical Therapy (available online, in these guidelines, at NCCN.org [NSCL-D]).
- See Systemic Therapy for Advanced or Metastatic Disease (pages 1248-1249).

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

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THERAPY FOR RECURRENCE AND METASTASIS

Locoregional recurrence

- Endobronchial obstruction
  - Laser/stent/other surgery
  - Brachytherapy
  - External-beam RT
  - Photodynamic therapy

- Resectable recurrence
  - Reresection (preferred)
  - External-beam RT

- Mediastinal lymph node recurrence
  - Concurrent chemoradiation (if RT not previously given)

- Superior vena cava (SVC) obstruction
  - Concurrent chemoradiation (if not previously given)
  - External-beam RT
  - Stent

- Severe hemoptysis
  - External-beam RT
  - Brachytherapy
  - Laser
  - Photodynamic therapy
  - Embolization
  - Surgery

Distant metastases

- Localized symptoms
  - Palliative external-beam RT

- Diffuse brain metastases
  - Palliative external-beam RT

- Bone metastasis
  - Palliative external-beam RT + orthopedic stabilization, if risk of fracture
  - Consider bisphosphonate therapy

- Solitary metastasis
  - See pathway for Stage IV, M1b, solitary site (page 1239)

- Disseminated metastases
  - See Systemic Therapy (facing page)

No evidence of disseminated disease

- Observation or Systemic chemotherapy¹ (category 2B)

Evidence of disseminated disease

- See First-line Therapy for Recurrence or Metastases (facing page)

¹See Systemic Therapy for Advanced or Metastatic Disease (available online, in these guidelines, at NCCN.org [NSCL-G]).

HISTOLOGY

- Adenocarcinoma
- Large Cell
- NSCLC NOS

Establish histologic subtype

Squamous cell carcinoma

EGFR mutation and ALK testing are not routinely recommended

FIRST-LINE THERAPY FOR RECURRENCE OR METASTASES

- EGFR mutation-negative, ALK-negative, or unknown
- EGFR mutation-positive

EGFR mutation discovered before first-line chemotherapy

- Switch maintenance: erlotinib or May add erlotinib to current chemotherapy (category 2B)

Progression

See Second-line Therapy (page 1244)

EGFR mutation discovered during first-line chemotherapy

- Erlotinib \( k \), \( l \), \( m \)

Progression

See Second-line Therapy (page 1244)

ALK-positive

Crizotinib

Progression

See Second-line Therapy (page 1244)

EGFR mutation-negative, ALK-negative, or unknown

See First-Line Therapy (page 1242)

See Systemic Therapy (facing page)

See First-line Therapy for Recurrence or Metastases

Establish histologic subtype

Squamous cell carcinoma

EGFR mutation and ALK testing are not routinely recommended

See First-Line Therapy (page 1243)

NSCL-13


In patients with squamous cell carcinoma, the observed incidence is 2.7% with a confidence that the true incidence of mutations is less than 3.6% in patients with squamous cell carcinoma. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharama G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.


For performance status 0-4.

In areas of the world where gefitinib is available, it may be used in place of erlotinib.

### ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION- AND ALK-NEGATIVE OR UNKNOWN

#### FIRST-LINE THERAPY

- **PS 0-1**
  - Doublet chemotherapy\(^h\) (category 1)
  - Bevacizumab + chemotherapy\(^h,o,p\) (if criteria met)\(^q\)
  - Cisplatin/pemetrexed (category 1) (if criteria met)\(^r\)
  - Cetuximab/vinorelbine/cisplatin\(^s\) (category 2B)

- **PS 2** → Chemotherapy\(^h\)

- **PS 3-4** → Best supportive care only
  - (see NCCN Guidelines for Palliative Care; to view the most recent version of these guidelines, visit NCCN.org)

#### RESPONSE EVALUATION

- Progression

- Tumor response or stable disease
  - 4-6 cycles (total)
  - Tumor response evaluation

#### MAINTENANCE THERAPY

- Continuation of current regimen until disease progression
  - Continuation maintenance\(^h\) bevacizumab (category 1) or cetuximab (category 1) or pemetrexed or gemcitabine\(^t\)
  - Switch maintenance\(^h\) pemetrexed or erlotinib
  - Observation

---

\(^{h}\)See Systemic Therapy for Advanced or Metastatic Disease (pages 1248–1249).

\(^{o}\)Bevacizumab should be given until progression.

\(^{p}\)Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

\(^{q}\)Criteria for treatment with bevacizumab + chemotherapy: nonsquamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.


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 + chemotherapy: nonsquamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients who do not have squamous histology, in comparison to cisplatin/gemcitabine.


Best supportive care only (see NCCN Guidelines for Palliative Care; to view the most recent version of these guidelines, visit NCCN.org)

PS 0-1
Chemotherapy h (category 1) or Cetuximab/vinorelbine/cisplatin s (category 2B)

PS 2
Chemotherapy h

PS 3-4
Best supportive care only (see NCCN Guidelines for Palliative Care; to view the most recent version of these guidelines, visit NCCN.org)

See Second-line Therapy (page 1244)

See Systemic Therapy for Advanced or Metastatic Disease (pages 1248–1249).


To view the most recent version of these guidelines, visit NCCN.org.

Best supportive care only (NCCN Guidelines for Palliative Care*) or Clinical trial

Erlotinib\(h, m\) or Best supportive care only (NCCN Guidelines for Palliative Care*)

Performance status 3-4

If not already given: Docetaxel\(h\) or Pemetrexed\(h, u\) or Erlotinib\(h, m\)

Performance status 0-2

Erlotinib\(h, m, v\) or Best supportive care only (see NCCN Guidelines for Palliative Care*)

Performance status 3-4

Performance status 0-2

Docetaxel\(h\) or Pemetrexed\(h, u\) or Erlotinib\(h, m\) or Platinum doublet ± bevacizumab (if erlotinib or crizotinib given as first-line and nonsquamous histologic type)

Performance status 0-2

Performance status 3-4

Performance status 3-4

*To view the most recent version of these guidelines, visit NCCN.org.

\(h\) See Systemic Therapy for Advanced or Metastatic Disease (pages 1248–1249).
\(m\) In areas of the world where gefitinib is available, it may be used in place of erlotinib.
\(u\) Pemetrexed is not recommended for squamous histology.
\(v\) Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

NSCL-16
PRINCIPLES OF PATHOLOGIC REVIEW

Pathologic Evaluation

- The purpose of pathologic evaluation is to precisely classify the histologic type of lung cancer and to determine all staging parameters as recommended by the AJCC, including tumor size, the extent of invasion (pleural and bronchial), adequacy of surgical margins, and presence or absence of lymph node metastasis. Further, determination of the specific molecular abnormalities of the tumor is critical for predicting sensitivity or resistance to a growing number of targeted therapies, primarily tyrosine kinase inhibitors (TKIs; see “Molecular Diagnostic Studies in Lung Cancer,” page 1246).
- The WHO tumor classification system has historically provided the foundation for the classification of lung tumors, including histologic types, clinical features, staging considerations, and the molecular, genetic, and epidemiology aspects of lung cancer.
- The pathology diagnostic report should include the histologic classification as described by the WHO for carcinomas of the lung with squamous morphology, neuroendocrine differentiation, and other variant carcinomas. The recently published classification of adenocarcinoma should be used for this tumor subtype in resection specimens and small biopsies. Use of bronchioalveolar carcinoma (BAC) terminology is strongly discouraged.
- The generic term “non-small cell lung cancer (NSCLC)” should be avoided as a single diagnostic term. In small biopsies of poorly differentiated carcinomas where immunohistochemistry (IHC) is used, the following terms are acceptable: “NSCLC favor adenocarcinoma” or “NSCLC favor squamous cell carcinoma.” Mutational testing (eg, epidermal growth factor receptor [EGFR]) should be performed in this setting.
- Although formalin-fixed paraffin-embedded tumor may be used for most molecular analyses, acquisition of fresh cryopreserved tumor tissue for advanced molecular studies should be considered.
- Judicious use of ancillary IHC studies in small tissue samples is recommended, thereby preserving tumor tissue for molecular studies particularly in patients with advanced-stage disease.

Adenocarcinoma Classification

- Adenocarcinoma in situ (AIS; formerly BAC): < 3 cm nodule, lepidic growth, mucinous, nonmucinous or, mixed mucinous/nonmucinous types.
- Minimally invasive adenocarcinoma (MIA): < 3 cm nodule with < 5 mm of invasion, lepidic growth, mucinous, nonmucinous, or mixed mucinous/nonmucinous types.
- Invasive adenocarcinoma, predominant growth pattern: lepidic > 5 mm of invasion, acinar, papillary, micropapillary, or solid with mucin.
- Invasive adenocarcinoma variants: mucinous adenocarcinoma, colloid, fetal, and enteric morphologies.

IHC staining

- Although the concordance is generally good between the histologic subtype and the immunophenotype seen in small biopsies compared with surgical resection specimens, caution is advised in attempting to subtype small biopsies with limited material or cases with an ambiguous immunophenotype.
- IHC should be used to differentiate primary pulmonary adenocarcinoma from squamous or large cell carcinoma, metastatic carcinoma, and malignant mesothelioma, and to determine whether neuroendocrine differentiation is present.
- Primary pulmonary adenocarcinoma
  - An appropriate panel of IHC stains is recommended to exclude metastatic carcinoma to lung.
  - TTF-1 is a homeomain-containing nuclear transcription protein of the Nkx2 gene family that is expressed in epithelial cells of the embryonal and mature lung and thyroid. TTF-1 immunoreactivity is seen in primary pulmonary adenocarcinoma in most (70%-100%) of nonmucinous adenocarcinomas subtypes. Metastatic adenocarcinoma to the lung is virtually always negative for TTF-1, except in metastatic thyroid malignancies in which case thyroglobulin is also positive.
  - Napsin A, an aspartic proteinase expressed in normal type II pneumocytes and in proximal and distal renal tubules, appears to be expressed in > 80% of lung adenocarcinomas and may be a useful adjunct to TTF-1.
  - The panel of TTF-1 and p63 may be useful in refining the diagnosis in small biopsy specimens previously generically classified as NSCLC.
- Neuroendocrine differentiation
  - CD56, chromogranin, and synaptophysin are used to identify neuroendocrine tumors.
  - Malignant mesothelioma versus pulmonary adenocarcinoma
    - The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelial type) is made by using a panel of markers including 2 with known immunopositivity in mesothelioma (but negative in adenocarcinoma) and 2 with known positivity in adenocarcinoma (but negative in mesothelioma). Immunostains relatively sensitive and specific for mesothelioma include WT-1, calretinin, D2-40, HM-BE-1, and cytokeratin 5/6 (negative in adenocarcinoma) and antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, and TTF-1 (negative in mesothelioma).
Molecular Diagnostic Studies in Lung Cancer

- EGFR and KRAS
  - EGFR is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of EGFR-activating mutations represents a critical biologic determinant for proper therapy selection in patients with lung cancer.
  - There is a significant association between EGFR mutations — especially exon 19 deletion, exon 21 mutation (L858R), and exon 18 (G719X) — and response to TKIs.\(^{16-19}\)
  - EGFR and KRAS mutations are mutually exclusive in patients with lung cancer.\(^{20}\)
  - KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy.\(^{21}\)
  - The prevalence of EGFR mutations in adenocarcinomas is 10% of Western and up to 50% of Asian patients, with higher EGFR mutation frequency in nonsmokers, women, and nonmucinous cancers. KRAS mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.\(^{22}\) The most common EGFR mutations result in an arginine for leucine substitution at amino acid 858 in exon 21 (L858R) and in frame deletions at exon 19. Mutations are more common in nonmucinous lung adenocarcinoma with lepidic pattern (former BAC pattern) and in lung adenocarcinoma with papillary (and or micropapillary) pattern.
  - Resistance to TKI therapy is associated with KRAS mutation and with secondary acquired EGFR mutations, such as T790M.
- EML4-ALK
  - Anaplastic lymphoma kinases (ALK) gene rearrangements, in a subset of anaplastic large cell lymphomas (ALCL), have been recognized for more than 15 years.\(^{23}\) The fusion between echinoderm microtubule–associated protein-like 4 (EML4) and ALK has recently been identified in a subset of patients with NSCLC. EML4-ALK NSCLC represents a unique subset of patients for whom ALK inhibitors may represent a very effective therapeutic strategy.\(^{24}\) Crizotinib is an oral ALK inhibitor that was recently approved by the FDA for patients with locally advanced or metastatic NSCLC who have the ALK gene rearrangement. (ie, ALK-positive).
  - EML4-ALK NSCLC occurs most commonly in a unique subgroup of patients who share many of the clinical features of patients with NSCLC likely to harbor EGFR mutations.\(^{25,26}\) However, for the most part, EML4-ALK translocations and EGFR mutations are mutually exclusive.\(^{25,27-29}\) EML4-ALK translocations tend to occur in younger patients and in those with more advanced NSCLC, although this relationship has not been reported for EGFR-mutant NSCLC.\(^{29,30}\)
  - The current standard method for detecting EML4-ALK NSCLC is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and IHC. A big advantage of FISH is that a commercially available probe set, developed for the diagnosis of ALK-rearranged ALCLs, is applicable for the diagnosis of ALK-rearranged lung adenocarcinomas. The IHC tests used to diagnose ALK-rearranged ALCLs in clinical laboratories worldwide are inadequate for detecting most ALK-rearranged lung adenocarcinomas.\(^{31,32}\) This is because of the lower level of ALK expression in ALK-rearranged NSCLCs compared with ALK-rearranged ALCLs. A molecular diagnostic test that uses FISH was recently approved by the FDA to determine which patients with lung adenocarcinoma are ALK-positive.

PRINCIPLES OF PATHOLOGIC REVIEW


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 (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 mo), median survival (8-10 mo), 1-y survival rate (30%-40%) and 2-y 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 EGFR mutation-positive.

First-Line Therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
- Cetuximab + vinorelbine/cisplatin is an option for patients with PS 0-1.
- Erlotinib is indicated as a first-line therapy in patients with EGFR mutation.
- Crizotinib is indicated as a first-line therapy in patients who are ALK-positive.
- 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 compared with 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.
- In locally advanced NSCLC, concurrent chemotherapy and thoracic irradiation is superior to radiation alone and sequential chemotherapy followed by radiation.
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed.
- New agent/nonplatinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).

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.

- 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.
  - Continuation of gemcitabine after 4-6 cycles of platinum-doublet chemotherapy.

- Switch Maintenance: Two recent 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.
  - Initiation of erlotinib after 4-6 cycles of first-line platinum-doublet chemotherapy.
  - Initiation of docetaxel after 4-6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).
  - Close follow-up of patients without therapy is a reasonable alternative to switch maintenance.

Second-Line Therapy

- In patients who have experienced disease progression either during or after first-line therapy, single-agent docetaxel, pemetrexed, and 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.
  - Erlotinib is superior to best supportive care.

Third-Line Therapy

- Erlotinib is superior to best supportive care.

Continuation After Disease Progression

- With the exception of erlotinib in patients with EGFR sensitizing mutations who have experienced objective regressions with erlotinib, no agent should be continued after disease progression has been documented. (refer to discussion section)
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE
Agents listed below are used in the treatment of patients with NSCLC. Most are used in combination, whereas others are used as monotherapy (eg, maintenance or second-line therapy).

- **Cisplatin**
- **Carboplatin**
- **Paclitaxel**
- **Docetaxel**
- **Vinorelbine**
- **Gemcitabine**
- **Etoposide**
- **Irinotecan**
- **Vinblastine**
- **Mitomycin**
- **Ifosfamide**
- **Pemetrexed**
- **Erlotinib**
- **Bevacizumab**
- **Cetuximab**
- **Albumin-bound paclitaxel**
- **Crizotinib**


22 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.
all lung cancer–related deaths (www.surgeongeneral.gov/library/smokingconsequences/).5–7 Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo[a]pyrene diol epoxide).6,8 The risk for lung cancer increases with the number of cigarettes packs smoked per day and with the number of years spent smoking (ie, pack-years of smoking history). Exposed nonsmokers also have an increased risk (relative risk [RR], 1.24) of developing lung cancer from “secondhand smoke” (www.surgeongeneral.gov/library/secondhandsmoke/reports/executivesummary.pdf).8–11 Other risk factors for lung cancer (eg, asbestos, radon, family history) are discussed in the NCCN Guidelines for Lung Cancer Screening (to view the most recent version of these guidelines, visit NCCN.org).

Prevention and Screening

Approximately 85% to 90% of lung cancer cases are caused by active smoking.5 Active smoking and secondhand smoke both cause lung cancer (see Reports from the Surgeon General, the next 2 links). A causal relationship exists between active smoking and lung cancer, in addition to other cancers (eg, esophageal, oral cavity, laryngeal, pharyngeal, bladder, pancreatic, gastric, kidney, ovarian, colorectal, and cervical cancers) and other diseases and conditions (www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf).

Smoking harms nearly every organ in the body. People who live with someone who smokes have a 20% to 30% increased risk for lung cancer (www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf). Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer (www.smokefree.gov). Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful (see Treating Tobacco Use and Dependence: 2008 Update, available at www.ahrq.gov/clinic/tobacco/tobaqrg.htm#Findings).

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), sustained-release bupropion, and varenicline. Studies have shown that varenicline is better than bupropion or a nicotine patch for smoking cessation.12–14 However, almost 30% of patients experienced nausea while using varenicline.15 The effectiveness of varenicline for preventing relapse has not been clearly established,16 and the FDA has issued an alert regarding neuropsychiatric symptoms (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm). Varenicline has also been associated with other disorders (eg, visual disturbances, movement disorders, unconsciousness, cardiovascular disorders), and therefore its use is banned in truck and bus drivers, pilots, and air traffic controllers.17 Bupropion is also associated with serious adverse events (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm169986.htm). Nicotine replacement has fewer adverse effects than varenicline or bupropion.18 However, despite their potential adverse effects, using agents to promote smoking cessation is probably more beneficial for motivated patients.18

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a fundamental obstacle to improving outcomes.19,20 Because localized cancer can be managed curatively, and survival in other solid tumors (eg, breast, cervix, colon, and prostate) seems to be increased through screening and early detection, lung cancer would be an appropriate candidate for a population-based screening approach. Pilot trials of spiral (helical) low-dose CT in lung cancer screening were promising, with stage I detectable lung cancer found in more than 80% of newly diagnosed cases.21–23

The National Lung Screening Trial (NLST; ACRIN protocol A6654) was a randomized, controlled trial involving more than 53,000 current or former heavy smokers that assessed the risks and benefits of low-dose helical CT scans compared with chest radiographs in detecting lung cancer.24 Recent published results from the NLST show that screening high-risk patients with low-dose helical CT decreases the mortality rate from lung cancer by 20% compared with chest radiographs.25 High-risk patients were either current or former smokers with a 30-pack year smoking history (former smokers had quit 15 years ago), were aged 55 to 74 years, and had no evidence of lung cancer.24,26 Additional information on NLST can be found at www.cancer.gov/nlst. The
new NCCN Guidelines for Lung Cancer Screening were published in JNCCN in March 2012, and are available on the NCCN Web site (NCCN.org).

The International Early Lung Cancer Action Program (I-ELCAP) is assessing whether annual screening with low-dose helical CT scan increases the detection of early stage lung cancer in patients at risk for cancer. Data from I-ELCAP showed that stage I lung cancer can be detected using annual low-dose CT screening. The 10-year survival rate was 92% for patients with stage I disease whose cancers were promptly removed; however, all patients who chose not to be treated died within 5 years. Additional information on I-ELCAP can be found at www.ielcap.org/index.htm. Screening can increase the diagnosis of early-stage lung cancers. Recent data from the NLST show that screening decreases the mortality rate.

**Classification and Prognostic Factors**

The WHO divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC and small cell lung cancer (SCLC; see the NCCN Guidelines for Small Cell Lung Cancer, available at NCCN.org). NSCLC accounts for more than 85% of all lung cancer cases and includes 2 major types: nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common type of lung cancer found in the United States and is the most frequently occurring cell type in nonsmokers. An international panel recently revised the classification for adenocarcinoma (see next section) to require immunohistochemical, histochemical, and molecular studies (see pages 1245–1247). The revised classification also recommends that use of general categories (eg, NSCLC) should be minimized, because more effective treatment can be selected when the histology is known.

**Adenocarcinoma**

Recently, the classification for adenocarcinoma was revised; the categories of bronchioloalveolar carcinoma (BAC) or mixed subtype adenocarcinoma are no longer used. If necessary, the term former BAC is used. The new categories include 1) adenocarcinoma in situ (AIS; formerly BAC), which is a pre-invasive lesion; 2) minimally invasive adenocarcinoma (MIA); 3) invasive adenocarcinoma (includes formerly nonmucinous BAC); and 4) variants of invasive adenocarcinoma (includes formerly mucinous BAC). The international panel and NCCN recommend that all patients with adenocarcinoma be tested for the EGFR mutation; the NCCN panel also recommends that these patients be tested for the ALK gene rearrangement.

**Immunohistochemical Staining**

Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma of the lung (eg, breast, prostate, colorec-
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	distinguish adenocarcinoma from malignant mesothelioma, and determine the neuroendocrine status of tumors. Immunohistochemical staining is described in the algorithm (see pages 1245–1247). Although cytology can be used to distinguish adenocarcinomas from squamous cell carcinomas, immunohistochemistry is also useful for poorly differentiated NSCLC in small biopsy and/or cytology specimens. Squamous cell carcinomas are often thyroid transcription factor -1 (TTF-1)–negative, p63-positive, and cytokeratin 5/6–positive, whereas adenocarcinomas are usually TTF-1–positive. Thus, a panel of these 3 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas. Other markers (eg, high-molecular-weight cytokeratin [34βE12], napsin A, mucicarmine) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.

Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma. Stains that are positive for adenocarcinoma but negative for mesothelioma include carinoembryonic antigen (CEA), B72.3, Ber-EP4, MOC31, and TTF-1. Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40 (podoplanin), and cytokeratin 5/6. A panel of 4 markers is used to distinguish mesothelioma from adenocarcinoma; 2 are positive in mesothelioma and 2 are positive in adenocarcinoma but negative in mesothelioma, and include calretinin, cytokeratin 5/6 (or WT-1), CEA, and MOC-31 (or B72.3, Ber-EP4, or BG-8).

TTF-1 is a transcription factor that regulates tissue-specific expression of surfactant apoprotein A, surfactant apoprotein B, surfactant apoprotein C, Clara cell antigen, and T1α. TTF-1 is very important in distinguishing primary from metastatic adenocarcinoma, because most primary carcinomas are TTF-1–positive; TTF-1 is typically negative for squamous cell carcinoma. However, TTF-1 is positive in tumors from patients with thyroid cancer. In addition, thyroglobulin is present in tumors from patients with thyroid cancer, whereas it is absent in lung cancer tumors. Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20−, whereas metastatic adenocarcinoma of the colorectum is usually CK7− and CK20+. CDX-2 is a marker for metastatic gastrointestinal malignancies that can be used to differentiate between primary lung tumors. All typical and atypical carcinoid tumors are positive for chromogranin and synaptophysin, whereas small cell lung carcinoma is negative in 25% of cases.

Although the cytologic diagnosis of NSCLC is generally reliable, it is more difficult to diagnose SCLC. However, many patients with SCLC have characteristic CT and clinical findings (eg, massive lymphadenectomy, mediastinal invasion). Most SCLCs are immunoreactive for TTF-1 and are typically negative for CK34βE12 and p63. Many SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM), and synaptophysin. However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs are immunoreactive for at least 1 of these neuroendocrine markers. Recent data suggest that microRNA (miRNA) expression can be used to distinguish SCLC from NSCLC.

Staging
The international staging system for lung cancer has been revised and adopted by the AJCC and by the Union Internationale Contre le Cancer. Recently, the lung cancer staging system was revised by the International Association of the Study of Lung Cancer (IASLC) and is available from the AJCC (7th edition). These NCCN Guidelines use the revised AJCC (7th edition) staging. The revised stage grouping and descriptors of the TNM classification scheme are shown in the staging tables for lung cancer (available online, in these guidelines, at NCCN.org).

The TNM staging revisions (AJCC 7th edition) became effective for all new cases diagnosed after January 1, 2010. With the revised staging, locally advanced disease is now stage III and advanced disease is now stage IV. The revised AJCC staging for 2010 includes upstaging and downstaging; for example, wet IIIB (ie, malignant pleural effusions) is upstaged to stage IV. These changes reflect the prognosis of patients with these different tumors. Pathologic staging uses both clinical staging information, which is noninvasive and includes medical history, physical examination, and imaging, and other invasive staging procedures, such as examination of lymph nodes using mediastinoscopy.

For 2005 through 2009, the overall 5-year relative survival rate for lung cancer was 15.9% (from
17 SEER geographic areas in the United States). Of lung and bronchial cancer cases, 15% were diagnosed while the cancer was still confined to the primary site (localized stage); 22% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 56% were diagnosed after the cancer had already metastasized (distant stage); and the staging information was unknown for the remaining 6%. The corresponding 5-year relative survival rates were 52% for localized, 25% for regional, 3.7% for distant, and 7.9% for unstaged (seer.cancer.gov/statfacts/html/lungb.html). However, these data include SCLC, which has a poorer prognosis.

Prognostic and Predictive Biomarkers

Several biomarkers have emerged as prognostic and predictive markers for NSCLC, including EGFR and the EML4-ALK fusion oncogene (fusion between echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK]). A **prognostic biomarker** is a biomolecule that indicates patient survival independent of the treatment received; that is, the biomolecule is an indicator of innate tumor aggressiveness. A **predictive biomarker** is a biomolecule that indicates therapeutic efficacy; that is, an interaction between the biomolecule and therapy predicts patient outcome. A more extensive discussion of biomarkers (eg, K-ras) is available in the complete version of the NCCN Guidelines for NSCLC (available at NCCN.org).

The presence of the EGFR exon 19 deletion (LREA) or exon 21 L858R mutation does not seem to be prognostic of survival for patients with NSCLC, independent of therapy. However, the presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit with EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy. The **EML4-ALK** fusion oncogene (ie, **ALK** gene rearrangement) is a new predictive biomarker that has been identified in a small subset of patients with NSCLC (see “EML4-ALK Gene Rearrangements” on page 1254, and pages 1245–1247 of the algorithm).

Testing for **EGFR** mutations and **ALK** gene rearrangements is recommended for select patients (eg, those with adenocarcinoma) so those with these genetic abnormalities can receive effective treatment (eg, erlotinib, crizotinib). Patients with adenocarcinoma may have other genetic abnormalities. Mutation screening assays for detecting multiple biomarkers (eg, SNaPshot Multiplex System) have been developed that can detect more than 100 point mutations, including **EGFR** (www.mycancergenome.org/molecular-pathology). However, these systems do not detect **ALK** gene rearrangements, because they are not point mutations. **ALK** gene rearrangements are detected using fluorescence in situ hybridization (FISH; see “EML4-ALK Gene Rearrangements” on page 1254). Ongoing research is assessing whether other biomarkers (eg, **BRAF**) may be useful therapeutic targets.

**EGFR** Mutations

**EGFR** is a transmembrane receptor that is detectable in approximately 80% to 85% of patients with NSCLC, and the levels of expression vary widely on a continual scale. The most commonly found **EGFR** mutations in patients with NSCLC are deletions in exon 19 (E19del [LREA deletion] in 45% of patients) and a mutation in exon 21 (L858R in 40%). Both mutations result in activation of the tyrosine kinase domain and are associated with sensitivity to the small-molecule TKIs (eg, erlotinib, gefitinib). These drug-sensitive mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients. Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and 18 (G719X). The T790M mutation is associated with resistance to TKI therapy and has been reported in approximately 50% of patients with disease progression.

DNA mutational analysis is the preferred method to assess for **EGFR** status, although FISH (to determine gene copy number) and immunohistochemistry (to determine level of expression) have been used. Various DNA mutation detection assays can be used to determine the **EGFR** mutation status in tumor cells. Direct sequencing of DNA corresponding to exons 18 to 21 (or just testing for exons 19 and 21) is a reasonable approach; however, more-sensitive methods are available. The multiplex mutation screening assay, SNaPshot Multiplex System, can detect more than 100 point mutations, including **EGFR**. **EGFR** mutation status may be better to assess on the primary tumor before therapy and not on the metastasis, although no consensus has been reached.

The prognostic effect of the drug-sensitive **EGFR** mutations—E19del (LREA deletion) and L858R—is not clear, whereas the predictive effects
of these mutations are well defined. Patients with these mutations have a significantly better response to erlotinib or gefitinib. Initial retrospective reports suggested that approximately 90% of patients with a tumor response to these drugs had mutations, whereas unresponsive patients did not. Subsequent retrospective studies have demonstrated an objective response rate of approximately 80%, with a median progression-free survival of 13 months to single-agent therapy in patients with a bronchioalveolar variant of adenocarcinoma and an EGFR mutation. A prospective study showed that the objective response rate in North American patients with nonsquamous cell histology and EGFR mutations (53% E19del [LREA deletion], 26% L858R, 21% other mutations) is 55%, with a median progression-free survival of 9.2 months. In patients treated with first-line chemotherapy with or without erlotinib, EGFR mutations were predictive of a better response in those receiving erlotinib (53% with mutations vs. 18% without). The response rates in the group of patients receiving only chemotherapy were 21% for those with mutations and 27% for those without.

In contrast, recent data suggest that erlotinib alone should be used as first-line systemic therapy in patients with proven EGFR mutations before use of standard first-line chemotherapy. Data show an improved progression-free survival with use of TKI inhibitors in patients with EGFR mutations when compared with standard chemotherapy, although overall survival is not statistically different.

**EML4-ALK Gene Rearrangements**

An estimated 2% to 7% of patients (approximately 10,000) have EML4-ALK gene rearrangements in the United States. These patients are resistant to EGFR TKIs but are similar to those with EGFR mutations (eg, those with adenocarcinoma, nonsmokers, or light smokers) except that they are often younger and male. In addition, ALK rearrangements are found in patients with adenocarcinoma but are not usually found in squamous cell or large cell carcinoma. ALK rearrangement testing is not routinely recommended for those with squamous cell carcinoma.

In these selected populations, estimates are that approximately 30% of patients will have EML4-ALK rearrangements. EGFR mutations and EML4-ALK rearrangements are generally mutually exclusive. Thus, erlotinib (or gefitinib) may not be effective as second-line therapy in patients with ALK rearrangements who experience relapse on crizotinib. Recently, a molecular diagnostic test (using FISH) was FDA-approved for detecting ALK. A FISH probe set (for ALK-rearranged anaplastic large cell lymphomas) seems to be better than immunohistochemistry tests for detecting EML4-ALK rearrangements.

Crizotinib (an inhibitor of ALK and MET tyrosine kinases) was recently approved by the FDA for patients with locally advanced or metastatic NSCLC who have the ALK gene rearrangement. Crizotinib was shown to yield very high response rates (> 80%) and improve survival when used in patients with advanced NSCLC who have EML4-ALK rearrangements and have experienced disease progression on previous therapy. Crizotinib is orally active with few side effects (eg, elevations in aminotransferases). However, a few patients have had life-threatening pneumonitis, and administration of crizotinib was stopped. Patients have responded rapidly to crizotinib, although many have developed resistance after approximately 1 year. However, other EMLK4-ALK inhibitors are in development. A randomized phase III trial (PROFILE-1007) is comparing crizotinib with standard second-line chemotherapy.

**Treatment Approaches**

History and physical, standard laboratory testing, and imaging (eg, brain MRI, PET/CT scan) are used to assess whether a patient has metastatic disease. For example, patients may have clinical stage II–III disease that is later found to be stage IV disease (more information is available in these guidelines at NCCN.org). Pathologic evaluation of the mediastinal nodes (eg, mediastinoscopy) is recommended for many patients with stages I–III NSCLC. It is not necessary, however, for patients with NSCLC whose disease is clearly metastatic, because lymph node status (eg, N2 vs. N3) will not change treatment. If metastatic disease is suspected, less-invasive staging procedures may be useful (eg, transesophageal endoscopic ultrasound–guided FNA [EUS-FNA], endobronchial ultrasound–guided transbronchial needle aspiration [EBUS-TBNA]).

Systemic therapy (consisting of chemotherapy, targeted therapy, or a combination), clinical trials, and/or palliative treatment are commonly used to
treat patients with metastatic NSCLC; these patients are not candidates for aggressive treatment (eg, combined modality treatment). The goal is to identify patients with metastatic disease before administering aggressive treatment (eg, chemoradiation, pneumonectomy) and thus spare them unnecessary futile (and potentially toxic) treatment. Radiation therapy (RT) is appropriate in select patients with stage IV disease; surgery is rarely performed in these patients (see “Surgery,” next section, and “Radiation Therapy,” on page 1257).

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial. Despite the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor. Recent data show that early palliative care combined with standard care improves quality of life, mood, and survival in patients with metastatic NSCLC, even though these patients received less-aggressive therapy than those receiving standard care alone.

**Surgery**

Typically, surgery (eg, pneumonectomy) is not appropriate for patients with metastatic disease. If surgery is planned (eg, clinical stage III), it may be aborted if metastatic disease is found during surgical evaluation. Surgical resection of a solitary brain metastasis may improve survival in select patients with stage IV disease and is recommended in the NCCN Guidelines (see page 1239 and the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org). Surgical resection of a solitary metastasis located in sites other than the brain remains controversial; however, stereotactic radiosurgery (SRS) or stereotactic ablative radiotherapy (SABR) may be useful in these settings (see page 1239).

**Systemic Therapy**

**Chemotherapy:** Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen. Many drugs are useful for stage IV NSCLC (see “Treatment of Recurrences and Distant Metastases” on page 1260, and pages 1248–1249 of the algorithm). These drugs include platinum agents (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinorelbine, vinblastine, etoposide, pemetrexed, and gemcitabine. Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents. Regimens include carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/vinorelbine, gemcitabine/cisplatin, cisplatin/pemetrexed, and docetaxel/cisplatin. Phase III randomized trials have shown that many of the platinum-doublet combinations have similar objective response rates and survival. Platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for patients. Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin; gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.

Note that albumin-bound paclitaxel can be substituted for paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or those for whom the standard premedications (ie, dexamethasone, H$_2$ and H$_3$ blockers) to prevent hypersensitivity are contraindicated.

**Targeted Therapies:** Specific targeted therapies have been developed for the treatment of advanced lung cancer. Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). Erlotinib is a small molecule inhibitor of EGFR; crizotinib is a small molecule inhibitor that targets ALK and MET. Cetuximab is a monoclonal antibody that targets EGFR.

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC. The ECOG recommends bevacizumab in combination with paclitaxel and carboplatin for select patients with advanced nonsquamous NSCLC based on the results of phase II/III clinical trials (ECOG 4599). To undergo treatment with bevacizumab and chemotherapy, patients must have nonsquamous NSCLC and no recent history of hemoptysis. Any regimen with a high risk for thrombocytopenia, and therefore possible bleeding, should be used with caution when combined with bevacizumab. For patients with nonsquamous NSCLC and PS 0 or 1 who are EGFR mutation–negative or unknown, bevacizumab in combination with chemotherapy is one of the recommended options (see page 1242).

Erlotinib was approved by the FDA in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. However, erlotinib is also recommended as first-line therapy in patients with
advanced, recurrent, or metastatic nonsquamous NSCLC who have a known active EGFR mutation or gene amplification, regardless of PS (see page 1241). This recommendation is based on the results of a phase III randomized trial (Iressa Pan-Asia study [IPASS]) in which patients with EGFR mutations who received gefitinib had increased progression-free survival (24.9% vs. 6.7%), response rates (71.2% vs. 47.3%), and quality of life with fewer side effects (eg, neutropenia) compared with those receiving chemotherapy (carboplatin/paclitaxel). Gefitinib is not readily available in the United States, and therefore erlotinib is often used. Erlotinib is an orally active agent that is very well tolerated by most patients.

An analysis of 5 clinical trials in predominantly Western populations (N = 223) with advanced NSCLC (stage IIIB or IV) found that patients with EGFR mutations who received gefitinib had a 67% response rate and an overall survival of approximately 24 months. The recent TORCH trial suggests that EGFR mutation testing should be performed in patients with advanced nonsquamous NSCLC. Survival was increased in patients with wild-type EGFR who received first-line chemotherapy compared with those who received erlotinib followed by second-line chemotherapy (10.8 vs. 7.7 months). The recent OPTIMAL trial found that progression-free survival was increased in patients with EGFR mutations receiving erlotinib. ASCO recommends that patients be tested for an EGFR mutation. However, NCCN and the European Society for Medical Oncology (ESMO) guidelines specify that only patients with nonsquamous histology (eg, adenocarcinoma) be assessed for EGFR mutations. Patients with squamous cell carcinoma are unlikely to have these mutations.

Crizotinib was recently FDA-approved for patients with locally advanced or metastatic NSCLC who are positive for the ALK gene rearrangement. The approval was based on an ongoing phase II trial that showed dramatic response rates (> 80%) in patients whose disease had previously progressed. Patients receiving crizotinib reported clinically significant improvements in pain, dyspnea, and cough.

A large phase III randomized trial (FLEX) assessed cisplatin/vinorelbine with or without cetuximab for patients with advanced NSCLC (most had stage IV disease). Adding cetuximab slightly increased overall survival (11.3 vs. 10.1 months; P = .04). Cetuximab/cisplatin/vinorelbine is an option for patients with advanced NSCLC, regardless of histology (see page 1242). However, the cetuximab/cisplatin/vinorelbine regimen has a category 2B recommendation in these guidelines because the benefits are very slight, it is a difficult regimen to administer, and patients have a poor tolerance for this regimen compared with other regimens (eg, almost 40% experienced grade 4 neutropenia). Patients may also have comorbid conditions that prevent them from receiving cisplatin (eg, poor kidney function). Although the FLEX trial results were statistically significant, some clinicians believe they were not clinically significant.

**Maintenance Therapy:** Maintenance therapy refers to systemic therapy that may be given to patients with advanced NSCLC after 4 to 6 cycles of first-line chemotherapy. However, patients are only candidates for maintenance therapy if they experienced response to their previous treatment (ie, tumor response) or have stable disease and have no disease progression. Continuation maintenance therapy refers to the use of at least one of the agents given in the first-line regimen. Switch maintenance therapy refers to the initiation of a different agent not included as part of the first-line regimen. Selection of appropriate maintenance therapy depends on several factors (eg, histologic type, PS).

For continuation maintenance therapy, targeted agents (initially given in combination with conventional chemotherapy) may be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to FDA approval. Bevacizumab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (ie, platinum-doublet chemotherapy given with bevacizumab) in patients with nonsquamous histology. Pemetrexed may also be given as continuation maintenance therapy in patients with nonsquamous histology (who are EGFR mutation–negative or unknown). A recent phase III randomized trial (PARAMOUNT) found that continuation therapy with pemetrexed slightly increased progression-free survival compared with placebo (4.1 vs. 2.8 months); overall survival data are not yet available. Cetuximab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (ie, cisplatin,
vinorelbine, and cetuximab therapy) in patients with nonsquamous histology (who are EGFR mutation–negative or unknown) or those with squamous histology.\textsuperscript{130}

Use of continuation maintenance therapy depends on several factors, such as whether the patient had minimal toxicity during treatment. A drug “vacation” may be more appropriate for some patients. Some clinicians believe that continuation maintenance therapy is only appropriate for select patients, because it has not been shown to improve overall survival or quality of life.\textsuperscript{134–136} In addition, maintenance therapy has not been shown to be superior to second-line therapy, which is initiated at disease progression. No randomized trials support the continuation maintenance of conventional cytotoxic agents beyond 4 to 6 cycles of therapy.\textsuperscript{134} However, some clinicians believe that the cytotoxic chemotherapy response should be continued if patients experience response.

A recent phase III randomized trial compared maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin/gemcitabine. Data show that continuation maintenance therapy with gemcitabine increased progression-free survival to a greater extent (3.8 months) than switch maintenance therapy with erlotinib (2.9 months) when compared with observation (1.9 months).\textsuperscript{137} Another phase III randomized trial assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.\textsuperscript{138} The data showed a slight difference in progression-free survival but no difference in overall survival. Thus, these guidelines recommend using gemcitabine as continuation maintenance therapy.

For switch maintenance therapy, 2 recent phase III randomized trials have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4–6 cycles) in patients without disease progression.\textsuperscript{139,140} Switch maintenance therapy with pemetrexed may be initiated in patients with histologies other than squamous cell carcinoma who are EGFR mutation–negative (or with unknown mutation status).\textsuperscript{141} The FDA has approved maintenance therapy with pemetrexed (www.accessdata.fda.gov/drugsatfda_docs/label/2011/021462s029s030s032lbl.pdf).\textsuperscript{142} Likewise, switch maintenance therapy with erlotinib may be initiated in patients with or without EGFR mutations, or with squamous cell carcinoma.\textsuperscript{137,139}

Both erlotinib and pemetrexed have a category 2A recommendation for switch maintenance (see page 1242). A phase III trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.\textsuperscript{142} However, switch maintenance therapy with docetaxel is a category 2B recommendation because many patients in the delayed chemotherapy arm did not receive docetaxel.

Recently, an updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC.\textsuperscript{143} The data showed that in patients with EGFR mutations, erlotinib alone was associated with fewer side effects than erlotinib and chemotherapy. Thus, switching to maintenance therapy with erlotinib is appropriate in patients found to have EGFR mutations during chemotherapy (see page 1241). The FDA has approved maintenance therapy with erlotinib (www.accessdata.fda.gov/drugsatfda_docs/label/2010/021743s14s16lbl.pdf).\textsuperscript{144}

Radiation Therapy

In patients with advanced lung cancer (stage IV), RT is recommended for 1) palliative care, 2) prevention of symptoms, 3) whole-brain RT and/or SRS for brain metastases (see page 1239), and 4) SABR, traditionally known as stereotactic body RT (SBRT) for lung lesions. In patients with extensive metastases, palliative RT can be used for primary or distant sites. Treatment of brain metastases is described in the NCCN Guidelines for Central Nervous System Cancers (to view the most recent version of these guidelines, visit NCCN.org).

The complete version of the NCCN Guidelines for NSCLC (available at NCCN.org) contains a “Principles of RT” section, which includes 1) general principles for advanced lung cancer; 2) target volumes, prescription doses, and normal tissue dose constraints for advanced lung cancer; and 3) radiation simulation, planning, and delivery.\textsuperscript{145–150} Whole-brain RT and SRS for brain metastases and the abbreviations for RT are also described in this complete version.

External-beam RT is recommended for local palliation or for prevention of symptoms (ie, pain, bleeding, and obstruction; see page 1240 and NSCLC-B, 8 of 8 [available online, in these guidelines, at NCCN.org]). The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, PS, and logistical considerations to
maximize quality of life. Shorter courses of RT provide similar pain relief as longer courses and are favored for patients with poor PS and/or shorter life expectancy. However, shorter courses of RT have a higher potential for retreatment. When higher doses (> 30 Gy) are warranted, 3D conformal RT should be used to reduce normal tissue irradiation.

Definitive local therapy to isolated or limited metastatic sites (oligometastases), including brain, lung, and adrenal gland, achieves prolonged survival in a small proportion of well-selected patients with good PS who have also received radical therapy to the intrathoracic disease. Definitive RT to oligometastases, particularly SABR, is an appropriate option in these cases if it can be safely delivered to the involved site.

SABR: SABR (traditionally known as SBRT) uses short courses of very high RT doses delivered precisely to the target. SABR can be used for patients with limited lung metastases and for palliative therapy. Studies also suggest that SABR can be used for bone, liver, and brain metastases. SABR is discussed more fully in the “Principles of RT” section of the full NCCN Guidelines for NSCLC (available at NCCN.org), including fractionation regimens, normal tissue constraints, and dose recommendations. Decisions regarding whether to recommend SABR should be based on multidisciplinary discussion.

Whole-Brain RT and SRS: Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life. Surgery followed by whole-brain RT is recommended (category 1) for select patients (those with good PS) with a single brain metastasis (see page 1239 and the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org). SRS is another option after surgical resection, although only a few retrospective case series support this option. Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with SRS with or without whole-brain RT. Recent data suggest that erlotinib may be useful for managing brain metastases.

Decisions regarding whether to recommend surgery, whole-brain RT, SRS, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing the potential benefit against the risks for each individual patient. Treatment should be individualized for patients with recurrent or progressive brain lesions.

Some concern exists that whole-brain RT adversely affects neurocognition. However, a study in 208 patients with brain metastases found that those who experienced response (with tumor shrinkage) after whole-brain RT had improved neurocognitive function, and that tumor progression affects neurocognition more than whole-brain RT. Survival was similar among 132 patients with 1 to 4 brain metastases who received SRS with or without whole-brain RT. In a subset of 92 of these patients, controlling the brain tumor with combined therapy was more important for stabilizing neurocognitive function. However, a study in 58 patients found that those who received SRS and whole-brain RT had fewer central nervous system recurrences but experienced worse neurocognition than patients receiving SRS alone. Some investigators have suggested that using resection with SRS (vs. resection with whole-brain RT) will decrease neurocognitive problems.

Prophylactic Cranial Irradiation: Prophylactic cranial irradiation (PCI) does not appear to improve survival in patients with NSCLC; however, it may be considered in individual patients. Although it closed early because of poor accrual, a randomized phase III trial (RTOG 0214) in patients with stage III NSCLC showed that the incidence of brain metastases was lower in those who received PCI (18% vs. 7.7%), but overall survival was not improved and impaired memory (immediate and delayed recall) was reported.

Initial Clinical Evaluation

These guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC. The clinical stage is initially determined from disease history (ie, cough, dyspnea, chest pain, weight loss) and physical examination together with a limited battery of tests (see page 1238). The panel also recommends that smoking cessation counseling be made available (www.smokefree.gov/). Based on initial evaluation, the clinical stage is determined and the patient is assigned to one of the pathways defined by the stage, specific subdivision of the particular stage, and tumor location.

Additional Pretreatment Evaluation

Other Imaging Studies: PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN NSCLC Panel reviewed the diagnostic performance of CT and PET...
scans. Because they detect tumor physiology as opposed to anatomy, PET scans may be more sensitive than CT scans, and therefore the panel believes that PET scans can play a role in the evaluation and more accurate staging of NSCLC, such as in identifying stage IV disease.\(^{189,190}\) However, PET/CT is even more sensitive and is recommended by NCCN.\(^{191–193}\) Positive PET/CT scan findings require pathologic or other radiologic confirmation (eg, MRI of bone).

EUS-FNA and EBUS-TBNA have proven useful in staging patients or diagnosing mediastinal lesions; these techniques can be used instead of invasive staging procedures in select patients.\(^{194}\) Compared with CT and PET, EBUS-TBNA has a high sensitivity and specificity for staging mediastinal and hilar lymph nodes in patients with lung cancer.\(^{195}\) In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results.\(^{196,197}\) However, in patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be performed to confirm the results.\(^{197,198}\)

The routine use of bone scans (to exclude bone metastases) is not recommended. Brain MRI is recommended for patients with stage IV disease.\(^{199}\)

**Initial Therapy for Metastatic Disease**

Recommended therapy for metastatic disease is described in this section, the sections on “Systemic Therapy” and “Treatment of Recurrences and Distant Metastases” (pages 1255 and 1260, respectively), and the algorithm (see 1248–1249).

**Lung Metastases**

When a lung metastasis is present, it usually occurs in patients with other systemic metastases, and the prognosis is poor. Therefore, many of these patients are not candidates for surgery; however, systemic therapy is recommended. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery.\(^{200}\) Intrapulmonary metastases have been downstaged in the recent TNM revised staging (ie, AJCC 7th edition).\(^{58,201,202}\)

**Pleural or Pericardial Effusion**

Pleural or pericardial effusion is a criterion for stage IV, M1a disease. Note that with the revised AJCC staging (7th edition), T4 with effusion has been reclassified as stage IV, M1a (see staging tables, available online, in these guidelines, at NCCN.org).\(^{58}\) Although pleural effusions are malignant in 90% to 95% of patients, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion through thoracentesis or pericardiocentesis is recommended (see page 1239). In certain cases in which thoracentesis is inconclusive, thoracoscopy may be performed. In the absence of nonmalignant causes (eg, obstructive pneumonia), an exudate or sanguinous effusion is considered malignant regardless of the results of cytologic examination. If the pleural effusion is considered negative, the algorithm tracks back to the confirmed T and N stage (in the complete version of these guidelines, available online at NCCN.org). However, all pleural effusions, malignant or not, are associated with unresectable disease in 95% of cases.\(^{203}\) In patients with effusions positive for malignancy, the tumor is treated as for M1a, with local therapy (eg, ambulatory small catheter drainage, pleurodesis, and pericardial window), and as for stage IV disease (see pages 1239 and 1241).

**Solitary Distant Metastasis**

The algorithm for patients with distant metastases (ie, stage IV, M1b) depends on the location of the metastases—a solitary nodule in the brain or adrenal gland—which is determined by PET/CT scan, brain MRI, mediastinoscopy, and bronchoscopy (see page 1239). The increased sensitivity of PET/CT scans compared with other imaging methods may identify additional metastases and spare some patients from unnecessary surgery. However, positive PET/CT scan findings require pathologic or other radiologic confirmation.

Patients with solitary brain metastases may benefit from surgical resection and/or RT (see page 1239, “Whole-Brain RT and SRS” on page 1258, and the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).\(^{172,173}\) The 5-year survival rates associated with this approach range from 10% to 20%\(^{120,204}\); median survival is approximately 40 weeks.\(^{176}\) Follow-up whole-brain RT (category 1) or SRS may be used.\(^{174,181,205}\) SRS alone or followed by whole-brain RT are additional treatment options.\(^{177,178}\) This therapy can be effective in patients who have surgically inaccessible brain metastases and in those with multiple lesions.\(^{206}\) After the brain lesions are treated, further treatment op-
tions for these patients with T1–2,N0–1 NSCLC or for those with T3,N0 include 1) surgical resection of the lung lesion followed by chemotherapy (category 2B for chemotherapy), 2) SABR of the lung lesion (category 2B), or 3) additional chemotherapy followed by surgical resection of the lung lesion (category 2B). Systemic therapy is an option after surgery for patients with higher-stage NSCLC.

Adrenal metastases from lung cancer are common, found in approximately 33% of patients at autopsy. In patients with otherwise resectable primary tumors, however, many solitary adrenal masses are not malignant. Any adrenal mass found on a preoperative CT scan in a patient with lung cancer should be biopsied to rule out benign adenoma. If an adrenal metastasis is found and the lung lesion is curable, resection has produced some long-term survivors (category 2B; see page 1239). However, some panel members believe that resection of adrenal metastases only makes sense if the synchronous lung disease is stage I or maybe stage II (ie, resectable). Systemic therapy is another treatment option for adrenal metastasis.

Surveillance

The surveillance guidelines are described on page 1240. A helical chest CT scan with or without contrast is recommended every 6 to 12 months postoperatively for 2 years (category 2B); a non–contrast-enhanced chest CT is recommended annually thereafter (category 2B), although the panel disagreed about the recommendations for helical chest CT scans. Information about smoking cessation (eg, advice, counseling, therapy) should be provided to aid the treatment of lung cancer and improve the patients’ quality of life (www.smokefree.gov/). Recent data show that low-dose CT screening of select patients at high risk for lung cancer (ie, 30 pack years of smoking) increases survival. However, use of low-dose CT for surveillance is not currently recommended for those who have previously undergone treatment for lung cancer.

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and metastases. Management of locoregional recurrences (eg, endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava obstructions, severe hemoptysis) is described on page 1240. For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in those who are severely compromised, and may improve quality of life. After treatment for the locoregional recurrence, observation or systemic chemotherapy (category 2B for chemotherapy) is recommended if disseminated disease is not evident. However, for observed disseminated disease, systemic chemotherapy or best supportive care is recommended. The type of systemic therapy depends on the histologic type, EGFR mutation status, and PS (see page 1241).

Management of distant metastases (eg, localized symptoms; diffuse brain, bone, solitary, or disseminated metastases) is described on page 1240. For distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis, external-beam RT can be used for palliation of symptoms. Bisphosphonate therapy or denosumab can be considered in patients with bone metastasis. Note that denosumab can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk for hypocalcemia. The FDA has approved the use of zoledronic acid in patients with bone metastases from solid tumors.

For patients with recurrent and metastatic disease, these guidelines now recommend that the histologic subtype should be determined before therapy so that the best treatment can be selected (see page 1241). EGFR mutation testing is recommened in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell) or in NSCLC not otherwise specified, because erlotinib is recommended in patients who are EGFR mutation–positive (see “EGFR Mutations” on page 1253). Recent recommendations from an international panel suggest that general categories be avoided (eg, NSCLC), because more effective treatment can be selected when the histology is known. However, very few patients with squamous cell carcinoma have EGFR mutations (< 4%), and therefore routine testing is not recommended in these patients.

Treatment recommendations and eligibility criteria for those with nonsquamous NSCLC who are EGFR mutation–negative (or with unknown mutation status) are described in the algorithm on page 1242. Treatment recommendations and eligibility criteria for those with squamous histology are
described on page 1243. These recommendations are also briefly summarized in the following paragraph. Data supporting these recommendations are described in the next section on “Trial Data.”

Cisplatin/pemetrexed is recommended (category 1) for patients with nonsquamous NSCLC who are EGFR mutation–negative (or with unknown mutation status) if eligibility criteria are met\(^\text{109}\). Bevacizumab/chemotherapy is another option.\(^\text{217}\) Patients with brain metastases were previously excluded from receiving bevacizumab because of concerns regarding central nervous system hemorrhage; however, data suggest that bevacizumab can be used in those with treated central nervous system metastases.\(^\text{218}\) Other chemotherapy options are also recommended, although some regimens may be more appropriate for certain patients, depending on PS and other factors (see next section on “Trial Data”). Panel members disagreed (category 2B) regarding the use of cetuximab with cisplatin and vinorelbine, because data only showed a slight improvement in survival with the addition of cetuximab (11.3 vs. 10.1 months; \(P = .04\)); additionally, this regimen is not generally used in the United States because of concerns regarding toxicity with cisplatin.\(^\text{130}\)

For patients with squamous cell carcinoma, cisplatin/gemcitabine is an option.\(^\text{109}\) Another option is cetuximab with cisplatin and vinorelbine, although this is a category 2B recommendation.\(^\text{130}\)

**Trial Data**

In a phase II/III trial (ECOG 4599), 878 patients were randomly assigned to either bevacizumab in combination with paclitaxel and carboplatin, or paclitaxel and carboplatin alone.\(^\text{122,129}\) Both regimens were well tolerated, with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin showed an improved median survival (12.3 vs. 10.3 months; \(P = .003\)) compared with paclitaxel and carboplatin alone.\(^\text{122}\) Overall 1- and 2-year survival rates were 51% versus 44% and 23% versus 15%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.\(^\text{122}\) However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin than with paclitaxel and carboplatin alone (grade 4 neutropenia: 25.5% vs. 16.8%; grade 5 hospitalization: 1.2% vs. 0%; grade 3 hypertension: 6.8% vs. 0.5%), and treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (15 vs. 2 patients; \(P = .001\)).

A recent analysis of ECOG 4599 found that adenocarcinoma histology was associated with improved survival in patients receiving bevacizumab/paclitaxel/carboplatin compared with chemotherapy alone (14.2 vs. 10.3 months).\(^\text{217}\) However, a trial (AVAil) comparing cisplatin/gemcitabine with or without bevacizumab did not show an increase in survival with the addition of bevacizumab.\(^\text{220,221}\)

A noninferiority trial in 1725 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) compared cisplatin plus gemcitabine versus cisplatin plus pemetrexed.\(^\text{109}\) Patients with either adenocarcinoma or large cell histology (ie, nonsquamous) had improved survival with cisplatin/pemetrexed (adenocarcinoma: 12.6 vs. 10.9 months). Patients with squamous cell histology had improved survival with cisplatin/gemcitabine (10.8 vs. 9.4 months). The cisplatin/pemetrexed regimen had significantly lower rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia (\(P \leq .001\); febrile neutropenia (\(P = .002\)); and alopecia (\(P < .001\)). Treatment-related deaths were similar for both regimens (cisplatin/pemetrexed, 9 patients [1.0%]; cisplatin/gemcitabine, 6 patients [0.7%]). A recent analysis of 3 phase III trials confirmed that pemetrexed improves survival for patients with nonsquamous NSCLC when used in first-line, second-line, and maintenance therapy.\(^\text{222}\)

In the FLEX trial, 1125 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) were randomly assigned to either cetuximab in combination with vinorelbine and cisplatin, or vinorelbine and cisplatin alone.\(^\text{130}\) The response rate was increased with cetuximab (36% vs. 29%; \(P = .012\)), and no difference was seen in progression-free survival. Overall survival was slightly better in patients receiving cetuximab (11.3 vs. 10.1 months; \(P = .04\)). However, patients receiving cetuximab experienced increased grade 3 or 4 febrile neutropenia (22% vs. 15%; \(P < .05\)) and grade 2 acne-like rash. Treatment-related deaths were similar in both groups (3% vs. 2%).

Data show that platinum-based combination therapy is superior to best supportive care for patients with advanced incurable disease. Cisplatin or carboplatin have been proven effective in combination with any of the following agents: docetaxel, etoposide, gemcitabine, paclitaxel, pemetrexed, vinblastine, and vinorelbine.\(^\text{103–109,112,113}\) Non–platinum-based regimens
are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).115-117

**Maintenance Therapy**

Patients receiving therapy should be evaluated for tumor response with a CT scan. Approximately 25% of patients show disease progression after the initial cycle of chemotherapy. Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles of chemotherapy223 or until disease progression. A meta-analysis suggests that continuing the initial regimen beyond 4 to 6 cycles is associated with increased progression-free survival; however, patients have more adverse events.224 Another review suggests that continuing chemotherapy beyond 4 to 6 cycles confers no benefit; however, many patients assigned to a longer duration of therapy did not receive the planned number of cycles.134

For patients with nonsquamous NSCLC who are EGFR mutation–negative (or unknown mutation status), continuation maintenance therapy regimens include bevacizumab (category 1), cetuximab (category 1), pemetrexed, or gemcitabine (see page 1242).122,130,133,137 Switch maintenance therapy regimens for these patients include pemetrexed or erlotinib.137,139,140 Observation is another option.

For patients with squamous cell histology, cetuximab (category 1) or gemcitabine can be used as a continuation maintenance therapy regimen (see page 1243).137,139 Switch maintenance therapy for these patients includes erlotinib or docetaxel (category 2B). Observation is another option. A phase III trial assessed switch maintenance therapy with docetaxel either given immediately after chemotherapy or delayed until progression.140 However, switch maintenance therapy with docetaxel is a category 2B recommendation in these guidelines, because many patients in the delayed chemotherapy arm did not receive docetaxel.

A phase III randomized trial (n = 663) assessed the effect of best supportive care with or without maintenance pemetrexed in patients with advanced NSCLC who had received platinum-based chemotherapy but whose disease had not progressed.140 In patients with nonsquamous NSCLC, overall survival was increased with pemetrexed compared with placebo (15.5 vs. 10.3 months; P = .002).

**Continuation of Erlotinib or Gefitinib After Progression: Has Its Time Come?**

Patients may continue to derive benefit from erlotinib or gefitinib after disease progression, and discontinuation of erlotinib or gefitinib leads to more rapid disease progression (symptoms, tumor size, and FDG-avidity on PET scan).225 This strategy mirrors the experience in other oncogene-addicted cancers, particularly HER2-amplified breast cancer. In women with HER2-amplified breast cancer who experience disease progression on trastuzumab, improved radiographic response rate, time to progression, and overall survival are observed when conventional chemotherapy is added to trastuzumab.226 Data support the continued use of erlotinib or gefitinib in patients with lung adenocarcinoma with EGFR mutations after development of acquired resistance to erlotinib or gefitinib when conventional chemotherapy is initiated.

Data are accumulating regarding how cancers become resistant to EGFR inhibitors. The most common known mechanism is the acquisition of a secondary mutation in EGFR, T790M, that renders the kinase resistant to erlotinib and gefitinib.127,228 Amplification of the MET oncogene is another validated resistance mechanism. Activation of the insulin-like growth factor 1 receptor (IGF-1R) pathway has been observed in laboratory models. To overcome all 3 types of resistance, EGFR must still be inhibited. In the case of MET amplification and IGF-1R activation, new inhibitors must be added to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely et al225 show that when cancers once sensitive to EGFR inhibitors begin to progress, discontinuation of the EGFR-TKI can lead to a much more accelerated cancer progression. In total, it is likely that continuing EGFR-TKIs is beneficial in many patients even after they develop resistance to EGFR-TKIs.

**Second- and Third-Line Chemotherapy**

Although many new active drugs are available for lung cancer, the reported response rates to second-line chemotherapy have generally been less than 10%. Docetaxel, pemetrexed, erlotinib, or platinum doublet (with or without bevacizumab) are recommended as second-line chemotherapy regimens for patients with a PS of 0 to 2 who experience disease progression during or after first-line therapy (see page 1244).229-232 Docetaxel has proven superior to...
best supportive care, vinorelbine, or ifosfamide, with improved survival and quality of life; docetaxel may be used for third-line therapy.\textsuperscript{229,230} When compared with docetaxel, pemetrexed has similar median survival but less toxicity.\textsuperscript{231,233} Pemetrexed is recommended in patients with adenocarcinoma or large cell histology (ie, nonsquamous NSCLC) for second- and third-line therapy.\textsuperscript{140} Erlotinib has proven superior to best supportive care, with significantly improved survival and delayed time to symptom deterioration.\textsuperscript{232} Erlotinib is recommended for second- or third-line therapy for progressive disease in patients with a PS of 3 or 4 who have the EGFR mutation (see page 1244). A platinum doublet with or without bevacizumab is an option for those with nonsquamous NSCLC (ie, adenocarcinoma, large cell, NSCLC not otherwise specified) whose disease has progressed after first-line therapy with erlotinib or crizotinib.\textsuperscript{122}

In a randomized, placebo-controlled, double-blind trial (NCIC CTG trial), 731 patients (stage IIIB or IV, PS 0–3) were randomly assigned (2:1) to receive either erlotinib or placebo after failure of first- or second-line chemotherapy.\textsuperscript{232} Patients treated with erlotinib showed an overall survival of 6.7 versus 4.7 months for placebo (hazard ratio, 0.70; $P < .001$). Progression-free survival was 2.2 months for the erlotinib group versus 1.8 months for placebo (hazard ratio, 0.61, adjusted for stratification categories; $P < .001$). However, 5\% of patients discontinued erlotinib because of toxic side effects. This trial confirms that erlotinib can prolong survival in patients after failure of first- or second-line chemotherapy. A randomized phase III trial in 829 patients found that oral topotecan was not inferior to docetaxel.\textsuperscript{234}

If disease progression occurs after third-line chemotherapy, patients with a PS of 0 to 2 may be enrolled in a clinical trial or treated with best supportive care (see the NCCN Guidelines for Palliative Care; to view the most recent version of these guidelines, visit NCCN.org).

References

Non–Small Cell Lung Cancer


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Non–Small Cell Lung Cancer


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